Table 3. Details of surgical procedures

Operation time (min)	
Median	250
Range	130–495
Type of gastrectomy	
Proximal gastrectomy	0
Pylorus-preserving distal gastrectomy	43 (24.4%)
Distal gastrectomy	131 (74.4%)
Total gastrectomy	2 (1.1%)
Reconstruction method	
Roux-en-Y	48 (27.3%)
Billroth I	85 (48.3%)
Gastro-gastrostomy	43 (24.4%)
Extent of lymph node dissection, no. (%)	
D1+α[a]	4 (2.3%)
D1+β[b]	142 (80.7%)
D2	30 (17.0%)
Length of skin incision (cm)	
Median	5
Range	3–20
Length of skin incision, no. (%)	
≤6 cm	171 (97.2%)
>6 cm	5 (2.8%)
Number of ports	
Median	5
Range	4–7
Completion of LADG[c]	
Yes	170 (96.6%)
No	6 (3.4%)
Conversion to open procedure ($n = 175$)[d]	
Yes	5 (2.9%)
No	170 (97.1%)
Blood loss (ml)	
Median	43.5
Range	0–490
Perioperative blood transfusion	
Yes	3 (1.7%)
No	173 (98.3%)

[a] D1+α, D1 dissection + dissection of the nodes along the left gastric and common hepatic arteries
[b] D1+β, D1+α dissection + dissection of the nodes along the celiac artery
[c] Completion of LADG was counted for all operated patients ($n = 176$)
[d] Conversion to open procedure was counted for all patients diagnosed before gastrectomy as having clinical stage IA or IB

suffered from both an anastomotic leakage and a pancreatic fistula. The proportion of patients with either anastomotic leakage or pancreatic fistula, the primary endpoint, was 1.7% (3/176; 80% CI, 0.6–3.8; one-sided $P = 0.0003$, binomial test of the null hypothesis that the proportion is equal or greater than 8%).

The overall proportion of in-hospital adverse events (grade 3 or 4 according to the CTCAE v 3.0) was 5.1% (9/176) and the proportion of grade 1 or greater events (excluding fever) was 9.1% (16/176). Grade 3 or greater postoperative bleeding, anastomotic stricture, and intestinal obstruction were observed in two patients, one patient, and one patient, respectively.

Re-operations were performed in three patients. The reasons for the re-operations were anastomotic stricture, pancreatic fistula, and obstruction. The patient with the obstruction had developed grade 3 disseminated intravascular coagulopathy (DIC) and required a blood transfusion. The postoperative mortality rate was zero.

Short-term clinical outcomes

Flatus was recognized in all the patients during the period of hospitalization. The median time from the end of surgery until the first episode of flatus was 2 days (range, 1–5 days).

Seventy-six of the 176 patients (43.2%; 95% CI, 35.8–50.9) requested an analgesic on postoperative days 5–10, although we expected this value to be 20% or lower.

The highest body temperature during the first 3 days after surgery was recorded. The median body temperature during this period was 37.9 °C (range, 36.6 °C–39.1 °C). A body temperature of 38 °C or greater was observed in 67 patients (38.1%) on postoperative day 1, in 38 patients (21.6%) on postoperative day 2, and in 11 patients (6.3%) on postoperative day 3.

The highest body temperature during hospitalization was recorded: 88 patients had a body temperature of 38 °C or higher during their hospital stay.

Discussion

The proportion of patients who developed anastomotic leakage or pancreatic fistula formation, the primary endpoint of this study, was 1.7%. The proportion of these two postoperative complications was as low as expected in this study design and was also lower than that reported in previous publications [14, 15].

In retrospective reports about LADG, the proportions of patients who developed anastomotic leakage were quite different (1.7%–14%) [8, 9, 12], while that of patients who developed pancreatic fistula formation was 1.0% [9]. The primary endpoint in the present prospective study demonstrated that the proportion of patients who developed these two postoperative complications was lower than expected, compared with the proportions in these retrospective reports. In addition, the proportion of patients who developed these complications was considered to be equivalent to that of those who developed complications after ODG, where the proportion of patients who developed anastomotic leakage has been reported as 0.6%–2.7% and that of patients who developed pancreatic fistula as 0.6% in Japan [12, 19, 20]. The overall proportion of in-hospital adverse events itself was 5.1%, which was also relatively

low [12, 15]. These results demonstrated that LADG can be performed very safely by credentialed surgeons.

One possible reason for the low proportion of in-hospital complications in the present study might be the strict criteria that were used to select the attending surgeons. We only selected surgeons who had performed more than 30 LADG procedures and more than 30 ODG procedures prior to this trial, because we were aware that LADG requires more experience to obtain sufficient skill than its conventional open counterpart. This low complication rate also showed that the experience of performing 30 LADG procedures with suprapancreatic node dissection was sufficient to achieve proficiency. The strict selection of the attending surgeons might also have contributed to the favorable results regarding the high proportion of successful LADG procedures and the low proportion of conversions to ODG. These rates were low enough to justify a subsequent phase III trial (LADG vs ODG) [7, 21].

A second possible reason for the low proportion of in-hospital complications in the present study might be the measures used to ensure the quality control of the actual surgeries. In addition to our strict criteria for selecting surgeons, we obtained a consensus regarding the details of the surgical procedure prior to the start of the clinical trial, and the procedures were reviewed using photographs and videotapes during the enrollment period.

A third possible reason for the low proportion of in-hospital complications in the present study was the low body mass index (BMI) of the registered patients. Patients with a BMI of more than 30 were excluded from this study; as a result, the median BMI was 21.8. In western countries, the median BMI was reported as 26–29, and higher morbidities (10%–26% as grade 1–4 adverse events) than that in this study (9.1%) were demonstrated [22, 23]. Thus, BMI should be taken into consideration to interpret the morbidity results. Of note, at the National Cancer Center Hospital, Tokyo, the proportion of patients with a BMI of 25 or more was 24.0%, which is higher than the proportion in this study (15.3%). This implies that the surgeons might have preferred nonobese patients for the present trial [24].

The accuracy of preoperative staging is a key factor in the implementation of a subsequent phase III trial. Some surgeons consider that LADG should not be applied for stage II or more advanced disease. From the viewpoint of these surgeons, the accuracy of the preoperative diagnosis needs to be confirmed in this phase II study. The accuracy of the preoperative diagnosis for stage I disease (Japanese classification) was 92.6%, which was sufficient to convince these surgeons of the feasibility of a subsequent phase III study.

The major advantage of LADG over ODG is that it is less invasive. Therefore, we evaluated the short-term clinical outcomes (proportion of patients who requested an analgesic on postoperative days 5–10, time from end of surgery until first episode of flatus, and body temperature) as secondary endpoints. A visual analog scale is the most common way of evaluating pain [6]. This scale is, however, a subjective indicator and is not appropriate for comparison with historical data in a single-arm setting. Instead, we adopted the proportion of patients who requested an analgesic as a measure of pain. The proportion of patients who requested an analgesic was more than 40%, which was higher than expected and higher than that described in previous reports [6, 7, 25]. This result was paradoxical. Because this study was a phase II study, this endpoint will need to be evaluated further in a subsequent phase III trial (LADG vs ODG).

The time from the end of surgery until the first episode of flatus was a good indicator of bowel function recovery. The time until flatus was as we expected and was similar to the results of a previous report [6].

Measures of inflammation are important for evaluating the invasiveness of surgery. Body temperature is one parameter of inflammation. A body temperature greater than 38 °C is one of the clinical manifestations of systemic inflammatory response syndrome (SIRS) [26], and patients can suffer greatly from this complication. The change in body temperature was as we expected and was similar to the results of previous reports [27, 28].

