Original Article

Title

Totally laparoscopic gastrectomy for gastric cancer after endoscopic submucosal dissection: a propensity score matching analysis

Authors

Yuma Ebihara[1], Shunichi Okushiba[2], Yo Kurashima[1], Takehiro Noji[1], Toru Nakamura[1], Soichi Murakami[1], Eiji Tamoto[1], Takahiro Tsuchikawa[1], Keisuke Okamura[1], Toshiaki Shichinohe[1], Satoshi Hirano[1]

Concise title

Totally LG for gastric cancer after ESD

Affiliations and addresses of the authors

[1]Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine, N15W7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan

[2]Departments of Surgery, Tonan Hospital N1W6, Chuo-ku, Sapporo, Hokkaido 060-0001, Japan

Corresponding author

Yuma Ebihara

Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine, N15W7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan

Tel: +81-11-706-7714; Fax: +81-11-706-7158; E-mail: yuma-ebi@wc4.so-net.ne.jp

Abstract

Purpose: A recently developed endoscopic mucosal resection (EMR) procedure, endoscopic submucosal dissection (ESD), makes *en-bloc* resection possible for mucosal cancer regardless of lesion size. ESD involves deeper and wider dissection of the gastric wall, and may therefore increase the difficulty of subsequent totally laparoscopic gastrectomy (TLG) and the risk of complications. However, the influence of ESD on subsequent TLG has yet to be demonstrated. The purpose of the present study was to clarify the influence of ESD on subsequent TLG.

Methods: Between March 2006 and December 2013, we retrospectively collected data of 38 patients undergoing TLG with ESD (ESD Group) and propensity score matched 38 patients undergone TLG without ESD (non-ESD Group) for treatment of gastric cancer at Tonan Hospital and Hokkaido University Hospital. The covariates for propensity score matching were: age, sex, American Society of Anesthesiologists score, body mass index, and type of surgery. Clinicopathologic characteristics and surgical outcomes were compared between the two groups.

Results: Operative times for TLG in ESD group and non-ESD group were 228.2 ± 53.9 and 228.1 ± 52.7 min (P=0.989), and blood loss was 45.7 ± 83.0, 71.3 ± 74.5 g, respectively (P=0.161). There were no significant differences between the groups of ESD and non-ESD in postoperative recovery and postoperative complications. In totally laparoscopic distal gastrectomy (TLDG), the patients with ESD-resected specimens of more than 50 mm in diameter had significantly longer operative times (P=0.009).

Conclusions: In this study, TLG is feasible procedure treatment of gastric cancer regardless of ESD. However, TLDG is more difficult in cases where the ESD-resected specimen is more than 50 mm in diameter.

Key words:

Totally laparoscopic gastrectomy, Endoscopic submucosal dissection, Early gastric cancer

Introduction

Endoscopic mucosal resection (EMR) is a recognized treatment for early gastric cancer (EGC). One-piece resection is considered to be the gold standard for EMR, as it provides accurate histological assessment and reduces the risk of local recurrence [1, 2]. Endoscopic submucosal dissection (ESD) is a new technique developed to obtain one-piece resection even in large and ulcerative lesions. In Japan, although the number of patients with EGC treated by ESD has increased, appropriate strategies for treating those with non-curative resection have not been established. If ESD specimens are diagnosed as non-curative lesions by pathologists, further treatment is needed and laparoscopy-assisted gastrectomy (LAG) is likely to be the first choice.

LAG with regional lymph node dissection has been used in the treatment of early gastric cancer (EGC) with low mortality and morbidity and improvement in patient quality of life [3]. We have performed totally LG (TLG) for EGC, including totally laparoscopic distal gastrectomy (TLDG), totally laparoscopic proximal gastrectomy (TLPG) and totally laparoscopic total gastrectomy (TLTG) with intracorporeal anastomosis, using a laparoscopic linear stapler. To our knowledge, there have been a few reports on how ESD affects surgical data and postoperative outcomes in LAG [4]. In particular, ESD causes iatrogenic deep and wide ulcers in the resected area during the healing process, which induces inflammation and subsequent fibrosis and even adhesions in the outer gastric wall. This study aimed to clarify the feasibility of additional TLG after ESD among patients who failed to achieve curative ESD.

