別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Kitano S, Shiraishi N	Laparoscopic gastric surgery.	Ed:Eldo E. Freesa, Michael Gagner, Michel Li	International Principals of Laparoscopic Surgery	Cine-Med Publishing Inc.	U.S.A.	2009	301-307

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nonaka S, Katai H, et al.	Clinical impact of a strategy involving endoscopic submucosal dissection for early gastric cancer: determining the optimal pathway.	Gstric Cancer	14(1)	56-62	2011
Saka M, Katai H, et al.	Present and future status of gastric cancer surgery.	Jpn J Clin Oncol	41(3)	307-313	2011
Iwata N, Kodera Y, et al.	Construct validity of the LapVR virtual-reality surgical simulator.	Surg Endosc	25(2)	423-428	2011
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Watanabe T, Kodera Y, et al.	Measurement of inserting motion of bladeless trocar at real surgery for development of a virtual training system for initial trocar placement in laparoscopic surgery.	Hepato-Gastro-enterology	58 (107-108)	854-858	2011
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Kitano S	What technique is suitable for laparoscopic suprapancreatic lymph node dissection?	Gastric Cancer	12	67-68	2009
Etoh T, Kitano S, et al.	Current trends of laparoscopic gastrectomy for gastric cancer in Japan.	Asian Journal of Endoscopic Surgery	2	18-23	2009
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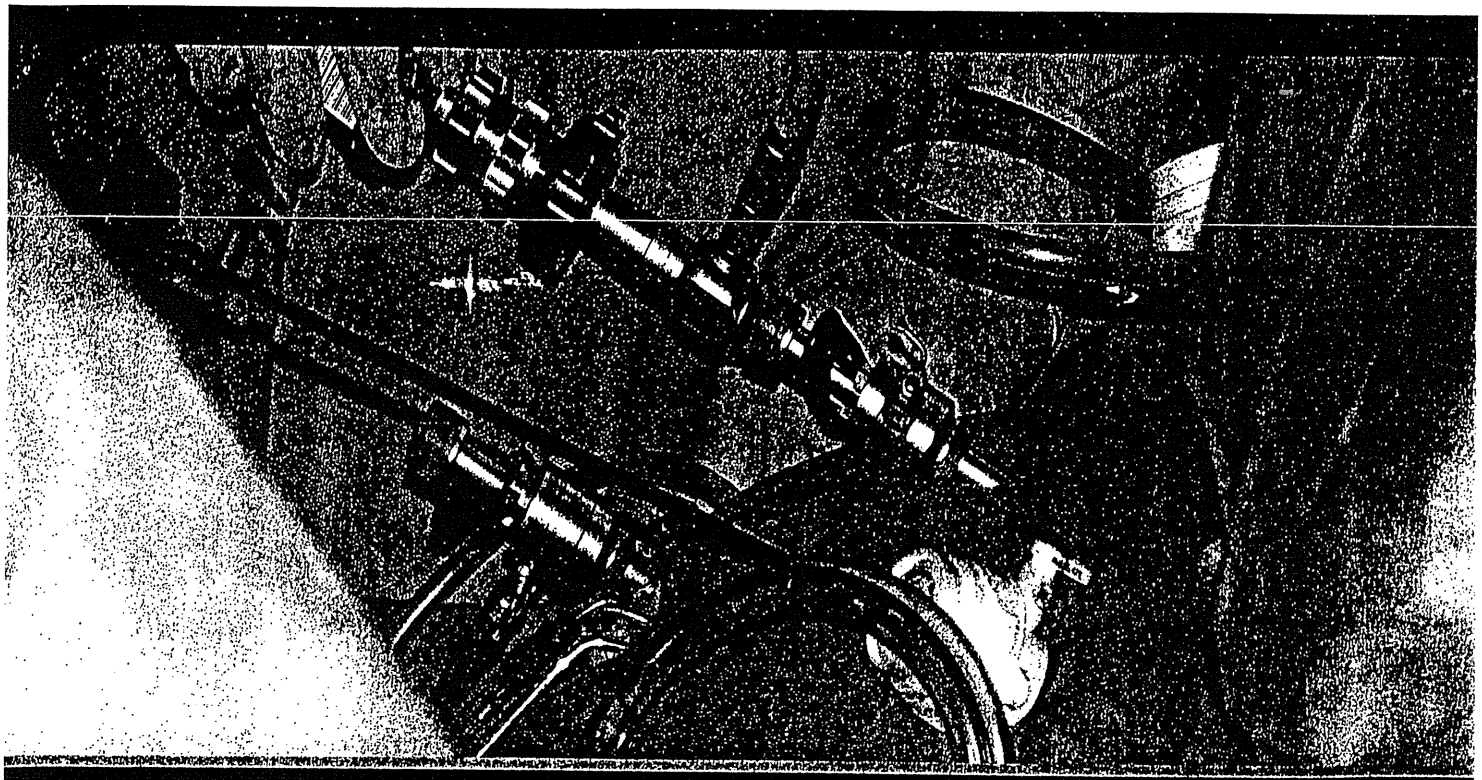
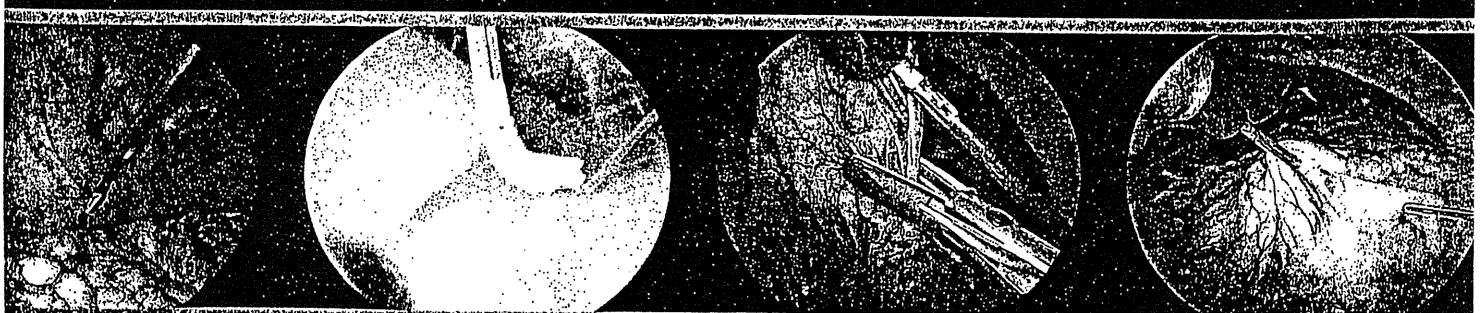
研究成果の刊行物・別刷



INTERNATIONAL PRINCIPLES OF LAPAROSCOPIC SURGERY



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Laparoscopic Gastric Surgery

Seigo Kitano, MD, FACS
Norio Shiraishi, MD

Introduction

Gastric cancer remains one of leading causes of cancer-related death worldwide. Recently, with rapid advances in diagnostic modalities and the popularity of mass screening, the incidence of early gastric cancer (EGC) has increased in Japan. Lymph node metastasis occurs only rarely in cases of EGC; the incidence is about 2% to 5% in cases of mucosal cancer and 11% to 15% in cases of submucosal cancer.(1) Therefore, most EGCs can be cured by local clearance alone.

