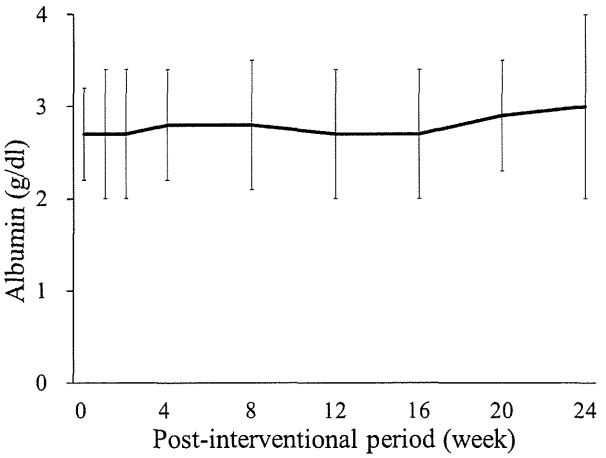

Fig. 4. Changes in the mean albumin levels at baseline (0) and during follow-up after stenting. Albumin levels after re-intervention were not included. Bars represent the standard deviation. There were no significant differences between baseline and post-interventional values by the Wilcoxon signed-ranks tests.

Overall Survival

At the time of analysis, 17 patients had died. The cause of death was gastric cancer in every case. The median survival time (MST) was 186 days and the 1-year survival rate was 11%.

DISCUSSION

The SEMS has been increasingly used for the palliation of malignant GOO, mainly due to biliary-pancreatic cancer. Some studies have reported the effects of SEMSs for GOO [3,4,9–11]. However, for the first time, we evaluated the effects of SEMSs for GOO due to advanced gastric cancer by a prospective multicenter study. We found that SEMSs in gastric cancer resulted in an acceptable improvement in oral intake with excellent technical success, without any complications.

Previous retrospective analyses concerning the effects of SEMSs for malignant GOO have reported similar clinical outcomes. Chandrasegaram et al. [4] reported that 69% and 77% patients could eat solids or puree on the 5th and 10th post-stenting days, respectively. Canena et al. [9] also reported that solid food intake (GOOSS score of 2–3) was achieved by 72% of patients within 5 days after stenting, which is similar to our study. They reported that the mean GOOSS score was 1.76 at 5 days after stenting, and 1.64 during the follow-up. Compared with these data, our patients maintained a good GOOSS score, ranging from 1.7 to 2.3 during follow-up. Although some other reports have mentioned a remarkably higher rate of clinical success with GOO, the definition of improvement of GOO differs [10–12]. An improvement of the GOOSS score by one or more points was obtained in 94% of patients in our series. However, this improvement in GOO failed to lead to improvement in nutritional parameters and general condition, including BW, PS, albumin levels, lymphocytes, and hemoglobin levels.

In the current study, five patients could not eat solid food after SEMS placement. All of them had a GOOSS score of 0 and a PS of 2. One patient died on the 6th day after stenting, and one died on the 17th day after stenting. One patient needed gastrojejunostomy, one needed central venous port placement, and the other patient did not receive any additional intervention because of a poor general condition. However, among 13 patients who could eat solid food after stenting, only two patients had a PS of 2 and the other 11 patients had a PS of 0 or 1. Considering these data, the ability to take solid food after stenting might partially depend on PS. Sasaki et al. [10] also showed that a poor PS was a poor predictive factor of solid intake. Patients with a PS of 2 would be more likely to be lying in bed, which makes oral intake difficult because advanced cancer in the stomach results in lost migration activity and patients require the assistance of gravity to let food pass through the stent. In fact, the patient with a PS of 2 who could not eat solid food after stenting could also not eat solid food after gastrojejunostomy.

The change in the GOOSS showed that GOOSS scores were maintained at approximately 2 from the 1st week to the 24th week after stenting. In Figure 1, GOOSS scores after re-intervention were not included. Four patients maintained GOOSS scores of 2–3 for 24 weeks after stenting without re-intervention, while three patients required re-intervention due to re-obstruction on the 69th, 105th, and 126th days. No et al. [12] reported that the median duration between SEMS placement for gastric cancer and the recurrence of obstructive symptoms was 125 days. Some studies, including those on gastric cancer and biliary-pancreatic malignancies, found that stent patency lasted for 4–17 months [4,9,11], although the duration of stent patency is thought to be difficult to evaluate objectively. Recurrent obstruction is caused by tumor ingrowth or overgrowth, and remains an important problem of SEMSs. Additional SEMS placement was performed for two cases in our series with good results. Recent reports have also described the effectiveness of additional SEMS insertion using a stent-in-stent procedure [4,11,12]. Additional SEMS placement may be a feasible choice for recurrent obstruction after stenting.

Chemotherapy is also expected to improve maintenance of stent patency, mainly as a result of reducing tumor ingrowth or overgrowth. In our series, chemotherapy was administered in most patients soon after stenting. Ability of oral intake of S-1 is important for treating patients with unresectable advanced gastric cancer because S-1 is a key drug for unresectable advanced gastric cancer [13]. Notably, one patient in our series with peritoneal metastasis underwent curative resection after SEMS placement and chemotherapy. Less invasiveness of endoscopic SEMS placement enabled the patient to start chemotherapy as soon as the 8th day after stenting. Furthermore, if this patient had undergone surgical gastrojejunostomy instead of SEMS placement, the next surgery of gastrectomy would have been difficult and complicated. In this patient, gastrectomy was performed without difficulty by fully mobilizing the duodenal bulbus and resecting the duodenum just distal to the SEMS. This patient showed the advantages of SEMS placement in terms of early administration of chemotherapy and the technical ease of gastrectomy when chemotherapy was effective. This patient is doing well with good oral intake for 16 months after stenting and 13 months after gastrectomy.

The MST after stenting was 186 days, which is compatible with that in a recent Korean report after stenting for gastric cancer (189 days) [12]. For patients who underwent chemotherapy including the S-1 regimen, the MST was 9.1 months, which is similar to the reported MST of patients with advanced gastric cancer who underwent S-1 chemotherapy (11.0 months) [13]. Therefore, the ability of chemotherapy with S-1 after stenting leads to a survival benefit.

CONCLUSIONS

We prospectively analyzed the effectiveness of endoscopic gastroduodenal SEMS placement for GOO due to unresectable advanced gastric cancer. This procedure was technically successful in every patient, and 72% of patients could eat solid food. The duration of post-interventional fasting and hospitalization was short. Gastroduodenal SEMSs are thought to be feasible, safe, and effective for GOO due to unresectable advanced gastric cancer. This palliative treatment might become the choice of treatment for GOO. A further study is being planned to compare SEMSs and gastrojejunostomy by a randomized controlled trial in our multicenter group.