Although the safety of LADG was confirmed in the present study, this result may not fit in western countries. LADG will remain an investigational treatment even in Japan until its effectiveness is fully evaluated in a phase III trial. We are now conducting a JCOG phase III trial (JCOG 0912) with a recruitment of about 1000 patients to confirm the noninferiority of LADG to ODG in terms of overall survival.

Conclusion

The present trial confirmed the safety of LADG performed by credentialed surgeons in terms of the incidence of anastomotic leakage or pancreatic fistula formation. A phase III trial to confirm the noninferiority of LADG to ODG in terms of overall survival is now ongoing.

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Appendix

Study participants

The following institutions and investigators participated in the trial: Hakodate Goryoukaku Hospital (A. Takagane), Yamagata Prefectural Central Hospital (N. Fukushima), National Cancer Center Hospital (H. Katai, M. Saka), Tokyo Medical and Dental University (K. Kojima, M. Inokuchi, H. Yamada), Cancer Institute Hospital (N. Hiki, T. Fukunaga, H. Yoshiba, M. Tokunaga), Kanagawa Cancer Center (T. Yoshikawa, H. Cho), Aichi Cancer Center Hospital (Y. Mochizuki, K. Misawa), Fujita Health University (I. Uyama, S. Kanaya, K. Taniguchi), Kinki University Hospital (H. Imamoto), Osaka Medical Center for Cancer and Cardiovascular Diseases (I. Miyashiro), Department of General and Gastroenterological Surgery, Osaka Medical College (N. Tanigawa), Wakayama Medical University (M. Iwahashi, K. Takifuji), Hiroshima City Hospital (M. Nishizaki), and Oita University (S. Kitano, N. Shiraishi, T. Eto).

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Original article

Trends in characteristics of surgically treated early gastric cancer patients after the introduction of gastric cancer treatment guidelines in Japan

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Abstract

Background. **The gastric cancer treatment guidelines (Guidelines) of the Japanese Gastric Cancer Association allow endoscopic treatment and a modified gastrectomy for the treatment of early gastric cancer (EGC). Endoscopic treatment is indicated for EGC with a minimal chance of nodal metastasis. Consequently, surgeons will likely treat an increasing number of EGC patients with greater chance of nodal metastasis using a reduced extent of lymphadenectomy. The aim of this study was to investigate the trends in characteristics and long-term oncological outcomes of surgically treated EGC patients after the introduction of the Guidelines.**

Methods. **Between 2001 and 2003, 696 patients underwent a gastrectomy according to the Guidelines. These 696 patients (the Guidelines group) were retrospectively compared with 635 patients (the control group) who had undergone a gastrectomy between 1991 and 1995 (before the introduction of the Guidelines).**

Results. **The incidence of nodal metastasis in mucosal cancers was higher in the Guidelines group than in the control group (6.5% vs 2.6%). The proportion of D2 or greater extended lymphadenectomy in the Guidelines group was lower than that in the control group (29.7% vs 62.5%). Nevertheless, the 5-year survival rate in the Guidelines group was similar to that in the control group (94.2% vs 92.3%).**

Conclusion. **Surgeons treated more cases of mucosal cancer with nodal metastasis after the introduction of the Guidelines. The long-term oncological outcomes for patients with EGC remained excellent. So far, the Guidelines for the treatment of EGC appear acceptable.**

Key words Early gastric cancer · Lymph node metastasis · Gastric cancer treatment guidelines

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Introduction

Early gastric cancer (EGC) is defined as invasion confined to the mucosa or submucosa, regardless of the presence of regional lymph node metastasis. In recent years, the incidence of EGC has reached more than 50% of all gastric cancer cases in Japan. Gastrectomy with D2 lymphadenectomy had been firmly accepted as a standard treatment for every stage of gastric cancer since the 1980s [1, 2]. EGC treated with radical surgery has an excellent survival rate, with 5-year survival rates of more than 90% being reported by both Western [3] and Japanese [4] investigators. However, ever since the clinicopathological features of EGC, such as the incidence of lymph node metastasis, were clarified in the late 1990s, gastrectomy with D2 lymphadenectomy for all patients with EGC has come to be considered as an overtreatment [5–8].

The gastric cancer treatment guidelines (Guidelines) were issued by the Japanese Gastric Cancer Association (JGCA) in March 2001 [9, 10]. The Guidelines were designed to provide standard indications for the selection of treatments for gastric cancer according to the clinical stages of the disease (JGCA classification). The Guidelines allowed endoscopic resection and a modified gastrectomy as treatment modalities for EGC, in addition to a standard gastrectomy. Endoscopic treatment can be utilized in patients with a minimal chance of lymph node metastasis. A modified gastrectomy, including limited lymphadenectomy, can be utilized in patients with EGC beyond the inclusion criteria for endoscopic treatment. Because patients with a minimal chance of lymph node metastasis were excluded as candidates for a gastrectomy, Japanese surgeons are interested in whether surgeons are actually facing an increasing number of EGC cases with a greater chance of lymph node metastasis. Furthermore, whether a modified gastrectomy with a reduced extent

of lymphadenectomy is sufficient treatment for these cases of EGC with a greater chance of lymph node metastasis is also a topic of interest. We retrospectively investigated the clinicopathological characteristics and long-term oncological outcomes of EGC patients who underwent a gastrectomy after the introduction of the Guidelines and compared our results with those obtained in patients treated before the introduction of the Guidelines.

Patients and methods

Patients

Between January 1991 and December 2003, 2218 patients with EGC underwent a gastrectomy with curative intent at the National Cancer Center Hospital, Tokyo. Between March 2001 and December 2003, 696 of these patients underwent a gastrectomy according to the Guidelines. These 696 patients (the Guidelines group) were retrospectively compared with 635 patients (the control group) who had undergone a gastrectomy between January 1991 and December 1995 (before the introduction of the Guidelines). Patients who had undergone a gastrectomy between January 1996 and February 2001 were excluded from this analysis because endoscopic resection and a modified gastrectomy for EGC were frequently performed as investigational treatments during this period. Surgical specimens were examined and scored according to the *Japanese classification of gastric carcinoma* [9]. The vital statistics for all the patients were obtained from the city registry office and the follow-up records. All the patients were followed up for at least 5 years.

Surgical procedures

Before the introduction of the Guidelines, a gastrectomy with D2 lymphadenectomy was performed as a standard treatment for every stage of gastric cancer. After the introduction of the Guidelines, definite recommendations for endoscopic treatment were confined to tumors in the mucosal layer; type I, IIa, or depressed type IIc with no ulcers; well- or moderately differentiated adenocarcinoma; and tumors smaller than 2 cm. A modified gastrectomy was utilized in patients with cT1N0 (stage IA) tumors and cT1N1 (stage IB) tumors less than 2.0 cm in size, excluding patients who fulfilled the criteria for endoscopic resection. The modified gastrectomy allowed a reduced extent of lymphadenectomy, compared with a D2 lymphadenectomy. While the N1 nodes were completely removed, some suprapancreatic N2 nodes, such as the node along the splenic artery, were excluded from the dissection.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA). The significance of the differences in the patients' clinicopathological features and the incidence of lymph node metastasis were determined using the χ^2 test and the Mann–Whitney *U*-test, as appropriate. A 5% significance level ($P < 0.05$) was considered statistically significant. The survival rate was calculated by the Kaplan-Meier method with 95% confidence intervals (CIs), and the hazard ratio was calculated by the Cox proportional hazards model with 95% CIs.