Until the late 1980s, gastrectomy with extended lymph node dissection (D2) was used routinely in Japan, even for the treatment of EGC. Although the prognosis of patients with EGC who undergo this curative surgery is excellent, their quality of life (QOL) is compromised by the occurrence of postgastrectomy syndrome. To improve QOL, minimally invasive treatments such as endoscopic treatment and laparoscopic surgery have been developed for EGC.

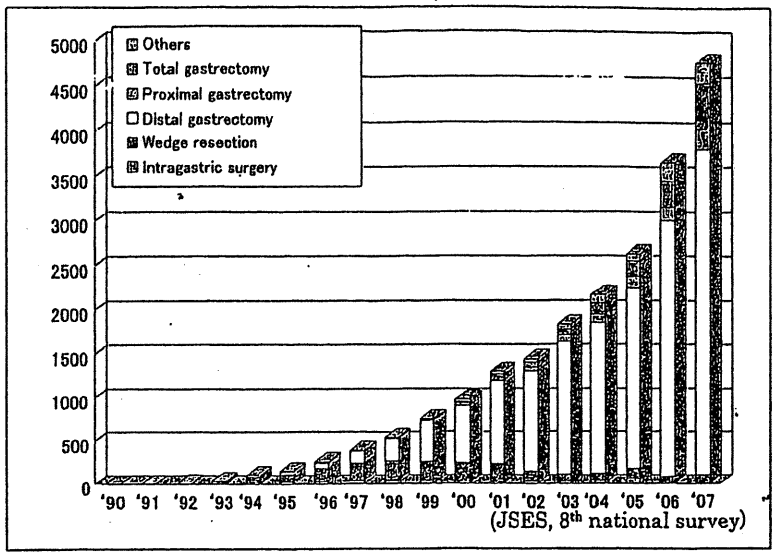
The most popular endoscopic procedures for EGC are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).(2) The indication for endoscopic treatment is EGC without risk of lymph node metastasis. For EGC with a risk of lymph node metastasis, laparoscopic gastrectomy (LG) with lymph node dissection is the treatment of choice, rather than conventional open gastrectomy with extended lymph node dissection.(3)

Herein, we report the present status of LG, the LG procedure, and evaluation of LG for EGC.

Current Status of Laparoscopic Gastrectomy in Japan

Since Kitano et al. first reported laparoscopy-assisted distal gastrectomy (LADG) in 1994,(4) many new laparoscopic techniques for cancer have been developed. Among them, laparoscopic wedge resection (LWR) by a lesion-lifting method and LADG are the most popular procedures in Japan and Korea. The national survey conducted by the Japan Society of Endoscopic Surgery (JSES) in 2008 showed that the number of LADGs was increasing rapidly, and that more than 15,000 patients in Japan underwent LADG for cancer between 1991 and 2007 (Figure 1).(5) Lymph node dissection in association with LADG is categorized in Japan by its extent as perigastric lymph node dissection (D1+α), additional lymph node dissection along the common hepatic artery and celiac artery (D1+β), or extended lymph node dissection (D2).(6) As the number of laparoscopic surgeons with advanced skills has increased, the extent of lymph node dissection has expanded to D1+β and D2, and the indication for LADG has been extended from early cancer to advanced cancer. In 2007, LADG with D1+β lymph node dissection accounted for approximately 40% of all LADGs. This operation is becoming a common laparoscopic procedure in Japan, and the number of LADGs with D1+α lymph node dissection is gradually decreasing. The use of LWR has also decreased since the use of endoscopic treatments, including ESD, has been popularized.

FIGURE 1. LAPAROSCOPIC GASTRECTOMY FOR CANCER IN JAPAN: JSES NATIONAL SURVEY



Indications and LADG Techniques

1. Indications for LADG

Laparoscopy-assisted distal gastrectomy (LADG) is used for the treatment of EGC with risk of lymph node metastasis and of advanced gastric cancer without serosal invasion. Although there have been many studies pertaining to EGC without risk of lymph node metastasis, the clinicopathologic features of the EGC remain controversial.(7-9) Before treatment, endoscopic examination and barium meal study are used to evaluate the histologic type, size, and depth of wall invasion of the EGC, and the risk of lymph node metastasis is then determined. The Japanese Gastric Cancer Association (JGCA) guidelines define EGC with a risk of lymph node metastasis as follows(6): 1) well-differentiated mucosal cancer of more than 2 cm in diameter; 2) well-differentiated mucosal cancer with ulceration; 3) poorly differentiated mucosal cancer; 4) submucosal cancer. The extent of lymph node dissection is based on the predicted frequency of lymph node metastasis. The JGCA guidelines recommend the following: D1+α for mucosal cancer or well-differentiated submucosal cancer less than 1.5 cm; D1+β for other macroscopically node-negative (N0) submucosal cancers and for macroscopically node-positive (N1) ECG less than 2 cm in diameter; and D2 for other ECGs.