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Esophageal submucosal dissection under steady pressure automatically controlled endoscopy (SPACE): a clinical feasibility study

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Background and study aims: Steady pressure automatically controlled endoscopy (SPACE) is a new insufflation system that provides constant carbon dioxide (CO_2) insufflation pressure during prolonged procedures. The system consists of an overtube, a surgical insufflator, and a newly developed leak-proof valve. The aims of this study were to validate the feasibility and safety of SPACE for esophageal endoscopic submucosal dissection (ESD).

Patients and methods: This was a clinical phase I trial, involving 10 patients who underwent esophageal ESD. The primary end point was the rate of adverse events within 30 days (grade 0 to 4). Secondary end points were changes in partial pressure of carbon dioxide ($PaCO_2$) and vital signs during ESD, completion rate of ESD, and degree of abdominal distension by patient assessment and radiographic grading.

Results: All adverse events were Grade 2 or less. Mild $PaCO_2$ elevation after ESD was noted; however, no associated symptoms were reported. The procedure was completed under SPACE alone in 8 of 10 patients. Minimal post-procedural bowel distension was observed.

Conclusions: In this small pilot study, SPACE was feasible and appeared to be safe. Further study with larger case numbers is required to demonstrate efficacy and safety.

Clinical trial registration: UMIN000005434

Introduction

With recent advances in technologies for endoscopic intervention [1–6], optimization of insufflation has always been key to success. Recently, a simple, flexible overtube system was developed, which achieves a constant-pressure environment in the upper gastrointestinal tract without the need to place a distal valve, and which uses currently available standard flexible gastrointestinal endoscopes and surgical insufflators. This new modality is called steady pressure automatically controlled endoscopy (SPACE). The system has been shown to be feasible and safe in a preclinical trial [7]. The aim of this study was to confirm the clinical feasibility and safety of SPACE in patients undergoing esophageal endoscopic submucosal dissection (ESD).

Patients and methods

Study design

This was a noncontrolled clinical phase I trial. The study protocol was approved by the Ethics Committee of the institute. The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (number UMIN000005434).

Patients

Patients were included if they were aged 20–80 years and had histologically proven squamous cell high grade intraepithelial neoplasia or carcinoma with mucosal invasion (T1a), and extension to less than two-thirds of the circumference of the esophagus. Patients were excluded if they had any of the following: significant abnormality in a respiratory function test; previous esophagectomy; a lesion located on the cervical esophagus or on the esophagogastric junction; severe anemia (hemoglobin < 9.0 g/dL); abnormal liver function test (aspartate aminotransferase > 100 IU/L and/or alanine transaminase > 100 IU/L); severe renal dysfunction (serum creatinine > 2.0 md/dL); infectious disease that required systemic treatment; pregnancy, possibility of pregnancy, or breastfeeding; uncontrolled psychiatric disease; treatment with systemic steroid therapy; unstable angina or uncontrolled hypertension and/or diabetes mellitus; noncorrectable coagulopathy, or anticoagulant therapy that could not be interrupted for ESD.

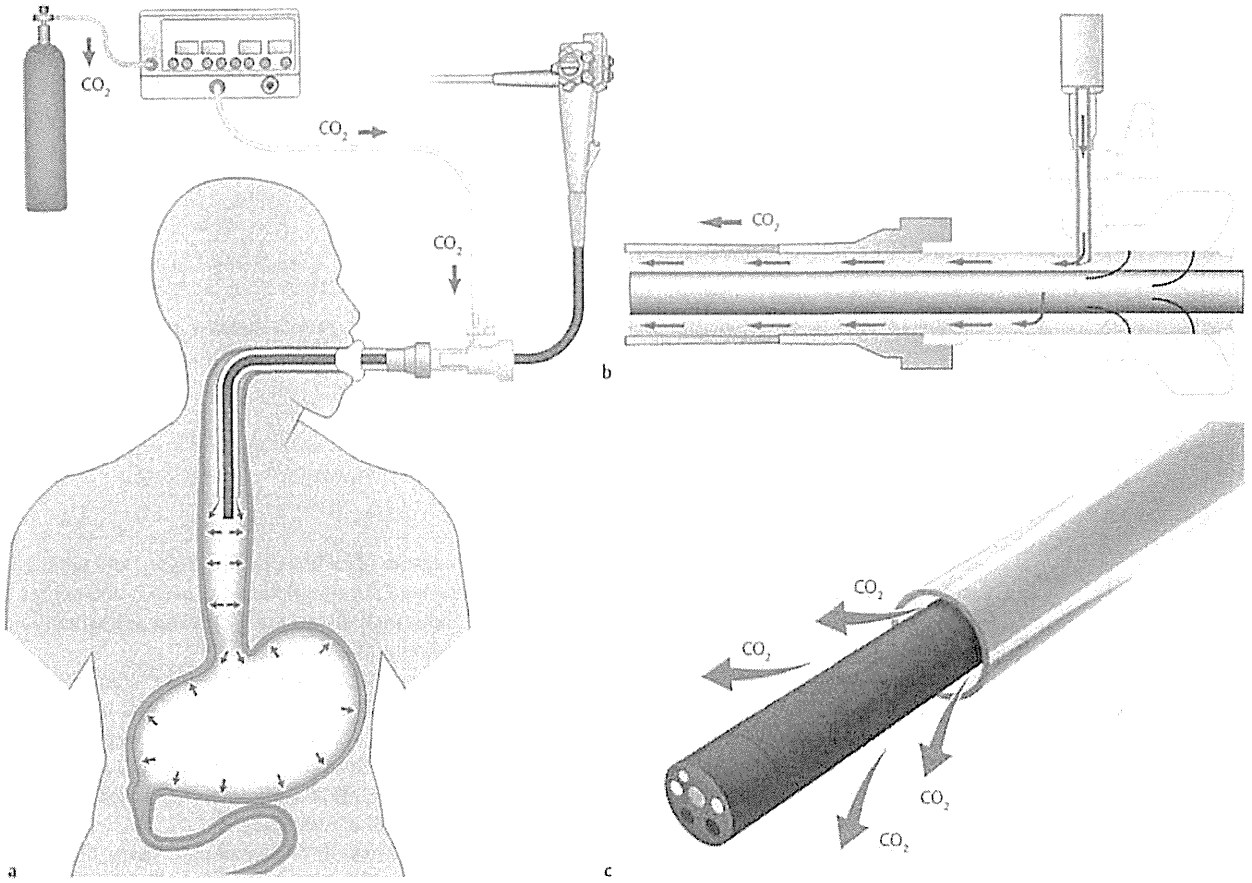

Fig. 1 The steady pressure automatically controlled endoscopy (SPACE) system. **a,b** The system consists of a newly developed detachable leak-proof device with an antireflux valve and a luer-lock connection (Leak Cutter; Top Co., Ltd.). Carbon dioxide is delivered from the surgical insufflator through the space between the overtube and the endoscope. Steady pressure environment is obtained without placement of a distal valve. **c,d** The antireflex valve is connected to the overtube.