Results

Patient characteristics

The male-to-female ratio in the Guidelines group (1.92: 1) was significantly lower than that in the control group (2.55: 1; Table 1). The median age in the Guidelines group (62 years) was significantly higher than that in the control group (60 years). There was no difference in the distribution of tumor location. The median tumor size in the Guidelines group (30.0 mm) was significantly larger than that in the control group (26.0 mm). The proportion of undifferentiated-type lesions in the Guidelines group (58.0%) was significantly higher than that in the control group (41.7%).

The incidence of lymph node metastasis in patients with mucosal cancers in the Guidelines group (6.5%) was significantly higher than that in the control group (2.6%; Table 2). No difference in the incidence of lymph node metastasis in patients with submucosal cancer was noted between the two groups. The proportion of D2 or greater extended lymphadenectomy in the Guidelines group (207/696; 29.7%) was significantly lower than that in the control group (397/635; 62.5%).

Survival

The median follow-up period in the Guidelines group was 5.5 years, while that in the control group was 7.5 years. During a 5-year follow-up period, 40 patients (5.7%) in the Guidelines group died; 9 of these patients (1.3%) died from recurrence. Thirty-eight patients in the control group (6.0%) died; 6 of these patients (0.9%) died from recurrence. The overall 5-year survival rates were 94.2% (95% CI, 92.4%–96.0%) in the Guidelines group and 92.3% (95% CI, 90.1%–94.5%) in the control group. If the relative risk for death was set at one for patients in the control group, the hazard ratio in the Guidelines group was 0.78 (95% CI, 0.53–1.15) for overall patients. The overall 5-year survival rates for the patients with mucosal cancer were 95.1% (95% CI,

Table 1. Clinicopathological characteristics of patients

	Guidelines (n = 696)	Controls (n = 635)	P value
Sex			
Male/female ratio	1.92	2.55	0.018
Age (years)			
Median	62	60	0.005
Range	31–89	21–86	
Tumor location			0.315
Upper third	88 (12.6%)	69 (10.9%)	
Middle and lower thirds	608 (87.4%)	566 (89.1%)	
Tumor size (mm)			0.05
Median	30.0	26.0	
Range	3–186	2–250	
Depth of invasion			0.121
Mucosa	307 (44.1%)	307 (48.3%)	
Submucosa	389 (55.9%)	328 (51.7%)	
Macroscopic appearance			0.203
Elevated	112 (16.1%)	126 (19.8%)	
Flat	11 (1.6%)	10 (1.6%)	
Depressed	573 (82.3%)	499 (78.6%)	
Histological type[a]			<0.001
Differentiated	292 (42.0%)	370 (58.3%)	
Undifferentiated	404 (58.0%)	265 (41.7%)	

Guidelines, gastric cancer treatment guidelines of the Japanese Gastric Cancer Association
[a]According to the *Japanese classification of gastric carcinoma* [9]
Differentiated type includes papillary adenocarcinoma and tubular adenocarcinoma. Undifferentiated type includes poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma

Table 2. Incidence of lymph node metastasis according to depth of invasion in the Guidelines and control groups

	Guidelines	Controls	P value
Depth of invasion			
Mucosa	20/307 (6.5%)	8/307 (2.6%)	0.02
Submucosa	78/389 (20.1%)	70/328 (21.3%)	0.671
Overall	98/696 (14.1%)	78/635 (12.3%)	0.334

Guidelines, gastric cancer treatment guidelines of the Japanese Gastric Cancer Association

92.8%–97.5%) in the Guidelines group and 93.7% (95% CI, 91.0%–96.4%) in the control group. The hazard ratio in the Guidelines group was 0.83 (95% CI, 0.44–1.58) for patients with mucosal cancer. The overall 5-year survival rates for the patients with submucosal cancer were 93.5% (95% CI, 91.0%–96.0%) in the Guidelines group and 91.0% (95% CI, 87.9%–94.1%) in the control group. The hazard ratio in the Guidelines group was 0.74 (95% CI, 0.46–1.19) for patients with submucosal cancer.

Discussion

The Guidelines allow endoscopic treatment and a modified gastrectomy for EGC. Candidates for endoscopic treatment include patients with small differentiated-type mucosal cancers. When these tumors were excluded from the indications for gastrectomy, the tumor size in the Guidelines group was larger and the proportion of undifferentiated-type lesions was greater in the Guidelines group, compared with these parameters in the control group, as expected.

The male-to-female ratio was significantly lower in the Guidelines group than in the control group. Differentiated-type carcinomas are more common among men than among women [11]. Because male patients tend to fulfill the criteria for endoscopic resection more commonly than female patients, more men may have undergone endoscopic treatment. The median age was also slightly higher in the Guidelines group. Considering that differentiated-type tumors, which are occasionally treated using endoscopy, are more common among elderly patients [12, 13], a lower median age in the Guidelines group would not be unexpected. However, the opposite result was obtained. This result might

reflect an increase in the number of elderly patients themselves as a result of the prolonged life expectancy in Japan.

The incidence of lymph node metastasis in mucosal cancers was reported to be 1.2%-3.3% [6, 14–17], and all of these patients with EGC underwent a standard gastrectomy. In the present study, the incidence of lymph node metastasis in mucosal cancers in the control group was similar to those study findings (2.6%), while that in the Guidelines group was significantly higher (6.5%). The reason for this difference is easily interpreted. After the introduction of the Guidelines, endoscopic resection was established as the standard therapy for EGC in patients with a negligible risk of lymph node metastasis; therefore, the incidence of surgically treated patients with lymph node metastasis increased.

The Guidelines recommend D2 gastrectomy only in selected patients. As a result, the proportion of patients undergoing gastrectomy with D2 or greater extended lymphadenectomy was significantly smaller in our Guidelines group (29.7%) than in the control group (62.5%). Nevertheless the 5-year survival rate in the Guidelines group (94.2%) was similar to that in the control group (92.3%) and was also similar to that for patients undergoing gastrectomy with D2 lymphadenectomy in previous reports [18, 19].

In conclusion, surgeons treated more cases of mucosal cancer with lymph node metastasis after the introduction of the Guidelines. The long-term oncological outcomes for patients with EGC remained excellent after the introduction of the modified operation. So far, the Guidelines for the treatment of EGC appear acceptable.

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Editorial

What technique is suitable for laparoscopic suprapancreatic lymph node dissection?

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Recently, laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection has become popular as a procedure for gastric cancer in Japan and Korea. According to a national survey conducted by the Japan Society of Endoscopic Surgery (JSES), more than 15000 patients with gastric cancer underwent LADG from 1991 to 2007 in Japan [1, 2]. The present indication for LADG is early gastric cancer, with the risk of lymph node metastasis, which is not suitable for endoscopic submucosal dissection (ESD). In Asian countries, D2 or D2 modified lymph node dissection (D1+No.7, 8a, 9, 11p) is usually performed during LADG. As the number of patients undergoing LADG has been increasing, evaluation of the surgical outcomes of this operation has begun. There are four randomized controlled trials (RCTs) and several retrospective studies of the outcomes of LADG. The meta-analysis by Memon et al. shows that the number of dissected lymph nodes in LADG is lower than that in open gastrectomy [3]. Indeed, Miura et al. show in a retrospective study that the number of dissected suprapancreatic lymph nodes (No. 9 and 11p lymph nodes) is smaller in LADG than in open gastrectomy [4]. Therefore, it is necessary to establish safe techniques of suprapancreatic lymph node dissection in LADG with D2 or D2 modified lymph node dissection. The new technique of a left-sided approach to suprapancreatic lymph node dissection introduced in the article by Fukunaga et al. in this issue [5] may be useful for complete suprapancreatic lymph node dissection.