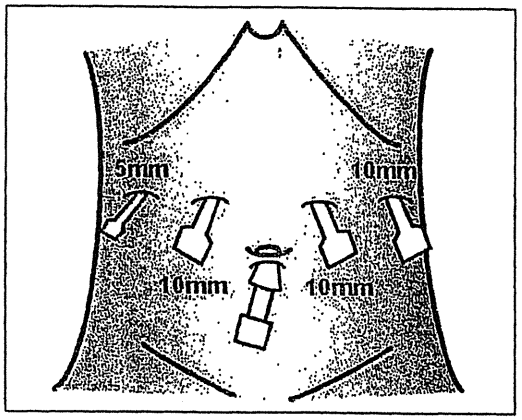
For advanced gastric cancer (AGC), D2 lymph node dissection is routinely performed in Japan. With development in techniques for laparoscopic D2 lymph node dissection, the number of patients with AGC who have undergone LADG with D2 lymph node dissection has increased slightly. The national survey conducted by the JSES revealed that only 12.2% of patients in Japan treated by LADG in 2007 underwent D2 lymph node dissection.(5) Laparoscopy-assisted distal gastrectomy with D2 lymph node dissection is performed for AGC only in a few institutions, and the indication is limited to N0 AGC that does not penetrate the gastric wall (T2). This is because of the technical difficulty of the procedure and the associated risk of peritoneal dissemination.

2. LADG Techniques

Kitano et al. began to practice LADG D1+α lymph node dissection in 1991 and reported it in 1994.(10) In LADG, laparoscopic procedures are used for lymph node dissection and resection of the stomach and reconstruction are achieved via minilaparotomy. Over the last 18 years, new surgical instruments, such as laparoscopic coagulation shears and laparoscopic vessel-sealing devices, have been developed, and they enable us to safely and easily perform LG with lymph node dissection. Our procedure for LADG with D1+β lymph node dissection and reconstruction by the Roux-en-Y method consists of the following:

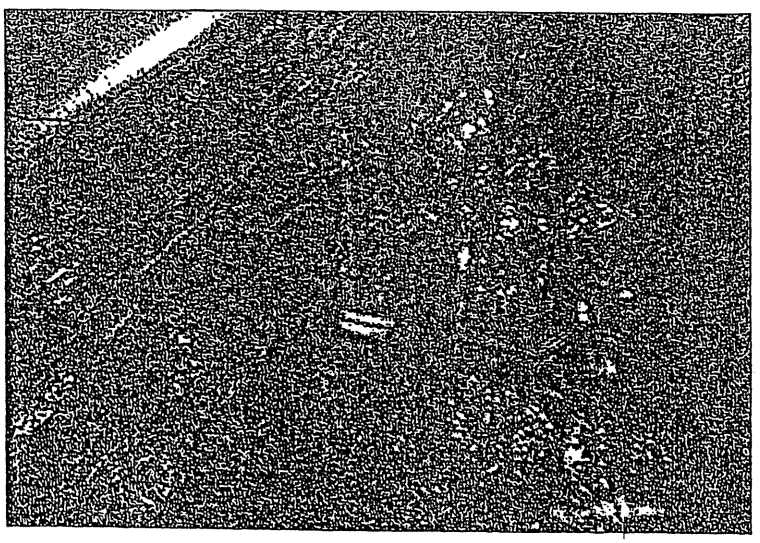
1. The patient, under general anesthesia, is placed supine in a 20° reverse Trendelenburg position with the legs open
2. The surgeon stands to the right of the patient, with one assistant standing at the patient's left side and one at the patient's right side
3. The laparoscopist stands between the patient's legs
4. A Hasson trocar is inserted in the subumbilical region, and carbon dioxide (CO_2) pneumoperitoneum at 10 mm Hg is created
5. Four trocars are then placed in the upper abdomen (Figure 2)
6. Under laparoscopic procedures, the greater omentum and the gastrocolic ligament are divided 3 to 5 cm from the gastroepiploic arcade toward the spleen, and the left gastroepiploic vessels are divided
7. After the gastrocolic ligament is dissected toward the second portion of the duodenum, the surface of the pancreas head and the right gastroepiploic vein are exposed (Figure 3).
8. The right gastroepiploic vein is clipped and cut to dissect the infrapyloric lymph nodes

FIGURE 2.



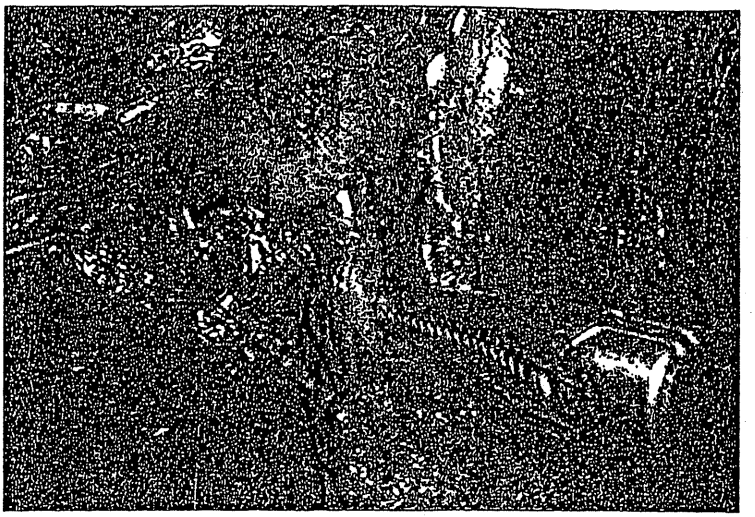
Trocar sites.

FIGURE 3.



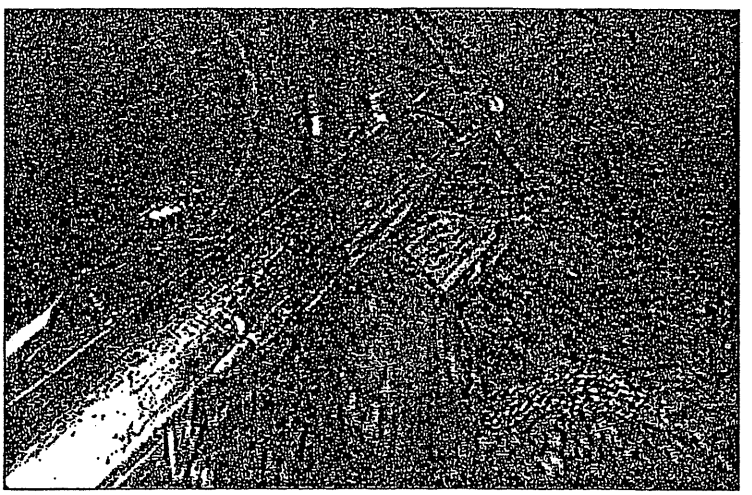
Dissection of the right gastroepiploic vein.

FIGURE 4.