Written informed consent was obtained from all patients prior to the procedure.

The SPACE system

The SPACE system consists of a standard endoscopic overtube (#16630 19.5 mm diameter and 210 mm length; Top Co., Ltd., Tokyo, Japan) and a newly developed detachable leak-proof valve with luer-lock connection (Leak Cutter; Top Co., Ltd.). The overtube is introduced into the esophagus under endoscopic guidance [7]. The Leak Cutter is then attached to the proximal end of the overtube. A commercially available surgical insufflator (UHI-3; Olympus Medical Systems, Tokyo, Japan) is connected to the system, and automatic intraluminal carbon dioxide (CO_2) insufflation is started through the space between the overtube and the endoscope (◎ Fig. 1).

ESD procedure

The esophagus was insufflated at an intraesophageal pressure of 10–14 mmHg and a flow speed of 35 L per minute. An endoscopist (T.Y.) performed ESD in the standard fashion. All procedures were performed using a high-vision zoom endoscope (EVIS GIF-H260Z; Olympus). An endoscopic knife (Flush knife BT 2.0 mm, DK2618JB-20 [Fujifilm, Tokyo, Japan] and/or SB knife short type, 221A [Sumitomo Bakelite Co., Ltd., Tokyo, Japan]) powered by a high-frequency electrosurgical unit (VIO 300 D; ERBE Elektromedizin, Tübingen, Germany) was used. The procedure was performed under SPACE alone; manual insufflation was not used provided visualization was sufficient for ESD to be performed safely. For patient safety, however, the protocol required an immediate switch to manual insufflation if perforation occurred during the ESD procedure.

Outcomes

The primary end point was the rate of adverse events (based on the National Cancer Institute common terminology criteria for adverse events, version 4.0) that occurred within 30 days after ESD. The adverse events included periprocedural and post-procedural complications. Secondary end points were completion rate of ESD under SPACE alone, changes in partial pressure of CO_2 ($PaCO_2$) and vital signs, the rate of en bloc resection with negative margins, total ESD time, and patient symptoms (abdominal distension and abdominal pain), which were measured using a 100-mm visual analog scale (VAS) at 2 and 6 hours after the procedure.

Arterial blood samples were obtained by radial or femoral artery puncture. Preprocedural $PaCO_2$ was measured after administration of intravenous sedative drug, and post-procedural $PaCO_2$ was measured after the entire procedure was completed and immediately before endoscope removal. Post-procedural bowel distension was evaluated by radiographic grading of an abdominal

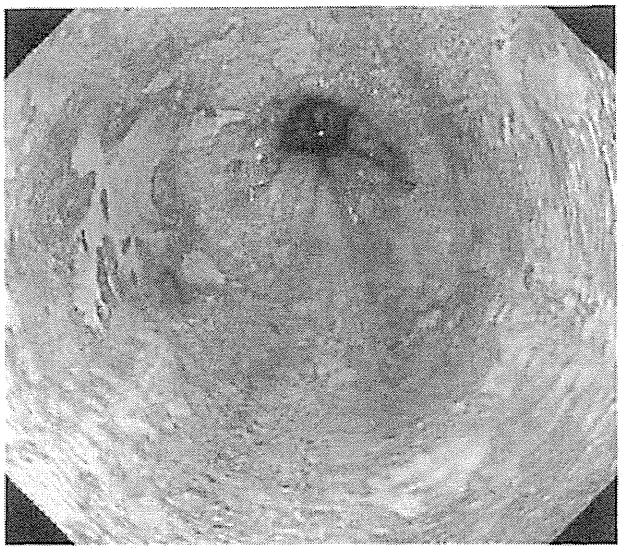

Fig. 2 Endoscopic view obtained under steady pressure automatically controlled endoscopy.

radiograph taken immediately after ESD in accordance with the criteria described by Souma [8].

Statistics

All data were analyzed using JMP software (ver. 8.0.1, SAS Institute Inc., Cary, North Carolina). Wilcoxon's rank-sum analysis was used to compare nonparametric continuous data. A *P* value of less than 0.05 was considered statistically significant.

Results

Characteristics of patients and lesions

From April 2011 to May 2012, a total of 11 patients agreed to participate in the study. One patient had an abnormal respiratory function test and was excluded from the study. The characteristics of the remaining 10 patients and lesions are shown in ○ Table 1.

ESD procedure

ESD was successfully completed in all 10 patients within a median of 52 minutes (○ Table 2). In eight patients, the procedure was completed under SPACE alone. In another patient, manual insufflation was added due to strong esophageal peristalsis. In the remaining patient, SPACE was switched to manual insufflation according to the protocol because the muscularis propria was exposed during submucosal dissection, which suggested a deep thermal injury (○ Fig. 2; ○ Video 1).

Video 1

Endoscopic submucosal dissection under steady pressure automatically controlled endoscopy.

Online content including video sequences viewable at: www.thieme-connect.de

Table 1 Patient and lesion characteristics.

Patient characteristics	
Age, median (range), years	64 (49–75)
Sex, n	
Male	8
Female	2
Lesion characteristics	
Location in thoracic esophagus, n	
Upper	3
Middle	2
Lower	5
Circumference, n	
Anterior wall	0
Posterior wall	7
Right wall	3
Left wall	0
Size, median (range), mm	13.5 (3–35)
Occupied circumference, n	
Half	9
Two-thirds	1

Table 2 Outcomes of endoscopic submucosal dissection using steady pressure automatically controlled endoscopy (SPACE).

Procedure time, median (range), minutes	52 (32–123)
Procedure completion, n (%)	10 (100)
SPACE alone	8 (80)
SPACE with manual[1]	1 (10)
SPACE switched to manual[2]	1 (10)
Intraoperative complications, n	
Mediastinal emphysema	0
Subcutaneous emphysema	0
R0 resection, n (%)	10 (100)
Adverse event within 30 days, n	
Dysphagia/laryngeal pain (Grade 1)	5
Chest pain (Grade 1)	3
Abdominal pain/bloating (Grade 1)	1
Atrial fibrillation (Grade 2)	1[3]
Hospital stay, median (range), days	10 (6–17)

[1] Additional use of manual insufflation due to strong esophageal peristalsis.
[2] Switched to manual insufflation because of suspicion of deep thermal injury.
[3] The onset was 27 days after the procedure.