There are technical disadvantages to laparoscopic surgery: surgical procedures are conducted under limited 2-D vision, with limited movement, by long forceps and no sensation of touch. These characteristics make laparoscopic lymph node dissection difficult. In laparoscopic lymph node dissections during LADG, the suprapancreatic lymph node dissection may be the most difficult. In conventional LADG, techniques of taping vessels and pushing the pancreas downward after the duodenal transection are often used for complete dissection of lymph nodes around the common and proper hepatic arteries as well as the splenic artery [6]. In laparoscopic suprapancreatic lymph node dissection, better methods are required for improving the operative field and handling the lymph node dissection. In their article, Fukunaga et al. [5] emphasize that not transecting the duodenum inside the abdominal cavity is useful for obtaining a clear view of the operative field during LADG.

In suprapancreatic lymph node dissection, creating a better operative field is fundamental for removing the lymph nodes completely and safely. The new technique by Fukunaga et al. [5] is described as an expansion of the hepatoduodenal ligament and the left gastropancreatic fold without transection of the duodenum, which achieves an improved field of view. Fukunaga et al. [5] show that for 12a lymph node dissection, the hepatoduodenal ligament can be expanded easily by pulling strongly on the pyloric region of the stomach in the left caudal direction owing to omission of duodenal transection. Also, the authors demonstrate that for No. 9 and 11p lymph node dissection, the gastropancreatic fold is easily maneuvered ventrally through the opened lesser sac after the dissection of lymph nodes on the left side of the left gastric vessels (left-sided approach). Additionally, for No. 8a lymph node dissection, stretching of the gastropancreatic fold causes expansion of the peritoneum covering the No. 8a lymph node, and the left-sided approach without duodenal transection suggested by the authors provides a dry operative field without bleeding and lymph fluid leakage. To create an operative field for laparoscopic techniques in the suprapancreatic area, retracting the stomach to enable expansion of the hepatoduodenal ligament and stretching the gastropancreatic fold may be more useful than taping the vessels or pushing the pancreas downward.

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Ryu et al. [7] evaluated surgical outcomes of 347 LADGs and reported that both the extent of lymph node dissection and surgical inexperience are risk factors for operative complications associated with LADG. Dissection of suprapancreatic lymph nodes is required during extended lymph node dissection of D2 or the D2 modified technique. It is possible that suprapancreatic lymph node dissection causes an increase in the incidence of operative complications, including pancreatic fistula in particular. Fukunaga et al. [5] analyzed the surgical outcomes of 391 patients who underwent LADG with the new techniques of laparoscopic lymph node dissection. The authors showed that the number of lymph nodes dissected with the new technique was comparable to the number with open gastrectomy [3], and that the duration of the operation was shorter than that of conventional LADG. The amount of blood loss was smaller and the incidence of complications including pancreatic fistula was lower than that of open surgery. These improved results may support the feasibility of the new laparoscopic procedures for suprapancreatic lymph node dissection.

Obesity is believed to be a serious risk in the successful completion of LADG [8]. In LADG for obese patients, suprapancreatic lymph node dissection is sometimes technically difficult because the borderline between the upper edge of the pancreas and the fat tissue containing the lymph nodes is not clear and because bleeding and leakage of lymph occurs easily from the cut edge of thick fat tissue. The study described by Fukunaga et al. [5] included 8 patients with BMI over 30 and as high as 35.6. The authors showed that all obese patients safely underwent LADG via the left-sided approach to suprapancreatic lymph node dissection without duodenal transection, and speculated that the new technique may be more suitable for obese patients than the conventional LADG because a clear operative field is easily obtained by retraction of the left gastropancreatic fold from the surrounding tissues. In the near future, this issue should be clarified by analyzing outcomes of a larger number of obese patients who have undergone this new technique.

For surgical staff there is a well-defined learning curve recognized during acquisition of LADG techniques. It has been reported by Kim et al. [9] and Fujiwara et al. [10] that surgeons need to experience more than 50 cases to achieve a plateau in this learning curve. Fukunaga et al. [5] stated that it was easier for both surgeons and assistants to acquire proficiency in the left-sided techniques than with the conventional procedure: requiring experience of approximately 10 cases to establish proficiency for the former. The reason for this shorter learning period is unclear. It may be that standardization or the mode of education in this new technique is well organized. At the same time, the period needed for acquisition of laparoscopic procedures may depend on the operative approach.

In conclusion, the new method of a left-sided approach to suprapancreatic lymph node dissection without duodenal transection seems to be convenient and useful in LADG. For popularization of this new technique, an oncologic evaluation must be undertaken and technical feasibility confirmed by a number of treatment settings in the near future.

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Scoring System for Evaluating Functional Disorders Following Laparoscopy-Assisted Distal Gastrectomy

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Background. **Practical questionnaires for evaluating duodenogastric reflux following gastrectomy are currently unavailable. The present study evaluated the usefulness of the frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) questionnaire in the diagnosis of duodenogastric reflux after laparoscopy-assisted distal gastrectomy (LADG), which minimizes the risk of adhesions affecting the gastrointestinal tract.**

Methods. **Subjects in this study comprised 163 patients who had undergone LADG (Billroth-I (B-I), n = 57, Roux-en-Y (R-Y), n = 106). All subjects underwent endoscopy at least 6 mo postoperatively. The FSSG questionnaire was administered a few weeks after endoscopy, and FSSG scores were compared with endoscopic findings.**

Results. **In the R-Y group, FSSG scores were significantly higher in subjects with remnant gastritis than in those without (P = 0.002), and a significant correlation was seen between FSSG scores and bile reflux (P = 0.046). In the B-I group, FSSG scores were significantly higher in subjects with reflux esophagitis than in those without (P = 0.01), but degree of remnant gastritis and residual food did not correlate significantly with FSSG scores. With a cut-off FSSG score of six points, sensitivity and specificity for predicting remnant gastritis in R-Y reconstruction were 71% and 76%, respectively.**

Conclusion. **The FSSG questionnaire is a viable and less invasive alternative to other modalities for evaluating duodenogastric reflux in R-Y reconstruction, but is unsuitable for B-I reconstruction after LADG.** © 2010 Elsevier Inc. All rights reserved.

Key Words: **duodenogastric reflux; reflux gastritis; laparoscopy-assisted distal gastrectomy; FSSG questionnaire; Roux-en-Y reconstruction.**

INTRODUCTION

Surgical resection is the only potentially curative treatment for gastric cancer. However, removal of the distal stomach reduces gastric reservoir capacity, impairs gastric emptying, and causes reflux of duodenal contents into the gastric remnant. These functional disturbances induce a variety of post-gastrectomy symptoms that adversely affect quality of life. Assessments of functional disorder provide important information for consideration in the selection of therapeutic strategies. To evaluate functional problems following distal gastrectomy, various studies have addressed pathophysiology of the upper gastrointestinal tract using 24-h bilirubin monitoring [1], biliary scintigraphy [2], pH monitoring [3], electrogastrography [4], and endoscopy.

Scoring systems using questionnaires have been developed with the aim of achieving objective measurement of functional disorders [5]. Evaluation on the basis of clinical symptoms is the simplest and quickest method, placing no extra economic or physical burdens on patients. However, post-gastrectomy symptoms are multifactorial and multifaceted, making it difficult to elucidate which functional disorder relates to a particular symptom.

Fukuhara *et al.* [1] reported that symptoms commonly experienced following distal gastrectomy

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correlate with the degree of duodenogastric reflux. Identification of this duodenogastric reflux may thus allow treatment to be planned for patients suffering from troublesome symptoms after gastrectomy. However, no practical questionnaires are currently available for evaluating duodenogastric reflux following gastrectomy.