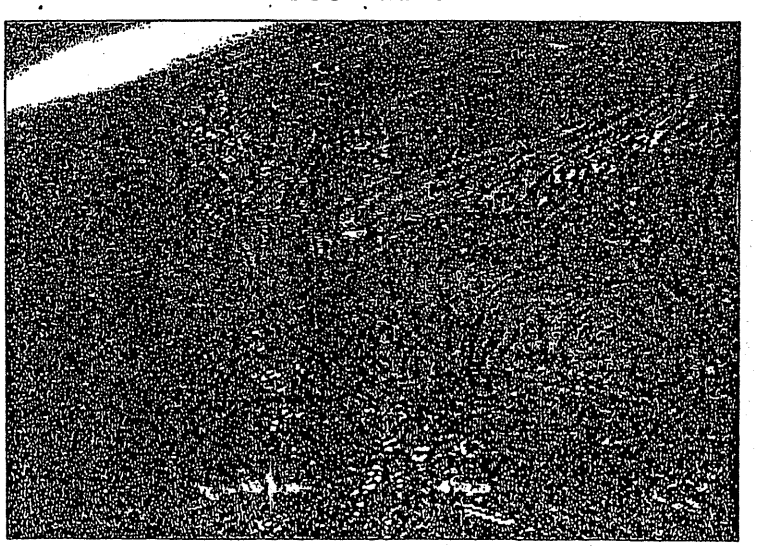
Dissection of the right gastroepiploic artery.

FIGURE 5.



Transection of the duodenum.

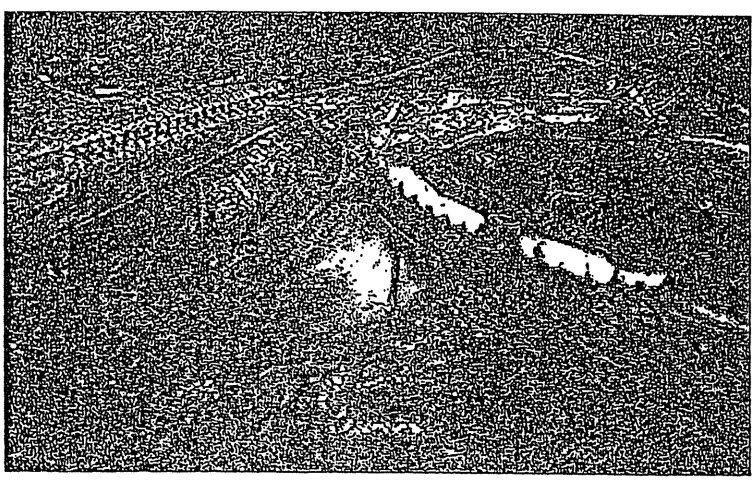
FIGURE 6.



Dissection of the right gastric artery.

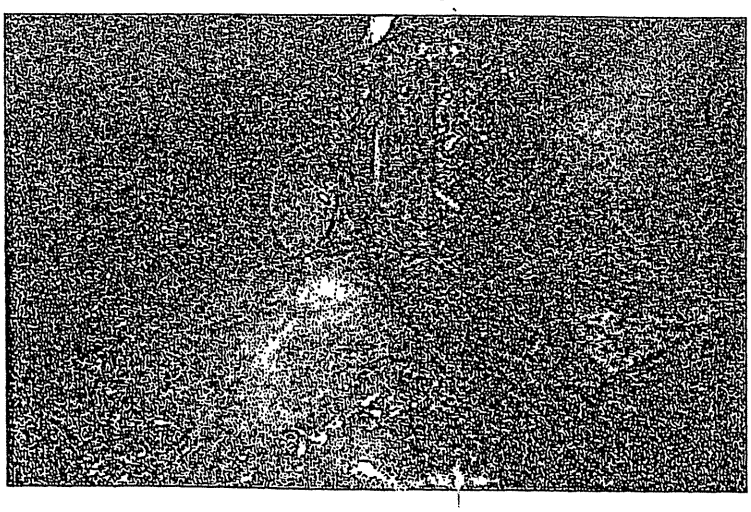
9. After identification of the gastroduodenal artery on the anterior surface of the pancreas, the right gastroepiploic artery is dissected and divided (Figure 4)
10. The liver is retracted upward with a snake retractor, and the lesser omentum is divided toward the esophagocardial junction with laparoscopic coagulation shears
11. After a hole is made at the apex of the duodenal bulb, the duodenum is transected with a laparoscopic linear cutter (Figure 5)
12. When the stump of stomach is lifted, the root of the right gastric artery is easily identified and divided (Figure 6)
13. To find the root of the left gastric vessels, the gastropancreatic ligament is stretched by lifting the lesser curvature of the gastric body
14. The lymph nodes along the common hepatic artery and the celiac artery are dissected from the right to the left side (Figure 7)
15. After the peritoneum above the right crus of the diaphragm is opened, the left gastric vessels are cut for dissection of lymph nodes along these vessels (Figure 8)

FIGURE 7.



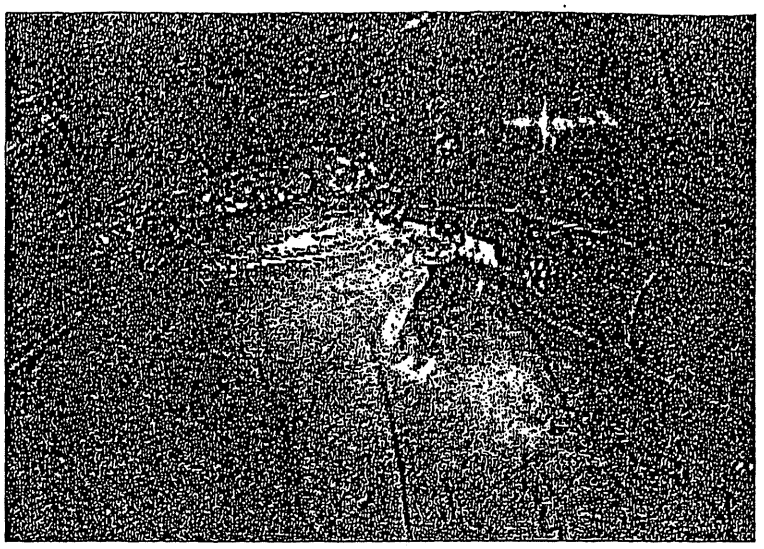
Lymph node dissection along the common hepatic artery.

FIGURE 8.



Dissection of the left gastric artery.

FIGURE 9.



Left cardiac lymph node dissection.