Adverse events

Mild dysphagia occurred in five patients. All of these patients could eat a regular diet and the symptoms resolved spontaneously within several days; symptoms were classified as Grade 1 (○ Table 2). Noncardiac chest pain occurred in three patients and abdominal pain in one patient. These symptoms were mild and resolved within several days without any medical treatment; they were classified as Grade 1.One patient developed atrial fibrillation 27 days after ESD during a hospital stay for the treatment of co-morbid hepatocellular carcinoma. This patient received an antiarrhythmic drug and recovered a sinus rhythm within 7 days. This event was classified as Grade 2 (nonurgent medical intervention indicated). No patient developed an adverse event of Grade 3 or more.

Cardiopulmonary parameters during SPACE-ESD

All patients experienced transient $PaCO_2$ elevation compared with their values before SPACE. The median difference was 5.0 mmHg (range 1.2–7.9 mmHg). Other cardiopulmonary parameters (blood pressure, heart rate, and oxygen saturation) did

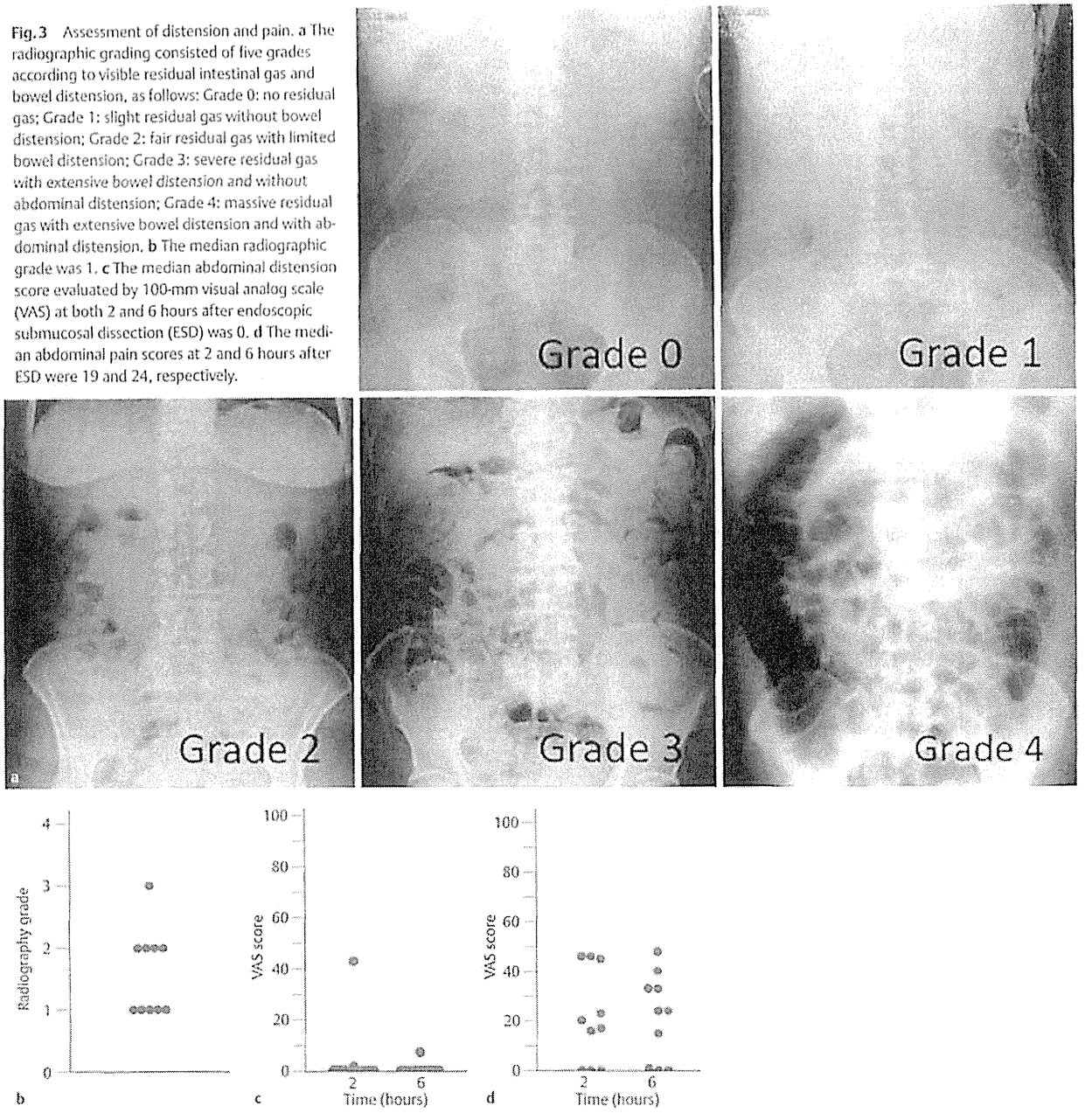

Fig. 3 Assessment of distension and pain. **a** The radiographic grading consisted of five grades according to visible residual intestinal gas and bowel distension, as follows: Grade 0: no residual gas; Grade 1: slight residual gas without bowel distension; Grade 2: fair residual gas with limited bowel distension; Grade 3: severe residual gas with extensive bowel distension and without abdominal distension; Grade 4: massive residual gas with extensive bowel distension and with abdominal distension. **b** The median radiographic grade was 1. **c** The median abdominal distension score evaluated by 100-mm visual analog scale (VAS) at both 2 and 6 hours after endoscopic submucosal dissection (ESD) was 0. **d** The median abdominal pain scores at 2 and 6 hours after ESD were 19 and 24, respectively.

not exhibit clinically significant changes during ESD (Wilcoxon's rank sum test). No patient developed hypotension and/or arrhythmia during the procedure.

Outcomes of ESD

En bloc resection with negative margins was achieved in all 10 patients (© Table 2). No patients developed mediastinal or subcutaneous emphysema after ESD. The median hospital stay was 10 days.

Distension and pain

Abdominal radiographs taken immediately after ESD revealed minimal distension of the small intestine, with a median radiographic grade of 1 (mild distension) (© Fig. 3a,b). The majority of patients did not complain of post-procedural abdominal distension, with a median score on VAS at both 2 and 6 hours of 0 (© Fig. 3c). Median post-procedural abdominal pain at 2 and 6 hours was 19 and 24, respectively (© Fig. 3d).