Patients and methods

Between March 2006 and December 2013, we identified 347 patients who underwent TLG with a preoperative diagnosis EGC at Tonan Hospital and Hokkaido University Hospital, Sapporo, Japan. The eligibility criteria were T1N0, T2N0 or T1N1 gastric cancers preoperatively diagnosed by endoscopy, computed tomography (CT) and endoscopic ultrasound. Informed consent was obtained from all patients. Specimens were evaluated according to the Japanese Classification of Gastric Carcinoma established by the Japanese Research Society for Gastric Cancer [5]. Patients who had a surgical risk greater than American Society of Anesthesiology (ASA) III, a previous history of upper abdominal surgery (excluding cholecystectomy, etc.) or needed combined surgery to treat another disease were excluded from this study. Postoperative morbidity was evaluated using the Clavien-Dindo classification [6].

Indication for and procedure of ESD

Absence of lymph node metastasis in the stomach is consider a prerequisite for ESD for EGC. The accepted extended indications for ESD as follows: (1) differentiated mucosal cancer without ulcer and of any size, (2) differentiated mucosal cancer, with ulcer $\leq$3cm in size, (3) differentiated submucosal cancer (sm1, <500 μm) $\leq$3cm in size, and (4) undifferentiated mucosal cancer $\leq$2cm in size. ESD was performed with an insulation-tipped diathermic knife (IT knife, type KD-IL; Olympus Optical Co, Tokyo, Japan) [7]. Formalin-fixed specimens were cut into multiple slices at an interval of 2 mm. All microscopic sections were stained with hematoxylin and eosin (H&E), were examined histologically by pathologists. The definition of a non-curative lesion was

massive cancer invasion into the submucosal layer, the presence of poorly differentiated adenocarcinoma, vessel involvement of cancer cells, or the presence of cancer cells in the resected margin [8].

Operative technique for TLG

In TLG, five trocars (Exel; Echicon End-Surgery, Cincinnati, OH, USA) are used, and the 12-mm paraumbilical port was subsequently extended to 3.0 cm while pulling out the specimen. After pneumoperitoneum was established, four trocars were placed in the upper abdomen. A laparoscope (3CCD Video System SX-2, Olympus, Tokyo, Japan) was introduced through this port, and four other trocars (three 10-mm trocars and one 5-mm trocar) were placed (Fig.1). We used laparoscopic coagulation shears (SONOSURG-X; Olympus Medical Systems, Tokyo, Japan) for lymph node dissection and vessel coagulation. TLDG was indicated for tumors in the lower part of the stomach. Billroth I anastomosis was performed using a delta-shaped anastomosis [9]. We used the functional end-to-end gastrojejunostomy technique in Roux-en-Y reconstruction. TLPG was indicated for tumors in the located upper part of the stomach. Double tract reconstruction or esophagogastrostomy was performed using linear staplers. TLTG was indicated for tumors located in the middle or upper part of the stomach. For esophagojejunostomy, we used the functional end-to-end esophagojejunostomy technique [10, 11].

The basic extent of lymph node dissection was more than D1+ no.7, 8a, 9 lymph nodes, but in the patients with severe comorbidity or in elderly patients who were more than 80 years old, D1+no.7 lymph nodes lymph node dissection was performed. Lymph node regions and dissection were decided according to the Japanese Classification of

Gastric Carcinoma published by Japanese Gastric Cancer Association [12]. Four experts participated in this study. All experts had experienced for more than 100 patients of TLG, and standardized all procedures of TLG and critical pathway of postoperative management.

Comparison between the two groups

Patients were divided into two groups for analysis: those who had ESD before TLG (ESD group) and those who did not (non-ESD group). The two groups were then compared with respect to the following parameters: operative and pathological data (operating time, blood loss, type of surgery, number of dissected lymph nodes, depth of cancer invasion and lymph node metastasis), and postoperative outcomes. Moreover, with regard to those patients undergoing ESD before TLDG, we investigated the relationship between the size of resected specimen by ESD and clinical outcome (operative and postoperative outcomes).

Propensity score matching

To compare TLG with ESD group with non-ESD group, we collected consecutive data of 347 patients who underwent TLG on the same period, and performed propensity score matching analysis using SPSS version 17.0 (SPSS, Chicago, IL) [13]. Each patient’s propensity score was calculated by a multivariable logistic regression model using the covariates of age, sex, ASA score, body mass index (BMI), and type of surgery. Patients in the ESD group and non-ESD group were one-to-one matched by closest propensity score on the logit scale. As a result, each 38 patients with ESD group and non-ESD group were selected.

Statistical analysis

Values are expressed as means (standard deviation). Data obtained were statistically analyzed by using Student's *t* test. Relationships between categorical variables were analyzed by chi-squared test and Fisher's exact test. Risk factors with $P < 0.050$ were considered to be significant. Statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL).