16. The left cardiac and superior gastric lymph nodes are then dissected (Figure 9)
17. A 5-cm minilaparotomy incision is made at the midline below the xyphoid, and a wound protector is placed
18. The distal portion of the stomach is exteriorized through the minilaparotomy, and distal gastrectomy is performed with a linear cutter
19. Pneumoperitoneum is recreated by sealing the wound protector, and the jejunum 20 cm distal to the ligament of Treitz is identified and exteriorized through the minilaparotomy
20. In the same manner as in open surgery, the jejunum is transected, and jejunojejunostomy and anastomosis between the jejunum and the gastric remnant are achieved with a functional end-to-end anastomosis by using a linear stapler
21. After placement of an informative drain under pneumoperitoneum, the minilaparotomy and trocar wounds are closed

Evaluation of LADG

There have been some case-controlled studies and several randomized controlled trials (RCTs) on the short- and long-term outcomes of LADG versus open gastrectomy.(11) Most studies on the short-term outcome of LADG have shown no difference in the incidence of operative complications between LADG and open gastrectomy.(12,13) The national survey conducted by the JSES showed that the incidence of intraoperative and postoperative complications was 1.6% and 8.2%, respectively. The most common intraoperative complication is bleeding. Common postoperative complications are anastomotic stenosis or gastric stasis, wound infection, and pancreatic injury.

Laparoscopy-assisted distal gastrectomy is considered a minimally invasive surgery for the following reasons: 1) decreased abdominal wall injury, 2) decreased amount of blood loss, 3) decreased exposure of the abdominal cavity to air, and 4) no manual manipulation of the other organs. Clinical advantages of LADG over open gastrectomy include less pain, rapid return of gastrointestinal function, better pulmonary function, shorter hospital stay, and decreased disturbance of immune function.(12,14,15)

Several recent studies on the long-term outcome of LADG showed the cancer recurrence rate to be the

same as that after open gastrectomy.(13,16,17) These findings suggest that, from an oncological standpoint, LADG is a feasible surgery for gastric cancer, especially EGC.

Conclusions

Laparoscopic gastric surgery, particularly LADG with lymph node dissection, has become popular in Japan as a minimally invasive surgery for cancer. With the development of advanced laparoscopic techniques, LADG with D1+α or D2 lymph node dissection has become possible, and the indications for LADG have expanded year by year. For worldwide acceptance of LADG as a standard operation, establishment of safe techniques and multicenter, randomized controlled trials are needed to clarify the oncologic feasibility of LADG for cancer.

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ORIGINAL ARTICLE

Clinical impact of a strategy involving endoscopic submucosal dissection for early gastric cancer: determining the optimal pathway

Satoru Nonaka · Ichiro Oda · Teruo Nakaya · Chika Kusano · Haruhisa Suzuki · Shigetaka Yoshinaga · Takeo Fukagawa · Hitoshi Katai · Takuji Gotoda

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Abstract
Background Endoscopic submucosal dissection (ESD) is a technique developed to enable the endoscopic resection (ER) of large and ulcerative neoplastic lesions that were previously unresectable using conventional endoscopic mucosal resection (EMR). We investigated the clinical outcomes of ER of early gastric cancer (EGC) before and after the introduction of ESD, with particular attention to surgery and its potential consequences.
Methods We reviewed 2,785 consecutive surgical patients with EGC and 2,469 consecutive lesions treated by ER with curative intent between 1990 and 2005. The study was divided into an EMR period (1990–1999) and an ESD period (2000–2005). We analyzed the clinical outcomes of endoscopic and surgical resections and defined 'potentially avoidable surgery' as cases of surgery performed for lesions curable by ER.
Results The rate of potentially avoidable surgery was 3.8% (52/1,369) in the EMR period and 0.2% (3/1,416) in the ESD period ($P < 0.001$). For ER patients, the rate of overall non-curative ER was 36.9% (154/417) in the EMR group and 17.0% (348/2,052) in the ESD group ($P < 0.001$). The rate of non-curative ER for lesions defined as having 'positive or difficult to estimate horizontal margins only' decreased significantly, from 26.1% (109/417) in the EMR group to 1.4% (29/2,052) in the ESD group ($P < 0.001$). Conversely, the rate of non-curative ER for lesions defined as having 'possible lymph node metastasis' significantly increased in the ESD group (15.5%; 319/2,052) compared to that in the EMR group (10.8%; 45/417) ($P < 0.01$).
Conclusions The application of a pathway involving ESD resulted in a significant decrease in the rate of potentially avoidable surgery, highlighting the advantages associated with performing ESD.

Keywords Early gastric cancer · Lymph node metastasis · Endoscopic submucosal dissection · Potentially avoidable surgery · Non-curative endoscopic resection

Abbreviations

ER	Endoscopic resection
EGC	Early gastric cancer
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
sm2	Submucosal deep invasion
sm1	Submucosal superficial invasion

Introduction

Therapeutic endoscopic resection (ER) has been performed for early gastric cancer (EGC) since the mid 1980s and is now accepted as the standard treatment for those patients with negligible risk of lymph node metastasis [1–8]. The conventional method by which EGCs were removed was by endoscopic mucosal resection (EMR). The limitations

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of applying EMR to all potentially endoscopically resectable lesions were size, location, and scarring from previous ulceration, so that only piecemeal removal was possible in such cases [9–11]. Unfortunately, piecemeal resection of EGC is associated with both difficulties in accurate histological assessment and a higher rate of local recurrence [12, 13]. Consequently, surgery was often chosen as the initial preferred method of treatment for lesions which were difficult to resect by EMR and those associated with difficulty in estimation of tumor depth.

A major breakthrough was achieved at the turn of the twenty-first century, with the advent of endoscopic submucosal dissection (ESD) [14–20]. ESD is a technique developed to enable the resection of large and ulcerative lesions, regardless of tumor location, that are unable to be removed using the conventional EMR procedure. The other major advantage of ESD is its ability to achieve a higher rate of en-bloc resection, thus providing more accurate histological assessment as compared to EMR [12, 21]. For the aforementioned reasons, ESD has translated into lower rates of local recurrence of gastric cancer as compared with EMR [22, 23]. The gastric cancer treatment guidelines of the Japanese Gastric Cancer Association for lesions that are considered curative by EMR are shown in Table 1 [24]. Based on the risk of lymph node metastasis determined from a large cohort of surgically treated cases of EGCs, ESD is now regarded as a curative procedure for lesions selected using the National Cancer Center expanded criteria (Table 2) [25].