Discussion

Insufflation is a fundamental and important process to ensure optimal visualization and working space during endoscopic procedures [1]. In flexible gastrointestinal endoscopy, insufflation is used at the discretion of the endoscopist, irrespective of intraluminal pressure. Recent advancements in endoscopic instrumentation and techniques have resulted in more lengthy and complicated endoscopic procedures, and therefore more intelligent insufflation is required [1–6].

Using the dedicated overtube system described in this report, automatic endoscopic insufflation was achieved inside the gastro-

intestinal tract. The system involves CO_2 being delivered via the overtube and anti-leak valve adaptor, which act in a similar way to a "port" during laparoscopic surgery. A constant pressure environment was achieved inside the gastrointestinal tract without occluding the downstream intestine. In a porcine experimental model, esophageal ESD under SPACE was performed safely, and it shortened the procedure time by 20% [7].

The study has successfully shown that the SPACE system can be used safely in humans. The procedure was completed under SPACE alone in 8 of the 10 patients. There were no adverse events of Grade 3 or above. Despite $PaCO_2$ values becoming transiently elevated after the procedure, there were no symptoms associated with hypercapnia. Minimal post-procedural bowel distension was observed.

Although the true effectiveness of SPACE has not been elucidated, it is theoretically beneficial for the following reasons: 1) SPACE allows for optimal and highly reproducible visualization; 2) total CO_2 consumption may be reduced, resulting in less discomfort and pain after the procedure; and 3) SPACE liberates the endoscopist from the manipulation of the air and/or water button during the procedure.

The study has several limitations. The sample size was small, and no control arm was included; therefore, the true superiority of SPACE over manual insufflation has not been confirmed. In addition, all procedures were performed by a single endoscopist. To further clarify the feasibility and safety of SPACE, a larger clinical trial, ideally a randomized, controlled trial comparing SPACE with manual insufflation, is needed.

In conclusion, this study successfully demonstrated that SPACE is clinically safe and feasible for esophageal ESD using a currently available flexible gastrointestinal endoscope, a surgical insufflator, and the newly developed overtube system. Although the true effectiveness of the system must be verified in further clinical trials, SPACE might become a key technology in future endoscopic interventions.

Competing interests: None

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Surgical Strategy for the Gastric Gastrointestinal Stromal Tumors (GISTs) Larger Than 5 cm: Laparoscopic Surgery is Feasible, Safe, and Oncologically Acceptable

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Background: The efficacy and feasibility of laparoscopic surgery (LAP) for gastric GISTs > 5 cm has not been adequately assessed. Here we investigated the clinical outcomes of these patients.

Patients and Methods: Twenty-seven consecutive patients who underwent resection for gastric GISTs > 5 cm were enrolled in this retrospective study. We assessed the tumor characteristics, surgical outcomes, tumor recurrence, and patient survival in the open surgery (OPEN) group and in the LAP group.

Results: The tumor size in the OPEN group was larger than that in the LAP group, but there were no differences in the mitotic count. There were no differences in operative complications. Finally, there were no differences in the disease-free and no patients in the LAP group died.

Conclusions: In patients with gastric GISTs > 5 cm, LAP can be performed with outcomes equivalent to those of OPEN if patient selection and intraoperative judgment are appropriate.

Key Words: gastrointestinal stromal tumor, laparoscopic surgery, gastric GIST, large GIST, minimal invasive surgery, intraoperative judgment

(*Surg Laparosc Endosc Percutan Tech* 2014;00:000–000)

The clinical practice guidelines for the management of gastrointestinal stromal tumors (GISTs) of the National Comprehensive Cancer Network (NCCN) and the Japanese Study Group on GIST note that surgical resection is the preferred first-line therapy for GISTs.[1,2] Because lymph node metastasis is rare in GISTs, lymphadenectomy performed for gastric adenocarcinoma is not a standard component of surgical management for these mesenchymal neoplasms. The primary goal is to achieve anatomic or nonanatomic resection with negative margins, and laparoscopic surgery (LAP) is feasible and appropriate for some patients with gastric GISTs < 5 cm.[2] However, there is no strong evidence supporting 5 cm as the most appropriate cutoff size for LAP.[2] Although clinical practice guidelines recommend an open surgical approach for patients with a tumor > 5 cm, depending on tumor location and growth patterns, LAP can be considered an option and is performed for some larger tumors at some facilities. Notably, LAP for gastric GISTs > 5 cm has been performed recently and is reported to be feasible and safe.[3]

In our hospital, we have recommended LAP for patients with gastric GISTs > 5 cm, but we do not hesitate to convert to open surgery if indicated. After LAP begins, we carefully evaluate the tumor size, location, and characteristics to make sure that capsule rupture is unlikely during further manipulation. Only then do we make the decision to continue with LAP. This study aimed to evaluate the validity and safety of LAP versus open surgery in patients with gastric GISTs > 5 cm.

PATIENTS AND METHODS

This retrospective study was approved by the Institutional Review Board. Of the 98 patients with gastric GIST who underwent surgery at our department between 1995 and 2011, 27 patients were enrolled in this study. All had tumors > 5 cm, received no preoperative neoadjuvant chemotherapy, and showed no clinically malignant factors during the operation.[3] The sample included all patients scheduled for either LAP or open surgery (OPEN). The surgical approach, that is, LAP or OPEN, was selected according to the surgeon's preference. Partial gastrectomy was positively adapted as the operative procedure and it was performed in compliance with the 3 oncologic principles in the relevant clinical practice guidelines: (1) the tumor was not touched directly; (2) resection was performed with an appropriate surgical margin; and (3) full-thickness resection of the gastric wall was performed. However, in some patients, the operative procedure was converted to either distal or proximal gastrectomy when deemed necessary during the operation because of the tumor location, growth pattern, or possible margin of resection. As a rule, the decision to perform OPEN or LAP in a patient was left to the discretion of the surgeon. LAP was indicated even in patients with tumors > 5 cm if it was judged to be safe after considering the tumor location, growth pattern, and other factors. OPEN was chosen preoperatively in patients in

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whom LAP was judged to be difficult because of the patient's general condition, the tumor size, or the tumor location.

All data were recorded in a prospectively compiled database. We compared the following in the LAP and OPEN groups: age, sex, tumor location, growth pattern, preoperative tumor size, operative procedure, operation time, volume of blood loss, presence/absence of intraoperative accidents, postoperative hospital stay, presence/absence of postoperative complications, tumor size in resected specimens, mitotic count, risk according to the Fletcher classification,[4] postoperative follow-up period, presence/absence of recurrence, presence/absence of postoperative adjuvant chemotherapy, disease-free survival rate, and overall survival period.