Results

Clinical characteristics of patients

Of the 347 patients who had TLG, 38 had previously undergone ESD. The reasons for further TLG were: massive invasion into the submucosal layer (37 patients); and presence of poorly differentiated adenocarcinoma (1 patient). Clinical characteristics of the 38 patients with ESD group and the 38 patients with non-ESD group are presented in Table 1. Patient demographics did not differ between the two groups. The variables (age, sex, ASA score, BMI, type of surgery), which were considered for propensity score matching, were similar between two groups. The comorbidities did not differ between the two groups.

Operative and pathological data

The operative and pathological data are summarized in Table 2. No significant differences were observed in operative time and blood loss between the two groups. The number of dissected lymph nodes did not differ between the two groups. Depth of cancer invasion was significantly different between the two groups, and the number of

patients with invasion beyond the muscle was greater in non-ESD group; however, the frequency of lymph node metastasis was not significantly different (P=0.644). The two patients (5.3%) with lymph node metastasis in ESD group were invasion into the submucosal layer.

Postoperative outcomes

There was no significant difference in the complication rate between the two groups (P=0.744). One case of anastomotic leakage occurred in ESD group was reoperated at the point of jejunojejunostomy in TLTG. No mortality occurred in either group (Table3). Recurrence was not observed in any patient after TLG during median follow-up period of 82.5 months (range, 15-108 months).

Relationship between diameter of ESD-resected specimen and perioperative outcomes

We investigated whether the size of ESD-resected specimen influenced the difficulty of the subsequent TLDG and perioperative outcome (Table 4). The 28 patients who had undergone ESD were divided into two groups; 17 patients had resected specimens of less than 50 mm, and 11 patients had resected specimens of more than 50 mm. There were no significant differences between the frequency of complications, blood loss, number of dissected lymph nodes and postoperative hospital stay between the two groups; however (data not shown), operative time was significantly shorter in the patients with resected specimens of <50 mm (P=0.009).

Discussion

EMR has been accepted as a standard treatment for EGC in Japan. The number of

patients with EGC treated by EMR has increased [14]. This trend reflects the increase in EGC cases identified by improvements in both diagnostic devices and EMR techniques. Many patients of EGC have received benefits from these advances and have avoided laparotomy and maintained a better quality of life (QOL). The recently developed EMR procedure, ESD, makes *en-bloc* resection possible for mucosal cancer regardless of lesion size. In addition, this procedure enables one-piece resection, thereby ensuring accurate pathology [1]. In this series, all cases received one-piece resection, and almost all patients (37 patients) showed massive invasion into the submucosal layer, with only one patient showing poorly differentiated adenocarcinoma.

After the first laparoscopy-assisted distal gastrectomy for EGC was reported in 1994 [15], laparoscopic gastrectomy began to be used by many surgeons around the world. There have been numerous reports on laparoscopy-assisted distal gastrectomy for EGC, and the technique has been widely accepted. However, there have been few reports on TLG due to the difficulty of reconstruction [16]. We adopted the policy of TLG from the initial period of laparoscopic gastrectomy at our hospitals, and we have not experienced conversion to open surgery as a result of intracorporeal anastomosis. There may be several advantages associated with TLG. In laparoscopy-assisted gastrectomy, extracorporeal anastomosis via mini-laparotomy incision may cause forceful tension and injuries to the structures around the anastomosis because of limited vision, particularly in obese patients [16]. In TLG, the whole anastomotic procedure can be clearly viewed, thereby eliminating such tension and injuries. TLG is a less invasive treatment after ESD than laparoscopy-assisted gastrectomy for EGC [17]. However, additional treatments for non-curative resection after ESD have not been established. To our knowledge, there have been a few reports ESD affecting the surgical and

postoperative course of LAG [4], although ESD causes deep and wide iatrogenic ulcers in the resected area during the healing process, which induces inflammation, subsequent fibrosis and even adhesion in the outer gastric wall. We experienced 6 patients (15.8%) with severe adhesion to other organ in ESD group. The histological view after ESD revealed inflammation and fibrosis all layers of the gastric wall. We found fibrosis in tissues including lymph nodes, and so experienced difficulty in performing lymphadenectomy. Nonetheless, the number of dissected lymph nodes did not differ between ESD group and non-ESD group; thus, the accuracy of lymphadenectomy was probably even. In TLDG, ESD-resected specimens with a diameter of more than 50 mm led to a longer operative time, but tumor location did not influence perioperative outcome (data not shown). Jiang et al [4] demonstrated a significantly higher rate of preservation of the celiac brunch of the vagus nerve and shorter postoperative stay in patients who underwent laparoscopy-assisted gastrectomy more than 2 months after endoscopic resection. We investigated whether the interval between ESD and subsequent TLG influenced the perioperative outcome. No relationship between the interval and perioperative outcome was recognized in this study. Kawata et al [18] reported no influence of additional gastric resection after ESD. However, they performed open gastrectomy for 93% cases (236/261 cases). This study is first report to clarify the influence of ESD on subsequent TLG. Pathological examinations in non-ESD group revealed that several cases had subserosa invation, but this was not observed for patients with ESD group. In this regard, TLG may be the first-choice radical treatment after ESD for EGC.