Table 1 JGCA guideline criteria for endoscopic resection

Differentiated adenocarcinoma
Intramucosal cancer
≤20 mm in size without ulceration

JGCA Japanese Gastric Cancer Association

Table 2 NCC expanded histopathological criteria for curative endoscopic resection

Early gastric cancer with negligible risk of lymph node metastasis
Differentiated adenocarcinoma
No lymphatic or venous invasion
Intramucosal cancer regardless of tumor size without ulceration
Or intramucosal cancer ≤30 mm in size with ulceration
Or submucosal superficial cancer (sm1) ≤30 mm in size
Resection margin
Tumor-free horizontal margin
Tumor-free vertical margin

NCC National Cancer Center

An important advantage of ESD is that it can also be considered as improving diagnostic assessment due to the suboptimal accuracy of the endoscopic staging of EGC, which is sometimes difficult because EGC shows unclear margins due to gastritis, and depth diagnosis is not always accurate [26–28]. Thus, the use of ESD has enabled us to achieve enhanced diagnosis of lesions where it may have been difficult to estimate the tumor depth or where there was a technical difficulty in resection with EMR. The treatment strategy in which additional surgery is performed after confirmation of the histological assessment of the ER specimen has already been established as one of the therapies for EGC [29–31]. We hypothesized that ESD might reduce the rate of potentially avoidable surgery by its improvement of diagnostic and therapeutic capacity compared to that of EMR. We retrospectively investigated the relationship between the surgical and endoscopic treatment of EGC before and after the introduction of ESD, with particular attention to the rate of surgical resection and its potential consequences.

Patients and methods

We retrospectively reviewed the clinical records and endoscopic and histological reports of 2,785 consecutive patients with EGC treated by surgery with curative intent and 3,102 consecutive EGC lesions treated by ER at the National Cancer Center Hospital, Tokyo, between 1990 and 2005. Informed consent was obtained from all patients in accordance with the institutional protocol. Our primary aim in this study was to retrospectively compare the rate of potentially avoidable surgery before and after the introduction of ESD and to compare the rates of non-curative ER and rates of complications between the EMR and ESD groups. All patients and lesions were discussed and the treatment strategies were determined in weekly multidisciplinary conferences involving endoscopists, surgeons, radiologists, and pathologists. The study was divided into an EMR period (1990–1999), during which the main endoscopic modality of treatment for EGC was EMR, based on the guideline criteria of the Japanese Gastric Cancer Association (Table 1) [24] and an ESD period (2000–2005), during which ESD became the predominant method by which EGCs were endoscopically resected, based on the National Cancer Center expanded criteria (Table 2) [25].

For surgical patients, we defined cases of 'potentially avoidable surgery' as those cases with surgically resected histopathological specimens within the guideline criteria of the Japanese Gastric Cancer Association [24]. In other words, the patients with potentially avoidable surgery were those who underwent surgery for lesions curable by ER.

In the ER patients, 2,469 lesions, after exclusions, were treated by ER with curative intent; 417 lesions from the EMR group included only those lesions that were treated by EMR during the EMR period, while 2,052 lesions from the ESD group involved only those lesions that were treated by ESD during the ESD period. Another 248 lesions that were treated by ESD in the EMR period and 90 lesions that were treated by EMR in the ESD period, all with curative intent, were excluded from this study (Fig. 1). In addition, other EGCs were excluded from this study because ERs were performed for palliative purposes or because the ERs were performed for residual/recurrent lesions from previous endoscopic treatments. Palliative ERs were performed in patients who refused or were unfit for surgery because of comorbidities and for those lesions found during pre-therapeutic staging to have submucosal deep invasion (sm2) or deeper invasion, as well as those lesions with undifferentiated adenocarcinomas as revealed by biopsies. Palliative ERs included 191 lesions (150 by ESD and 41 by EMR) and residual/recurrent ERs included 104 lesions (100 by ESD and four by EMR) during each respective period (Fig. 1).

The curability of ER was divided into categories of curative and non-curative; the non-curative category included lesions that could not be precisely evaluated histologically based on the National Cancer Center expanded criteria and the tumor margins [25]. Non-curative ER was separated into two groups based on histological results: 'non-curative with positive or difficult to estimate horizontal margins only' and 'non-curative with a possible risk of lymph node metastasis irrespective of horizontal margin', based on submucosal deep invasion (sm2: ≥500 μm), positive lymphatic and/or venous invasion, intramucosal cancer more than 3 cm in size in the presence of ulceration, submucosal superficial invasion (sm1: <500 μm) in a lesion greater than 3 cm in size, predominantly undifferentiated type adenocarcinoma, and positive vertical margin (Table 3). Therefore, non-curative ERs with a possible risk of lymph node metastasis were cases of ER carried out in patients who went on to require additional surgery. In other words, these patients were those who underwent ER for lesions curable by surgery. Complications including perforation and delayed bleeding that required blood transfusion were also investigated in the EMR and ESD groups.

Clinical outcomes were analyzed using the χ^2 test and Fisher's exact test (Statview; Abacus Concepts, Berkeley, CA, USA), and $P < 0.05$ was considered statistically significant.