OPEN

As a routine in our hospital, a midline incision is made in the supraumbilical region, and the wound edge is protected using a wound retractor. After clinically malignant factors (peritoneal seeding, liver metastasis, and direct invasion)[5] are confirmed to be absent, dissection and vascular processing are performed around the tumor. The tumor is then excised using a stapling device. Intraoperative endoscopy is performed if necessary during tumor resection so that the stapling can be performed under endoscopic calibration. In patients with tumors located near the cardia or the pylorus, the defect created by tumor resection is closed manually to preserve the cardia or the pylorus. The defect is also closed manually to minimize stomach deformation in the case of patients in whom stapling of the tumor is performed along the lesser curvature, which is likely to increase gastric deformation.

LAP

Initially, exploratory LAP is performed through the supraumbilical port to rule out any clinically malignant factors. During this step, the surgeon should be careful to keep the tumor within the laparoscopic display to prevent injury to the pseudocapsule of the tumor by the tip of the laparoscopic forceps outside the visual field of the laparoscope. The operative procedure was converted from LAP to OPEN if the tumor was substantially outside the visual field of the laparoscope. If no clinically malignant factors are seen during exploratory LAP, indicating that LAP can be performed safely, additional working ports are placed and LAP is performed through 3 or 4 ports. The details of this procedure have been reported previously.[5] Briefly, intraoperative endoscopy with carbon dioxide insufflation is performed in all patients to determine the tumor location, the distance to the cardia or pylorus, and so forth. The tumor is resected using a stapling device when indicated. In patients in whom the tumor is located close to the cardia or pylorus or in those in whom stapling could cause massive gastric deformation, extracorporeal resection and hand sewing are performed by mini-laparotomy as appropriate. Each specimen is placed carefully in an isolation bag, and the wound created for the port is extended minimally to enable specimen delivery.

Statistical Analysis

All data were prospectively recorded in a database. The data from the OPEN group and from the LAP group were analyzed statistically using the computer program JMP8.0.2 (SAS Institute, Cary, NC). The Student t test, χ^2 test, and the Fisher exact test were used for statistical analysis, and $P < 0.05$ was considered to be statistically significant.

TABLE 1. Background Data of Patients

	OPEN (n = 15)	LAP (n = 12)	P
Age (y)	66 (37-76)	64 (18-78)	0.783
Sex, M/F (n)	10/5	7/5	0.656
Tumor size (cm)	7.5 (5.3-13.0)	5.5 (5.1-8.0)	0.032
Location (n)			
Upper	9	9	0.396
Middle	3	2	
Lower	3	1	
Lesser curvature	4	7	
Greater curvature	4	5	
Growth pattern (n)			0.484
Intragastric	6	3	
Wall	2	2	
Extragastric	7	7	

Data are represented as median (range).
n indicates number of patients.

RESULTS

Patient Characteristics

The clinical characteristics of the patients are summarized in Table 1. The preoperative tumor diameter was > 5 cm in all subjects, but the preoperative diameter in the OPEN group was significantly larger ($P = 0.032$). In the OPEN group, the tumor was located along the greater curvature in 4 patients and along the lesser curvature in 4 patients. In the LAP group, the tumor was located along the greater curvature in 7 patients and along the lesser curvature in 4 patients. Thus, there were no significant intergroup differences in terms of tumor location. The tumor growth pattern did not differ significantly between the 2 groups.

Surgical Outcome

The patients' surgical outcomes are summarized in Table 2. In the OPEN group, 2 patients with a tumor

TABLE 2. Surgical Procedure and the Surgical Outcome of Patients

	OPEN (n = 15)	LAP (n = 12)	P
Procedure (n)			
Partial/proximal/distal	12/2/1	12/0/0	0.118
Conversion (n)	—	3	
Stapling (n)			
Staple/hand sewn	10/5	9/3	0.667
Operative time (min)	110 (53-205)	125 (45-200)	0.453
Blood loss (mL)	80 (10-850)	15 (10-770)	0.215
Intraoperative complication (n)	0	0	
Posthospital stay (d)	15 (8-35)	11 (5-30)	0.523
Complication (n)	1*	1†	

Data are represented as median (range).
*Wound infection.
†Blood stream infection.

TABLE 3. Data of Patients With Conversion to Open Surgery With the Intraoperative Judgment

No.	Age (y)	Sex	Tumor Size (cm)	Location	Growth Pattern	Reason
1	66	M	7	Middle less	Extragastric	Dense adhesion to liver (suspicious of invasion)
2	70	M	7.5	Upper greater	Extragastric	Failure of the tumor into the visual field of the laparoscope by size and location
3	78	M	7.5	Upper greater	Extragastric	Failure of the tumor into the visual field of the laparoscope by size and location

located near the cardia underwent proximal gastrectomy, 1 patient with a giant tumor (14 cm) located in the corpus underwent distal gastrectomy, and the remaining 10 patients underwent partial gastrectomy. In the LAP group, laparoscopic partial gastrectomy was performed successfully in all patients. The operative procedure was converted to open surgery in 3 patients (Table 3). In patient no. 1, the tumor located along the lesser curvature showed extragastric growth and had adhered to the inferior surface of the left hepatic lobe (Fig. 1A). After direct tumor invasion (a clinically malignant factor) was ruled out by detailed laparoscopic observation, the adhesion was freed under laparoscopic guidance. However, the adhesion was dense and extensive, and laparoscopic manipulation was judged to involve a high risk of injury to the pseudocapsule of the tumor. Therefore, LAP was converted to OPEN, and combined resection of the liver floor with intense adhesion was performed (R0 surgery). In the other cases, we could not see the entire tumor in the field of the laparoscope because of tumor size, location, or growth pattern. Because there is a possibility of injury to the pseudocapsule of the tumor if the tip of the forceps is outside the visual field of the laparoscope (Fig. 1B), we decided to convert from LAP to OPEN. There were no differences in the resection or suturing techniques between the 2 groups. In addition, no intergroup differences were noted in terms of operation time or volume of blood loss (intention-to-treat basis). There were no intraoperative complications or serious postoperative complications in either group. The postoperative hospital stay period was 10 to 12 days.

Pathology Results

The tumor diameter of resected specimens, number of mitoses, and the Fletcher risk classification[4] category are shown in Table 4. The tumors were significantly larger in the OPEN group than in the LAP group ($P = 0.032$). However, there were no differences in the mitotic count or the Fletcher risk classification between the 2 groups.