The long-term outcome of TLG for EGC is unknown, but at our hospitals, we have encountered no cases of recurrence after TLG for EGC to date. Nevertheless, further

clinical observations and prospective controlled studies are necessary to elucidate its long-term effects.

Conclusions

TLG can be a feasible procedure treatment of gastric cancer regardless of ESD in terms of surgical outcomes. However, TLDG is more difficult in cases where the ESD-resected specimen is more than 50 mm in diameter.

Conflicts of interest

All authors state that they have no commercial associations that might pose a conflict in connection with the submitted article.

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Figure Legend

Fig. 1: Positions of surgical ports

Four 12-mm trocars are placed in paraumbilical, bilateral abdominal and epigastric regions. One 5-mm trocar is placed in left hypochondral area.

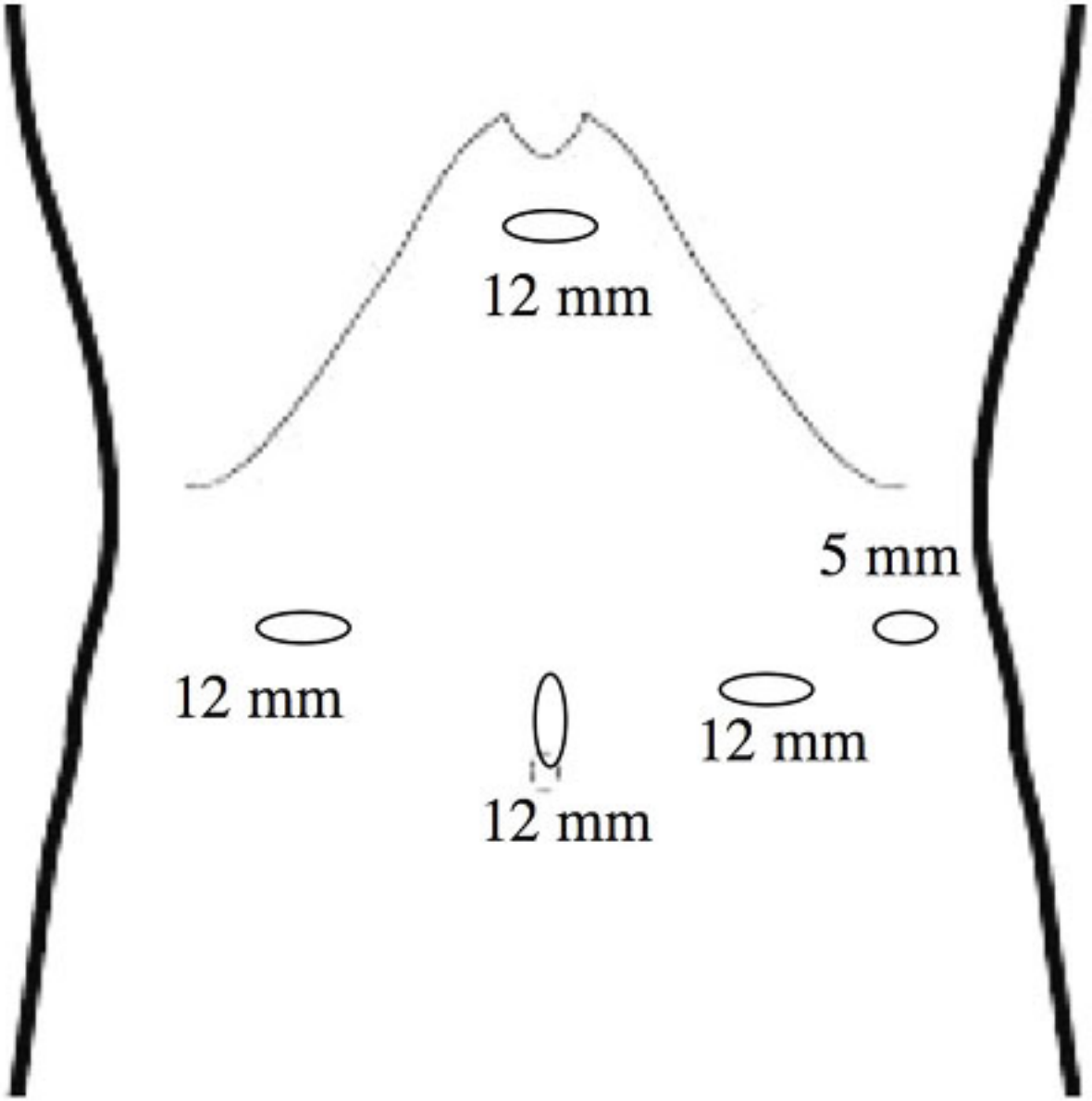
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Table 1: Clinical characteristics