As a method for objectively evaluating symptoms of gastroesophageal reflux disease (GERD) and their frequency, and the effects of treatment, Kusano *et al.* [6] developed the frequency scale for the symptoms of GERD (FSSG). This study retrospectively evaluated the usefulness of the FSSG questionnaire for identifying duodenogastric reflux following distal gastrectomy.

Previous studies have indicated that postoperative adhesive bowel obstruction can be induced by surgical manipulation [7]. On the contrary, a study using an animal model identified no peritoneal adhesions following laparoscopy-assisted distal gastrectomy (LADG) [8]. To exclude other causes for symptoms, such as postoperative gastroparesis, efferent loop obstruction, and stricture as a result of intra-abdominal adhesion, the present study enrolled patients who had undergone LADG, to minimize the risk of adhesions affecting the gastrointestinal tract.

METHODS

Of 210 consecutive patients who had undergone LADG at the Department of Esophagogastric Surgery of the Tokyo Medical and Dental University between September 1999 and November 2007, 163 (77.6%) participated in this study. Forty-seven patients (22.4%) had stopped coming to our hospital, and were followed-up at their local clinic. Patients were classified retrospectively by reconstructive procedure into Billroth-I (B-I) and Roux-en-Y (R-Y) groups. We began using R-Y reconstruction as the first choice from January 2004. Before then, B-I reconstruction had been used as the first choice. All patients were treated by three expert surgeons. The procedure for lymph node dissection remained unchanged during the study period. All study protocols were approved by the institutional review board of Tokyo Medical and Dental University, and written consent was obtained from all patients prior to enrolment.

More than 6 mo after the surgery, subjects underwent upper gastrointestinal endoscopy to evaluate the condition of the lower esophageal mucosa and gastric remnant, and to detect the presence of bile and food residue in the gastric stump. Endoscopic findings of the gastric remnant were evaluated using the "residue, gastritis, bile" (RGB) classification [9]. Incidences of gastritis and residue of grade 2 or greater were calculated. Endoscopic findings were evaluated by two expert endoscopists.

A few weeks after of endoscopy, subjects were administered the FSSG questionnaire [6]. This comprises 12 questions that are scored to indicate the frequency of symptoms as follows: never = 0; occasionally = 1; sometimes = 2; often = 3; and always = 4 (Table 1).

FSSG scores were compared with endoscopic findings, and the ability of the FSSG questionnaire to assess condition of the gastric stump and esophagus was examined.

Statistical Analysis

All values are expressed as mean ± standard deviation (SD). Comparisons between groups were made using the χ^2 test and Student's *t*-test. Values of $P < 0.05$ were considered statistically significant. Statistical analyses were performed using StatView software (Abacus Concepts, Berkeley, CA).

RESULTS

Characteristics and operative records of subjects are summarized in Table 2. The reconstruction method used was B-I for 57 patients, and R-Y for 106 patients. Correlations between endoscopic findings and FSSG scores are given in Table 3. In R-Y reconstruction, the incidence of remnant gastritis at grade 2 or more was 6.6%, and FSSG scores were significantly higher in subjects with remnant gastritis (8.7 ± 6.8) than in those without (3.9 ± 3.7; $P = 0.002$). Bile reflux into the gastric remnant was observed in five subjects (4.7%), and FSSG scores were significantly higher in subjects with bile reflux (7.8 ± 4.1) than in those without (4.1 ± 4.0; $P = 0.046$). Degree of residual food and reflux esophagitis were not significantly correlated to the FSSG score. With the cut-off FSSG score set at six points, sensitivity and specificity for predicting remnant gastritis following R-Y reconstruction were 71% and 76%, respectively. The area under the receiver operating characteristic (ROC) curve was 0.72 (Fig. 1).

In B-I reconstruction, residual food, bile reflux and reflux gastritis were not significantly correlated to FSSG scores. FSSG scores were significantly higher in subjects with reflux esophagitis (10.7 ± 7.8) than in those without (5.8 ± 4.6; $P = 0.010$).

Incidences of remnant gastritis and bile reflux were significantly higher in B-I than in R-Y ($P < 0.0001$ each), but incidence of esophagitis did not differ between these two reconstructions (Table 4).

DISCUSSION

Duodenogastric reflux occasionally occurs after gastrectomy and is associated with various symptoms, including abdominal pain, nausea, vomiting, and loss of appetite. Several clinical and experimental studies have shown that reflux of bile acids and pancreatic proteolytic enzymes can damage the gastric mucosa and, in conjunction with various bacteria, increase levels of carcinogenic substances such as nitrosamines [10–12].

In an earlier 24-h bilirubin monitoring study, the incidence of reflux symptoms in patients following distal gastrectomy correlated well with the percentage of time that bile refluxed into the gastric remnant [1]. In addition, a significantly greater degree of bile reflux, as determined by an isotope-derivative, was demonstrated in symptomatic patients than in asymptomatic patients after gastrectomy [13]. These findings suggest that certain symptoms may offer a useful guide to

TABLE 1

The FSSG Questionnaire: Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease

	Question	Frequency				
		Never	Occasionally	Sometimes	Often	Always
1	Do you get heartburn?					
2	Does your stomach get bloated?					
3	Does your stomach ever feel heavy after meals?					
4	Do you sometimes subconsciously rub your chest with your hand?					
5	Do you ever feel sick after meals?					
6	Do you get heartburn after meals?					
7	Do you have an unusual (e.g., burning) sensation in your throat?					
8	Do you feel full while eating meals?					
9	Do some things get stuck when you swallow?					
10	Do you get bitter liquid (acid) coming up into your throat?					
11	Do you burp a lot?					
12	Do you get heartburn if you bend over?					

identifying patients with bile reflux into the gastric remnant after distal gastrectomy.

The FSSG questionnaire covers symptoms commonly observed in duodenogastric reflux. The present study revealed a significant correlation between FSSG scores and presence of bile reflux at endoscopy, with significantly higher FSSG scores in subjects with remnant gastritis following R-Y reconstruction. In B-I reconstruction, however, bile reflux and remnant gastritis did not correlate significantly with FSSG scores. Secretion of intestinal hormones that regulate gastric acid and gastrointestinal motility is stimulated by contact of digestive contents with the duodenal epithelium. As the digestive contents pass through the duodenum in B-I reconstruction, acid secretion and gastric motility in this reconstruction may be more affected by intestinal hormones than in R-Y reconstructions. Indeed, one study showed that patients are more likely to experience various symptoms (such as heartburn, epigastric discomfort, altered bowel habit, and dumping syndrome) after B-I reconstruction than after R-Y reconstruction [14]. Symptoms after B-I reconstruction appear to be multifactorial, so elucidating those that are attributable solely to duodenogastric reflux following B-I reconstruction is difficult. We thus consider FSSG scores to be inadequate for detecting duodenogastric reflux in B-I reconstruction.

Identification of patients with duodenogastric reflux who might benefit from pharmacotherapy is important. In this study, a cut-off score of six points yielded a sensitivity and specificity for detecting duodenogastric reflux of 71% and 76%, respectively. Reflux gastritis may thus be present when FSSG score is six points or more. Conservative treatments with bile acid-binding

TABLE 2

Patient Characteristics

	R-Y (106)	B-I (57)	*P* value
Age (y) (range)	62.9 ±1 3.1 (27–92)	60.8 ± 8.8 (36–77)	N.S.
Gender (male/female)	69/37	42/15	N.S.
BMI (kg/m^2)	23.0 ±3.3	22.2 ± 2.4	N.S.
ASA-PS			
1	64	37	N.S.
2	38	18	
3	4	2	
LN dissection			
D1	88	40	N.S.
D2	18	17	
Stage			
IA	80	49	N.S.
IB	18	6	
II	8	2	

Values are mean ± SD.