Oncologic Outcome

The long-term outcomes of patients after surgery are summarized in Table 5. The median follow-up period was 69 months in the OPEN group and 57 months in the LAP group. Postoperative adjuvant chemotherapy was administered to 3 patients in the OPEN group and to 1 patient in the LAP group. The disease-free survival and overall survival of all patients are shown. Two patients in the OPEN group and 1 patient in the LAP group had recurrence. There was no significant difference in recurrence-free survival between the 2 groups ($P = 0.317$). During follow-up, 2 patients in the OPEN group died, 1 from pancreatic cancer, whereas no death was seen in the LAP group ($P = 0.003$).

DISCUSSION

According to the NCCN guidelines, surgery is the standard first-line therapy for gastric GISTs.[1] Partial gastrectomy, which preserves organ function and integrity, is the first-choice procedure because it does not require local lymph node excision. Therefore, LAP is preferred for patients with relatively small tumors, and many studies, including the one that we conducted,[5] have established the validity and safety of LAP in patients with tumors with a diameter of 5 cm or smaller.[6,7] On the basis of these findings, a description of LAP for GISTs < 5 cm was added to the revised versions of Japanese clinical practice guidelines for management of GISTs, with the condition that "LAP should be performed by experienced surgeons." There are few comprehensive reports that focus on gastric GISTs > 5 cm in diameter. Although a case report of hand-assisted LAP by Yano et al[8] and reports by Karakousis et al[9] and by De Vogelaere et al[10] describe patients with tumor diameters > 5 cm, the optimal size cutoff for LAP for larger GISTs has not been fully established. To the best of our knowledge, the present series is one of the largest series of cases with gastric GISTs > 5 cm. In addition, no other

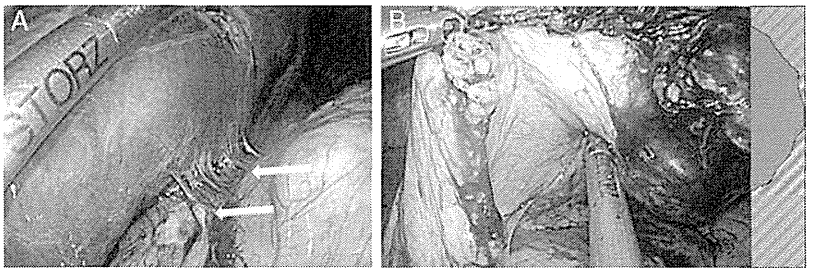

FIGURE 1. A, In 1 patient in the laparoscopic group, exploratory laparoscopy revealed dense and extensive adhesions (white arrows). Laparoscopic manipulation was judged to involve a high risk of injury to the pseudocapsule of the tumor. Accordingly, open surgery was performed instead of laparoscopic surgery. B, The region that is outside of the visual field of the laparoscope is indicated using shading.

TABLE 4. Histopathologic Findings and Risk Classification of Patients

	OPEN (n = 15)	LAP (n = 12)	*P*
Tumor size (cm)	8.0 (5.3-22)	7.3 (5.1-8.0)	0.036
Mitotic count (n)			0.585
< 5/50 HPF	10	9	
5≪10/50 HPF	2	2	
> 10/50 HPF	3	1	
Fletcher classification (n)			0.152
Very low	0	0	
Low	0	0	
Intermediate	7	9	
High	8	3	

Data are represented as median (range).
HPF indicates high power field.

TABLE 5. Follow-up Results of Patients

	OPEN (n = 15)	LAP (n = 12)	*P*
Follow-up (mo)	69 (13-154)	57 (7-120)	
Recurrence (n)	2	1	0.317
Death (n)	2	0	0.003

Data are represented as median (range).

study has reported the characteristics of the LAP group in detail.

We believe that tumor size, location, and growth pattern are particularly important factors in determining the feasibility and safety of LAP for gastric GISTs. We did not perform LAP in patients with tumors that were 10 cm or larger in diameter and, at the beginning, open surgery was selected as the operative approach for these patients. In this group of patients, the preoperative evaluation indicated difficulty in adequate visualization of the entire tumor during laparoscopy and the possibility of injury to the pseudocapsule of the tumor by the tip of the forceps outside of the visual field of the laparoscope (Fig. 2). Because tumor spillage can result in catastrophic consequences in terms of disease progression, recurrence, and poor survival,[11,12] we consider LAP being contraindicated for these patients.

Regarding tumor location, mobilization around the tumor is often technically difficult if the tumor is located along the lesser curvature. This location can increase the risk of unexpected injury to the pseudocapsule, attainment of an inadequate resection margin, stenosis, or gastric deformation when mobilization or stapling is performed despite the risks. Therefore, mini-laparotomy combined with laparoscopy or open surgery should be used for such patients. As in the report of Karakousis et al,[9] patients with tumors located adjacent to the esophagogastric junction were excluded from LAP. Thus, tumor location needs to be considered carefully when determining the indication for partial gastrectomy with LAP. In patients with a tumor located close to the cardia or pylorus, it is advisable to preserve the cardia and pylorus as much as possible by selecting OPEN rather than LAP. However, oncologic