Variables		**Group ESD (n=38)**	**Group non-ESD (n=38)**	***P* value**
Mean age (years) *		67.5 (8.5)	66.7 (9.1)	0.677
Gender				0.426
	Males	27	30	
	Females	11	8	
Body mass index (kg/m^2) *		22.9 (3.2)	23.0 (2.4)	0.814
ASA score (1:2)		21:17	23:15	0.642
Comorbidity		18 (15.8)	17 (15.8)	1.000
	Diabetes mellitus	3	4	
	Hypertension	7	6	
	Hyperlipidemia	3	2	
	Heart disease	4	2	
	Chronic liver disease	2	1	
	Pulmonary disease	2	3	
Type of surgery				0.533
	LTG	3 (7.9)	2 (5.3)	
	LPG	7 (18.4)	11 (28.9)	
	LDG	28 (73.7)	25 (65.8)	

Values in parentheses are percentage. *Values are mean (standard deviation). ESD; Endoscopic submucosal dissection. LTG; Laparoscopic total gastrectomy, LPG; Laparoscopic proximal gastrectomy, LDG; Laparoscopic distal gastrectomy.

Table 2: Operative and pathological data

Variables		Group ESD (n=38)	Group non-ESD (n=38)	*P* value
Operation time (min) *		228.2 (53.9)	228.1 (52.7)	0.989
Blood loss (g) *		45.7 (83.0)	71.3 (74.5)	0.161
No. of dissected lymph nodes*		25.9 (11.6)	26.8 (15.3)	0.692
Depth of cancer invasion				0.225
	Mucosa	1 (2.6)	3 (7.9)	
	Submucosa	37 (97.4)	32 (84.2)	
	Muscle	0 (0)	1 (2.6)	
	Subserosa	0 (0)	2 (5.3)	
Lymph node metastasis		2 (5.3)	3 (7.9)	0.644

Values in parentheses are percentage. *Values are mean (standard deviation). ESD; Endoscopic submucosal dissection.

Table 3: Postoperative outcomes

Variables	Group ESD (n=38)	Group non-ESD (n=38)	*P* value
Morbidity (Clavien-Dindo classification)	5 (13.2)	6 (15.8)	0.744
Grade II	3	4	
Wound infection	2	1	
Pancreatic juice fistula	0	1	
Ileus	1	0	
Delayed gastric emptying	0	2	
Grade IIIa	1	2	
Anastomotic stenosis	1	1	
Abdominal infection	0	1	
Grade IIIb	1	0	
Anastomotic leakage	1	0	
Mortality	0	0	
Time to resume soft diet (days) *	4.2 (1.0)	4.6 (1.9)	0.249
Postoperative hospital stay (days) *	16.5 (6.9)	15.9 (6.4)	0.694

Values in parentheses are percentage. *Values are mean (standard deviation). ESD; Endoscopic submucosal dissection.

Table 4. Relationship between the diameter of ESD-resected specimen and perioperative outcomes in TLDG

Variables	< 50 mm (n=17)	≥ 50mm (n=11)	P value
Operation time (min) *	198.2 (41.1)	247.3 (48.2)	0.009
Blood loss (g) *	27.2 (47.6)	77.5 (120.6)	0.132
No. of dissected lymph nodes *	22.2 (11.3)	25.7 (6.7)	0.502
No. of postoperative complications	2	1	0.823
Postoperative hospital stay (days) *	16.2 (4.5)	16.1 (9.4)	0.983

Values in parentheses are percentage. *Values are mean (standard deviation). ESD; Endoscopic submucosal dissection. LDG; Laparoscopic distal gastrectomy.