N.S. = not significant; BMI = body mass index; ASA-PS = American Society of Anesthesiologists physical status; LN = lymph node.

TABLE 3

Endoscopic Findings and FSSG Scores

	R-Y (106)		B-I (57)	
	FSSG scores	*P* value	FSSG scores	*P* value
Residual food (*n*)				
Present	4.3 ± 4.6 (26)	N.S.	6.0 ± 4.6 (10)	N.S.
Absent	4.2 ± 3.9 (80)		6.8 ± 5.7 (47)	
Gastritis (*n*)				
Present	8.7 ± 6.8 (7)	0.002	7.7 ± 6.2 (23)	N.S.
Absent	3.9 ± 3.7 (99)		5.9 ± 5.0 (34)	
Bile reflux (*n*)				
Present	7.8 ± 4.1 (5)	0.046	5.6 ± 4.6 (25)	N.S.
Absent	4.1 ± 4.0 (101)		7.5 ± 6.1 (32)	
Esophagitis (*n*)				
Present	2.5 ± 1.9 (8)	N.S.	10.7 ± 7.8 (10)	0.010
Absent	4.4 ± 4.2 (98)		5.8 ± 4.6 (47)	

Values are mean ± SD.
N.S. = not significant.

agents (e.g., cholestyramine) or ursodeoxycholic acid, which decreases the amount of cholic acid, have been used for patients who exhibit bile reflux symptoms after distal gastrectomy. However, although pharmacotherapy has been reported as successful in some cases, it is not uniformly effective [15–17]. Gastric stasis may also be involved in the pathogenesis of reflux gastritis [18], since this phenomenon allows noxious duodenal contents to remain in contact with the gastric mucosa for a longer time. Moreover, the higher pH allows the proliferation of microorganisms that can transform biliary salts to unconjugated biliary acids, which are particularly harmful to the gastric mucosa [19]. Pharmacotherapy for gastric stasis with promotility agents (e.g., metaclopromide, mosapride, domperidone, and erythromycin) can be effective, but the utility of these

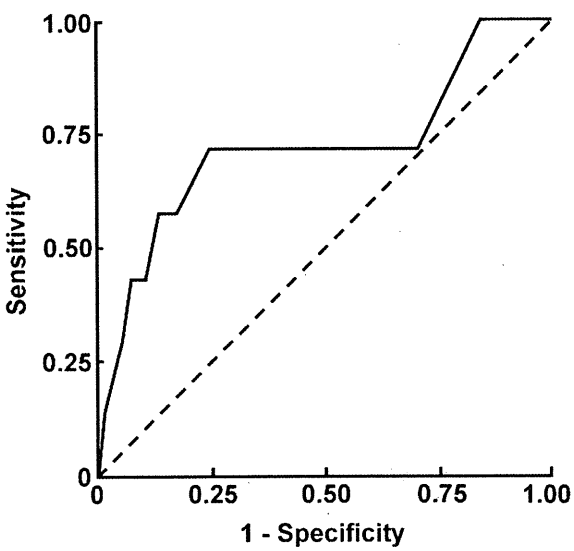

FIG. 1. The receiver operating characteristic (ROC) curve of FSSG score in predicting reflux gastritis.

TABLE 4

Endoscopic Findings of the Gastric Remnant and the Lower Esophagus

	R-Y (106)	B-I (57)	*P* value
Residual food (*n*)			
Present	26	10	N.S.
Absent	80	47	
Remnant gastritis (*n*)			
Present	7	23	<0.0001
Absent	99	34	
Bile reflux (*n*)			
Present	5	25	<0.0001
Absent	101	32	
Esophagitis (*n*)			
Present	8	10	N.S.
Absent	98	47	

N.S. = not significant.

agents against reflux gastritis after gastrectomy has not been demonstrated [20–23]. As no effective treatments for reflux gastritis have yet been established, a trial of pharmacotherapy for several months is probably appropriate. If such a trial fails and the patient cannot endure the persistent symptoms, or has complications such as malnutrition or weight loss, biliary diversion should be considered [24].

A number of studies have compared the efficacies of various reconstruction methods [1, 2]. The present study agrees with previous reports [25, 26] in finding that remnant gastritis is significantly more common following B-I than R-Y reconstruction. FSSG scores were significantly higher following B-I than after R-Y procedures, indicating a greater severity of bile reflux following B-I reconstruction.

In the present study, FSSG scores were higher in patients with reflux esophagitis than in those without this complication after B-I reconstruction, but no significant correlation was seen between presence of reflux esophagitis and FSSG score in R-Y reconstruction. However, endoscopic observation showed similar incidences of reflux esophagitis between the two reconstructions. Symptoms of reflux esophagitis may be exacerbated by other conditions after distal gastrectomy, including delayed gastric emptying [27], and may also depend on the degree of bile reflux and pH status of the gastric remnant. Diagnosing reflux esophagitis from FSSG scores after distal gastrectomy thus appears difficult. Several studies have identified the critical roles played by conjugated bile acids and pepsin in esophageal reflux [28, 29]. In a study using a pH monitor and Bilitec 2000, esophageal mucosal injury occurred only in patients with mixed reflux (acid and bile reflux) after distal gastrectomy [30]. Conjugated bile acids and pepsin are inactivated in the higher pH environments within the stomach and esophagus created by proton pump inhibitors (PPIs) [29, 31]. Sucralfate is a well-known

inhibitor of peptic activity and protects the mucosa against both acid- and pepsin-induced damage [32]. Reflux esophagitis following distal gastrectomy could thus be treated effectively using a PPI or sucralfate.

The FSSG questionnaire is easy to understand, and takes only few minutes to complete. Our results suggest that this questionnaire is viable for evaluating duodenogastric reflux, and could offer a feasible alternative to other modalities in this regard. This tool may assist in treatment selection for patients with troublesome symptoms following distal gastrectomy. However, the results of the present study should be verified in a large-scale study to determine the clinical efficacy of the FSSG questionnaire following distal gastrectomy.

SUPPLEMENTARY DATA

Supplementary data associated with the article can be found in the online version, at doi:10.1016/j.jss.2010.08.041.

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REVIEW ARTICLE

Current trends of laparoscopic gastrectomy for gastric cancer in Japan

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Keywords
Laparoscopic gastrectomy; long-term outcome; retrospective multicenter study

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Abstract

Laparoscopic gastrectomy with lymph node dissection, such as laparoscopy-assisted distal gastrectomy (LADG), is widely accepted for the treatment of early gastric cancer with a risk of lymph node metastasis. In Japan, a nationwide survey conducted by the Japan Society of Endoscopic Surgery has shown that the number of laparoscopic gastrectomies is gradually increasing. So far, the following advantages of laparoscopic surgery for the treatment of gastric cancer have been well documented: favorable clinical course after operation, pulmonary function and immune response. A retrospective multicenter study in Japan has shown that the short-term outcomes of laparoscopic gastrectomy are beneficial and that the long-term outcomes are the same as those for open surgery. Recently, the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group conducted a multi-institutional, phase II trial (JCOG0703) to evaluate the safety of LADG for clinical stage I gastric cancer. In the future, laparoscopic surgeons will need to design and implement education and training systems for standard laparoscopic procedures, evaluate clinical outcomes through multicenter randomized controlled trials and clarify the oncological aspects of laparoscopic surgery in basic studies.