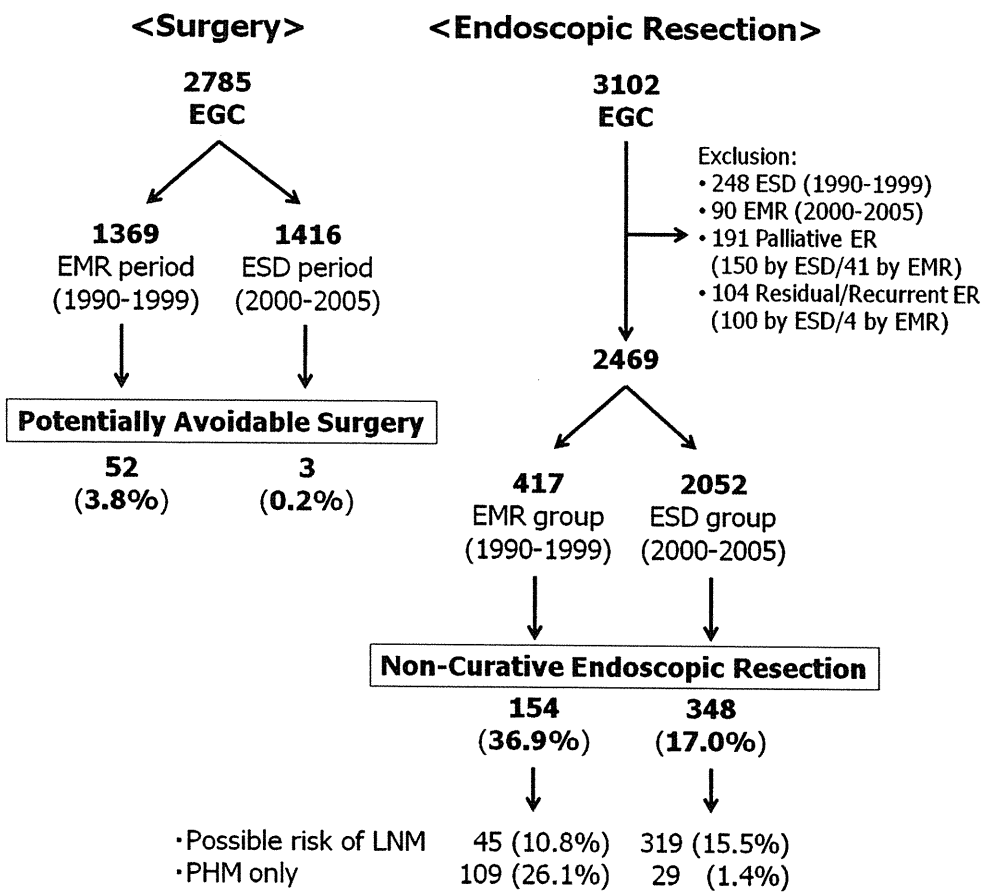

Fig. 1 Outline of the study, including rates of potentially avoidable surgery and non-curative endoscopic resection based on the histological results. *EGC* Early gastric cancer, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *ER* endoscopic resection, *LNM* lymph node metastasis, *PHM* positive or difficult to estimate horizontal margin

Table 3 Non-curative endoscopic resection

Non-curative with possible risk of lymph node metastasis
Submucosal deep invasion (sm2)
Positive lymphatic and/or venous invasion
Intramucosal cancer >30 mm in size with ulceration
Submucosal superficial invasion (sm1) >30 mm in size
Predominantly undifferentiated type adenocarcinoma
Positive vertical margin
Non-curative with positive or difficult to estimate horizontal margins only

Table 4 Rates of potentially avoidable surgery

	EMR period (1990–1999)	ESD period (2000–2005)	*P*
Treated surgically	1,369	1,416	
Guideline lesion	52 (3.8%)	3 (0.2%)	<0.001
Technical difficulty	21	0	<0.001
Incorrect assessment	31	3	<0.001

EMR endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

Results

Potentially avoidable surgery

The study results are outlined in Fig. 1. The rate of potentially avoidable surgery was 3.8% (52/1,369) in the EMR period and 0.2% (3/1,416) in the ESD period ($P < 0.001$) (Table 4). There were two possible contributory factors to potentially avoidable surgery: technical difficulty with ER and incorrect pre-therapeutic assessment of EGC. EMR was not possible in 21 patients where technical difficulty arose from there being a remnant stomach due to prior surgery; scarring from previous ulceration close to the lesion; and the location of the lesion, in particular those very close to the pylorus and the gastroesophageal junction. Thirty-one patients did not undergo EMR due to incorrect pre-therapeutic endoscopic findings suggesting submucosal invasion and unclear margins. In the ESD group, all attempted lesions were treated successfully with ESD, and, in the ESD period, there were three surgical patients with incorrect preoperative assessments with lesions thought to have submucosal invasion (Table 4).

Non-curative ER with possible risk of lymph node metastasis and positive or difficult to estimate horizontal margins only

The rate of overall non-curative ER was 36.9% (154/417) in the EMR group and 17.0% (348/2,052) in the ESD group ($P < 0.001$) (Fig. 1) (Table 5). Reasons for non-curative ER are summarized in Table 6. The rates of sm2 invasion and positive lymphatic and/or venous involvement did not differ between the two groups. However, rates of intramucosal cancer more than 3 cm in size with ulceration, sm1 lesions more than 3 cm in size, and predominantly undifferentiated type adenocarcinoma in the ESD group significantly increased compared to those in the EMR group. The rate of positive vertical margins significantly decreased in the ESD group. In Table 6, we have listed the causes of non-curative endoscopic resection. Lesions considered non-curative with possible risk of lymph node metastasis may have been considered as such for one or a combination of overlapping criteria. To put this another way, the rate of non-curative ER with possible risk of lymph node metastasis regardless of horizontal margin increased in the ESD group (15.5%; 319/2,052) compared to that in the EMR group (10.8%; 45/417) ($P < 0.01$) (Table 5). Conversely, the rate of non-curative ER with positive or difficult to estimate horizontal margins only dramatically decreased in the ESD group (1.4%; 29/2,052)

Table 5 Rates of non-curative endoscopic resection

	EMR group % ($n = 417$)	ESD group % ($n = 2,052$)	*P*
Non-curative with possible LNM	10.8 (45)	15.5 (319)	<0.01
Non-curative with PHM only	26.1 (109)	1.4 (29)	<0.001
Total	36.9 (154)	17.0 (348)	<0.001

EMR endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *LNM* lymph node metastasis, *PHM* positive or difficult to estimate horizontal margin

Table 6 Causes of non-curative endoscopic resection

	EMR group % ($n = 417$)	ESD group % ($n = 2,052$)	*P*
sm2 cancer	8.9 (37)	7.5 (153)	NS
Positive lymphatic and/or venous invasion	5.3 (22)	5.4 (110)	NS
Intramucosal cancer >30 mm in size with ulceration	0 (0)	1.7 (34)	<0.004
sm1 cancer >30 mm in size	0 (0)	2.3 (48)	<0.0003
Predominantly undifferentiated type	1.4 (6)	3.8 (79)	<0.01
Positive vertical margin	4.6 (19)	2.2 (46)	<0.007
Positive horizontal margin	31.4 (131)	3.0 (62)	<0.001

In some patients there was more than one cause

EMR endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *sm2* submucosal deep invasion, *sm1* submucosal superficial invasion, *NS* not significant

compared to that in the EMR group (26.1%; 109/417) ($P < 0.001$) (Table 5).