Introduction

Gastric cancer remains a major health problem worldwide. In Japan, approximately 100 000 patients will develop gastric cancer each year, and because of improved diagnostic procedures and widespread mass screening, the cancer is diagnosed at an early stage in least 50% of patients. The 5-year survival rate of patients with early gastric cancer (EGC) who have undergone surgical treatment has reached 90% or more in Japan (1–3). On the basis of the low incidence of node involvement in most EGC patients, current surgical trends for EGC have shifted from surgery with extended lymph node dissection to minimally invasive surgery, thereby providing a better postoperative quality of life.

Laparoscopic surgery has become popular as a minimally invasive procedure. The potential benefits of laparoscopic gastrectomy for gastric cancer, including reduced pain, rapid return of gastrointestinal function, shorter hospital stay and decreased stress response, may make it an attractive option for patients with the disease (4–7). Laparoscopic gastrectomy has been widely accepted in Japan for the management of patients with EGC. Recently, the use of laparoscopic gastrectomy for advanced gastric cancer has been attempted. Herein, the authors review the literature on the indications, clinical outcomes, results of a multicenter study and the future perspective of laparoscopic gastrectomy for gastric cancer in Japan.

Abbreviations: EGC, early gastric cancer; LADG, laparoscopy-assisted distal gastrectomy; LATG, laparoscopy-assisted total gastrectomy; LAPG, laparoscopy-assisted proximal gastrectomy; ODG, open distal gastrectomy

Current status of laparoscopic gastrectomy in Japan

Nationwide survey of laparoscopic gastrectomy

Since the first laparoscopy-assisted distal gastrectomy (LADG) by Billroth I reconstruction for an EGC patient in 1991 (8), a national survey conducted by the Japan Society of Endoscopic Surgery (JSES) every two years has

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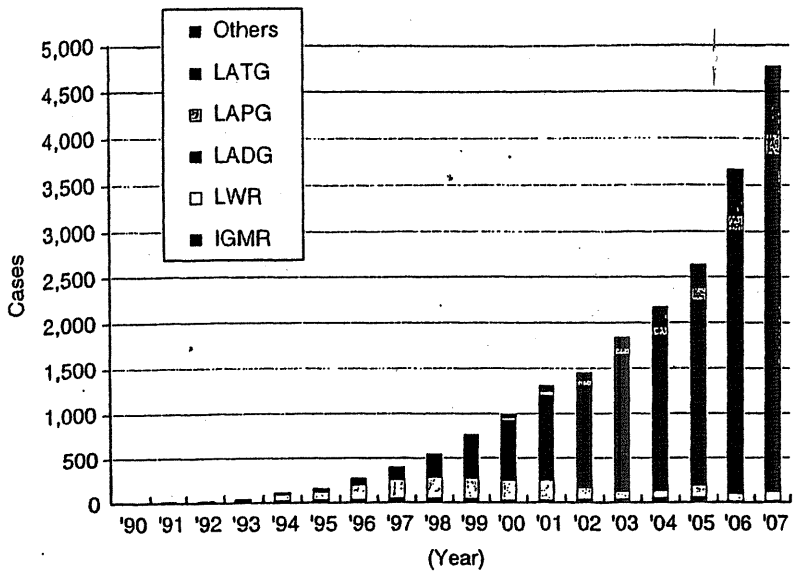

Figure 1 Annual experiences with laparoscopic gastrectomy in Japan. According to the ninth national survey conducted by the Japan Society of Endoscopic Surgery, the number of cases of laparoscopic gastrectomies, including laparoscopy-assisted distal gastrectomy (LADG), laparoscopy-assisted total gastrectomy (LATG) and laparoscopy-assisted proximal gastrectomy (LAPG), has increased year by year. IGMR, intragastric mucosal resection; LWR, laparoscopic wedge resection.

shown increasing use of laparoscopic procedures for EGC in Japan. According to the ninth nationwide survey, the total number of laparoscopic gastrectomies between 1991 and 2007 was 21 048, while 4765 gastric cancer patients underwent laparoscopic gastric surgery in 2007 alone (9) (Figure 1). The number of LADG has increased rapidly, and advanced laparoscopic procedures such as laparoscopy-assisted total gastrectomy (LATG) and laparoscopy-assisted proximal gastrectomy (LAPG) have increased gradually because of the recent advances of laparoscopic surgery technology. However, the use of laparoscopic local resection, such as laparoscopic wedge resection and intragastric mucosal resection, has decreased as a result of the development of endoscopic treatments, including endoscopic submucosal dissection, that make it possible to perform en-bloc dissection for larger cancers limited to the mucosa.

Development of new instruments and techniques of lymph node dissection and anastomosis

The introduction of new instruments, such as a vessel sealing system, ultrasound coagulation devices, and circular or linear staplers, has greatly contributed to the development of laparoscopic surgery. For example, when dissecting No. 8a lymph nodes, it is easy to dissect the connective tissue surrounding the nerve sheath around the common hepatic artery with coagulation shears. The vessel sealing system is useful for dividing thick tissues such as gastrosplenic ligament.

With the development of laparoscopic techniques and instruments, surgeons have been able to performe advanced laparoscopic procedures including LATG, LAPG and laparoscopic extended lymph node dissection (10–15). In both the LATG and LAPG procedures, making reconstruction laparoscopically is a problem. To decrease the frequency of anastomotic troubles and to prevent gastritis of the gastric remnant, Roux-en Y methods through a small laparotomy with linear or circular staplers have been developed. – for example, esophagojejunal anastomosis after LATG by the EEA OrVil. 25 mm device (Covidien, USA). Further evaluation of these new reconstruction methods is expected.

Indication of laparoscopic gastrectomy for gastric cancer

Because it is difficult to diagnose lymph node metastasis preoperatively, its risk is estimated by tumor size, depth of cancer invasion, presence of ulceration and histological type (16). In 2004, the Japanese Gastric Cancer Association issued a revised edition of the Gastric Cancer Treatment Guidelines (17). Treatment modalities were determined in detail based on the depth of wall invasion and status of lymph node metastases:

- D1+alpha (perigastric lymph node dissection) for mucosal cancer, for which endoscopic mucosal resection is not indicated and for histologically differentiated submucosal cancer of < 1.5 cm in diameter
- D1+beta for preoperatively diagnosed submucosal cancer without lymph node metastasis (N0), for which D1+alpha is not indicated
- D1+beta for early cancer < 2.0 cm in diameter with only perigastric lymph node metastasis (N1)

Table 1 Trends in complications after laparoscopic gastrectomy (Japan Society for Endoscopic Surgery [JSES] nationwide survey, 2008)

JSES nationwide survey	Seventh (2002–2003)	Eighth (2004–2005)	Ninth (2006–2007)
Intraoperative complications			
LADG	3.5% (94/2671)	1.9% (71/3792)	1.7% (112/6615)
LATG	0.8% (1/128)	5.1% (16/312)	2.1% (22/1023)
LAPG	8.3% (10/120)	2.7% (6/223)	1.3% (11/811)
Postoperative complications			
LADG	14.3% (393/2671)	9.0% (341/3792)	8.2% (543/6615)
LATG	28.9% (37/128)	7.1% (22/312)	14.1%(144/1023)
LAPG	33.3% (40/120)	14.3% (32/223)	9.1% (874/811)

LADG, laparoscopy-assisted distal gastrectomy; LAPG, laparoscopy-assisted proximal gastrectomy; LATG, laparoscopy-assisted total gastrectomy.

- D2 for early cancer > 2.0 cm in diameter, with lymph node positive.

According to these guidelines, lymph node dissection is generally performed by laparoscopic gastrectomy. In 2010, the third edition of the Japanese Gastric Cancer Association guidelines will be published. In this edition, laparoscopic gastrectomy may play a more important role in the treatment of gastric cancers.

Outcomes of laparoscopic gastrectomy

Incidence of complications after laparoscopic gastrectomy according to the JSES nationwide survey

The incidence of operative complications from the JSES ninth nationwide survey in 2008 is shown in Table 1. As reported elsewhere, the incidence of operative complications in laparoscopic procedures appears similar to that of open surgery (9). In addition, the complication rate is gradually decreasing in all procedures. These data suggest that laparoscopic surgery for gastric cancer is becoming safer. Among the postoperative complications, anastomotic problems such as stenosis and leakage occurred most frequently.

Comparison of short-term outcome between LADG and conventional open gastrectomy for EGC

Several studies on the short-term outcome of LADG for EGC have been reported. With regard to operative findings, several studies has shown longer operation time and lower blood loss for LADG than for open distal gastrectomy (ODG) (7,15,18), but research indicates that increased training reduces the operation time for LADG (19).

There have been several comparative studies of surgical morbidity between LADG and ODG. Most of these studies have shown the same or a lower incidence of complications associated with LADG in comparison with ODG (5,7,15,18). Even in obese patients, morbidity and length of hospital stay were not increased, although LADG required a longer operating time in obese patients than in non-obese patients (20–22).

Several studies on the lower invasiveness of LADG relative to ODG found several advantages of LADG. Prospective and retrospective analyses by a single institution showed earlier recovery of bowel function after LADG than after ODG (23). Also, pain was reported to be significantly less after LADG than after ODG. LADG offers particular advantages to elderly patients with EGC over those of ODG, including rapid return of gastrointestinal function, fewer complications and a shorter hospital stay (24). The shorter hospital stay also helped to reduce costs. A case-controlled study reported that the shorter hospital stay made LADG less expensive than conventional open gastrectomy (25,26). Other short-term advantages of LADG were shown by a randomized trial with a small sample size at a single institution, in which better postoperative pulmonary function was present after LADG than after ODG because there was less pain after LADG (27).

Evaluation of long-term results of laparoscopic gastrectomy

Over the last 18 years, laparoscopic gastrectomies have rapidly become popular in Asia. However, for laparoscopic gastrectomy for cancer to become an accepted operation worldwide, standardized safe techniques and evaluations of the procedure's clinical results are still necessary. To encourage the spread of the procedure, evidence of positive oncological outcomes is necessary. Therefore, multicenter randomized controlled trials are required in this area.

Most retrospective published studies have comprised a small number of patients and shown short-term follow-up only; as such, there are few studies addressing the long-term outcome of LADG (28–30). One recent study included meta-analysis of randomized evidence to determine the relative merits of LADG versus ODG for proven gastric cancer (31). Only four trials were considered suitable for meta-analysis (27,32–34), which included a total of 82 patients who underwent LADG and 80 who underwent ODG. Thus, there are significant limitations in interpreting current data due to the limited number of published randomized controlled trials, the small sample sizes to date and the short duration of follow-ups. Large multicenter randomized controlled trials are required to delineate significantly quantifiable differences between the two procedures.

Multicenter study of laparoscopic gastrectomy

Clinical outcomes of a retrospective multicenter study in Japan

We conducted a retrospective, multicenter study of a large series of patients in Japan to evaluate preliminary short- and long-term outcomes of laparoscopic gastrectomy for early gastric cancer (35). The study group included expert surgeons who performed laparoscopic gastrectomies in 16 participating centers (Japanese Laparoscopic Surgery Study Group). A total of 1294 patients (872 men, 422 women) undergoing laparoscopic surgery was enrolled in this study from 1994 to 2003. Distal gastrectomy was performed in 1185 patients (91.5%), total gastrectomy in 55 (4.3%) and proximal gastrectomy in 54 (4.2%); all procedures were performed laparoscopically. Overall morbidity and mortality rates associated with these operations were 14.8% and 0%, respectively. Conversion to open surgery was required in only 14 cases (1.1%) because of intraoperative complications: bleeding in nine cases, mechanical trouble in three and other problems in two. Histologically, 1212 patients (93.7%) had stage IA disease, 75 (5.8%) had stage IB disease and seven (0.5%) had stage II disease (International Union Against Cancer staging system). There were only six cancer recurrences: one local recurrence, one lymph node recurrence, two peritoneal disseminations, one liver metastasis and one skin metastasis at the abdominal wall different from the port-site (median follow-up, 35 months; range, 13–113 months). Five-year disease-free survival rate was 99.8% for stage IA disease, 98.7% for stage IB disease and 85.7% for stage II disease. Although these data may be considered preliminary, they appear to indicate that laparoscopic surgery for EGC yields good short- and long-term oncologic outcomes.

A prospective multicenter study in Japan

The Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group is conducting a multi-institutional, phase II trial (JCOG0703) to evaluate the safety of LADG for clinical stage I gastric cancer (36). The primary endpoint is incidence of anastomotic leak and pancreatic fistula. The secondary endpoints are overall survival, relapse-free survival, proportion of completion of LADG procedures, proportion of conversion from LADG to ODG procedure, surgical morbidity and short-term clinical outcomes.

Patients included in this trial must meet all of the following criteria: (i) histologically proven stomach adenocarcinoma, (ii) clinical Stage IA (T1N0) or IB (T1N1/T2N0) tumor according to the 13th edition of the Japanese Classification of Gastric Carcinoma (37), (iii) no indication of endoscopic mucosal resection according to the Japanese endoscopic treatment guidelines, (iv) tumor located in the middle or lower third of the stomach that can be treated by distal gastrectomy, (v) no involvement of the duodenum, (vi) 20–80 years of age, (vii) an Eastern Cooperative Oncology Group performance status of 0 or 1, (viii) body mass index $< 30\,kg/m^2$, (ix) no recurrent tumor after endoscopic mucosal resection, (x) no prior upper abdominal surgery or intestinal resection, (xi) no prior chemotherapy or radiotherapy for any malignancy, (xii) adequate organ function and (xiii) written informed consent.

The study was activated in November 2007 and completed enrollment of 171 patients in September 2008. The data collected will be beneficial to determine the role of laparoscopic gastrectomy in the treatment of stage I gastric cancers.

The next step will be to plan a phase III study of laparoscopic gastrectomy for advanced gastric cancer to evaluate oncological feasibility. However, several points must be considered in a randomized controlled trial of laparoscopic gastrectomy for the treatment of advanced gastric cancer. First is whether a randomized controlled trial for early gastric cancer is necessary at all because our retrospective data so far has shown good short- and long-term outcomes. Second are the indications of depth of invasion and lymph node metastasis. The third concern is whether to include treatment of upper gastric cancers with LAPG or LATG.

Conclusions and perspectives

Though laparoscopic gastrectomy has come into wide use at a surprisingly quick speed, there are still several issues that must be overcome for further safe application of laparoscopic gastrectomy in the daily clinical setting. First, a multicenter randomized controlled trial is needed to confirm the long-term outcome of LADG for gastric cancer. Second, we must strive to reduce the number of operative complications. Therefore, the prevalence of standardized techniques and the development of education and training systems are important. Recently, several training simulators and animal training centers focusing on improving laparoscopic techniques have been developed. In addition, the JSES has begun designing a Board Certification Examination for laparoscopic procedures. Third, to establish the acceptability of laparoscopic gastrectomy with D2 dissection against advanced gastric cancers, safe techniques must be developed in the future. As laparoscopic surgeons, we believe that the laparoscopic gastrectomy procedure, with its attendant minimal invasiveness, will become the worldwide standard in the treatment of gastric cancer.

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