Complications

The rate of perforation in the EMR group (6.0%; 25/417) was significantly higher compared to that in the ESD group (3.0%; 62/2,052) ($P < 0.003$). All perforations were detected endoscopically during the procedure, except for one patient in the ESD group with a delayed perforation who had a gastric tube after esophagectomy. Seven patients in the EMR group and one patient in the ESD group underwent emergency surgery because the perforations were difficult to manage endoscopically using endoclips. Blood transfusion was required in one patient in each group.

Discussion

This retrospective study shows that the rate of potentially avoidable surgery decreased significantly and the overall non-curative ER rate also decreased with the development of ESD. In the ESD group, the rate of non-curative endoscopically resected specimens with positive or difficult to estimate horizontal margins only significantly decreased compared with that in the EMR group, but the rate of non-curative ERs with possible risk of lymph node metastasis increased significantly.

The rate of potentially avoidable surgery was 3.8% (52/1,369) during the EMR period and 0.2% (3/1,416) during the ESD period ($P < 0.001$) (Table 4). We believe this may be as a result of two factors, the technical progress of ER and improved diagnostic accuracy. The progress of ER with EMR, and now ESD, over the past two decades has involved major breakthroughs in endoscopy and has revolutionized the treatment of EGC. The advent of ESD has enabled us to achieve a higher rate of en-bloc resection in situations not possible before. These include remnant stomachs, scarring from previous gastric ulceration, and certain technically difficult locations. Despite the recent development of new technology such as narrow band and autofluorescence imaging [32, 33], there have been no significant changes in our ability to diagnose the depth of invasion of EGC [27, 28]. Other studies have reported that the endoscopic staging of EGC is not always accurate and is correct in only 80–90% of cases, even with endoscopic ultrasonography [26, 34–36]. In our study, we found that incorrect preoperative assessments such as endoscopic overstaging leading to potentially avoidable surgery dropped significantly with the use of ESD (Table 4), but we believe that the increased use of ESD for enhanced diagnosis, rather than improvements in other diagnostic modalities, resulted in this reduction.

For reference, the rate of surgery for lesions included within the National Cancer Center expanded criteria was 4.7% (67/1,416) during the ESD period (data not shown). These lesions consisted of 18 intramucosal cancers >20 mm without ulceration, 33 intramucosal cancers ≤30 mm in size with ulceration, and 16 sm1 cancers ≤30 mm in size. It is believed that surgery on some of these lesions was potentially avoidable, but a direct comparison using the guideline criteria of the Japanese Gastric Cancer Association and the National Cancer Center expanded criteria cannot be made because of differences between the two sets of criteria.

The rate of non-curative ER, secondary to positive or difficult to estimate horizontal margins only, in the ESD group (1.4%; 29/2,052) significantly decreased compared to that in the EMR group (26.1%; 109/417) ($P < 0.001$) (Table 5). This reflects the inability of EMR to resect large lesions en bloc, the lesion often being resected in multiple fragments, making it difficult to ensure complete resection [9–11]. The other main problem that arises with performing EMR, even for small lesions, is the uncertainty regarding inaccurate resection margins. Several previous articles have reported higher rates of local recurrence caused by piecemeal resection and positive tumor margins [12, 13, 22, 23, 37]. The development of ESD has addressed these problems, as it enables an en-bloc resection with tumor-free margins.

On the other hand, the rate of non-curative ERs with possible risk of lymph node metastasis (which should ideally be managed by gastrectomy with lymph node dissection) increased in the ESD group (15.5%:319/2,052) compared to that in the EMR group (10.8%:45/417) ($P < 0.01$) (Table 5). This five percent difference could have occurred due to several reasons, but the primary cause was most likely the increase in the number of patients who underwent diagnostic ESD for borderline lesions which were either difficult to resect technically by EMR or difficult to estimate tumor depth accurately. Specifically, the introduction of the National Cancer Center expanded criteria and the ability of ESD to resect larger lesions are two possible reasons for the increase in the number of intramucosal cancers more than 3 cm in size with ulceration and sm1 lesions more than 3 cm in size for which ER was undertaken. An increase in the number of lesions with predominantly undifferentiated adenocarcinoma also occurred, most likely because the heterogeneity of gastric carcinoma may increase in larger-size lesions. Thus, this five percent rise in the rate of non-curative ERs with possible risk of lymph node metastasis has to be weighed against the potential advantages in undertaking ESD and the significantly reduced rate of potentially avoidable surgery. Oda et al. [31] reported that the actual rate of lymph node metastases, as determined from surgically resected

specimens, in a group of cases of 'non-curative ESD with possible risk of lymph node metastasis', was 6.3%. This emphasizes the fact that this cohort of patients should receive additional surgery.

In the present study, the rate of perforation in the EMR group (6.0%) was significantly higher compared to that in the ESD group (3.0%) although it is widely recognized that the rate of perforation with ESD is higher than that with EMR [22]. There is no evident explanation for this result, but one possible reason may be that EMR procedures were performed more aggressively because of curative intent in the EMR group.

The surgically resected stomach never returns to its natural state. Currently, the pathway whereby we use ESD as the optimal therapeutic strategy for the treatment of EGC seems to reduce the rate of potentially avoidable surgery and allows us to more appropriately select those cases that would benefit from additional surgery, as it enables more accurate histological assessment, particularly in difficult EGC cases. As a result, this pathway has brought about major benefits for patients by reducing potentially avoidable surgery, because with this strategy the final diagnosis is obtained with higher reliability due to precise feedback from histological assessments. However, it would be prudent to advise caution in performing ESD for EGC unless the indications have been carefully reviewed in the individual to ensure that the EGC is within the established selection criteria. We would emphasize that recognition of resectability and curability are two very different matters. It is also important to recognize the role of ESD in providing enhanced diagnostic information, thus contributing to the optimal therapy being undertaken for the appropriate indication.

Limitations

This study was retrospective and there were differences in criteria for ER between the two groups. In addition, the transitional phase was at the turn of the twenty-first century, but it was not clearly delineated as both procedures were being used at that time. However, we believe that by analysis by procedure (EMR and ESD) we have minimized the impact of this last factor.

Conclusions

We believe that a pathway of undertaking ESD in lesions where it may be difficult to estimate the depth of invasion and in technically difficult cases results in a significant decrease in the rate of potentially avoidable surgery, this being due to the advantages associated with not only a potentially curative procedure, but also one which provides enhanced diagnostic information and consequently enables more appropriate therapy.

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Conflict of interest None.

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