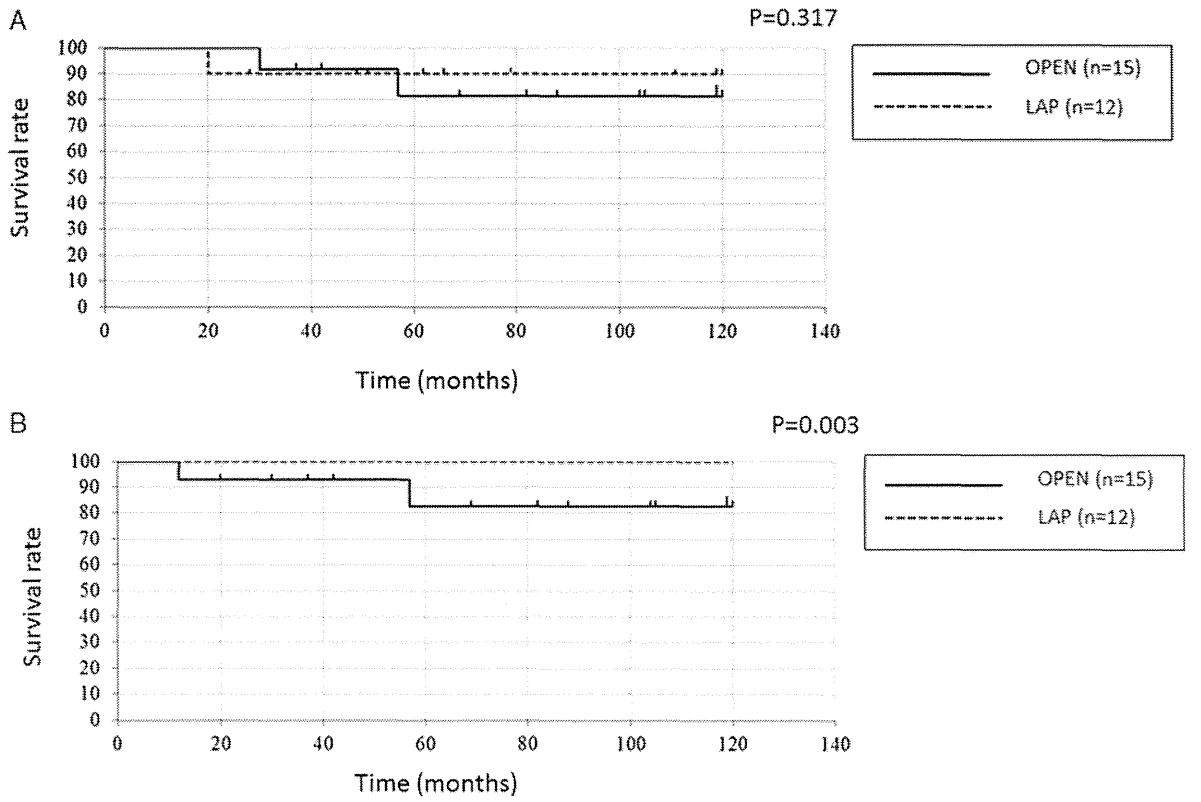

FIGURE 2. Disease-free survival curve for the open surgery (OPEN) group and the laparoscopic surgery (LAP) group (A). Overall survival curve for the OPEN group and the LAP group (B).

curability should be given preference over preservation of organ function. Proximal or distal gastrectomy was selected in 3 of our patients.

Despite the large size of the tumor, the gastric stapling under laparoscopic guidance is still technically easier in patients with extragastric tumor growth compared with those with intragastric tumor growth. However, if the base of the tumor is wide, it is difficult to obtain an adequate margin of resection in patients even with extragastric tumor growth, and stapling in such patients can lead to a positive margin or injury to the pseudocapsule. In such patients, the surgeon should consider converting the operative procedure to OPEN at an early stage. In addition, care should be taken to avoid unexpected injury to the pseudocapsule by the manipulation of forceps in patients with a tumor that protruded out of the stomach. Conversely, we encountered patients with intragastric tumor growth in whom stapling under laparoscopic guidance was possible if the margin of resection could be ensured with concomitant use of intraoperative endoscopy.

We performed exploratory laparoscopy in all patients in whom LAP was planned based on the preoperative work-up. LAP was started after confirming that there were no clinically malignant factors and that resection seemed appropriate and possible from an oncologic viewpoint. Three of the (planned) LAP patients were converted to open surgery. In 1 patient, a tumor showed extragastric growth and was firmly adhered to the inferior surface of the liver. There was a high risk of injury to the pseudocapsule in this patient, and thus we converted to open surgery. Postoperative pathologic examination did not show invasion of the tumor into the liver, but rapid conversion to open surgery seems essential for such patients. In the other 2 patients, we could not frame the entire tumor in the field of the laparoscope owing to their size, location, and growth pattern, and therefore we decided to convert to OPEN to avoid the danger of tumor injury. The perioperative outcome of LAP was comparable to that of OPEN if the oncologic principles were followed, and the long-term prognosis after LAP was not inferior to that after open surgery.

Our present data show that it is feasible to perform LAP safely in patients with tumors >5 cm with outcomes that are not inferior to OPEN, but these principles should be followed: (1) the patients should be selected carefully on the basis of preoperative data; (2) the decision to change the resection technique to open surgery should be made immediately if warranted by intraoperative findings; and (3) oncologic principles must always be followed.

We conclude that LAP can be performed safely in patients with gastric GISTs >5 cm, if patient selection and intraoperative judgment are appropriate. Notably, the perioperative outcomes and long-term prognosis of LAP were not inferior to OPEN in this study. The indications for LAP may thus be expanded to include patients with gastric GISTs >5 cm; however, long-term follow-up data and a larger prospective multicenter study are needed to confirm these findings.

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ORIGINAL ARTICLE

Single-incision laparoscopic partial gastrectomy for gastric submucosal tumors without compromising transumbilical stapling

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Keywords
Gastric submucosal tumor; GIST; SILS

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Abstract

Introduction: Although SILS has become an increasingly popular type of surgery, its application for gastric submucosal tumors (SMT) has been only sporadically reported. We herein describe 12 recent cases with gastric SMT located in the greater curvature or anterior wall. The aim is to validate technical feasibility and safety of single-incision laparoscopic partial gastrectomy. Thus far, this is one of the largest series of patients with gastric SMT who underwent SILS.
Methods: From July 2009 to April 2013, single-incision laparoscopic partial gastrectomy was attempted in 12 consecutive patients with gastric SMT. Three trocars were assembled in the umbilical incision, and the lesion was mobilized and staple-resected with endoscopic stapling devices.
Results: SILS surgery was successfully completed without any additional trocars. The median operating time was 96.5 min, and median blood loss was 7.5 mL. The median tumor size was 30 mm, with histopathologic diagnosis of gastrointestinal stromal tumor (10) and schwannoma (2). There was no immediate postoperative morbidity. During a median follow-up of 12 months, all patients were on full regular diet without any gastrointestinal symptoms.
Conclusion: SILS with transumbilical gastric stapling is a safe and practical alternative to conventional multiport laparoscopy in patients with gastric SMT, except for cases originating in the lesser curvature and close to the cardia/ pylorus.

Introduction

With the recent improvements in instrumentation and procedures, SILS has become increasingly popular for various gastrointestinal procedures (1–3). Theoretically, gastric submucosal tumors (SMT) are one of the best candidates for SILS, as partial gastrectomy for gastric SMT is a relatively simple procedure that requires no lymph node dissection (4,5). However, SILS only offers a limited range of motion. For example, particularly when the stapling device is inserted via the umbilicus, stapling becomes complicated because of the device's limited handling among the crowded transumbilical instruments.

Despite the potential that SILS offers, few reports are available in the surgical literature (6,7), and the role of SILS in the surgical management of gastric SMT is not yet fully understood. The aim of this study was to evaluate the feasibility and safety of SILS partial gastrectomy for gastric SMT, with technical considerations including specimen retrieval and application of transumbilical gastric stapling. To our knowledge, this is one of the largest series of patients with gastric SMT who underwent SILS.

Table 1 Preoperative characteristics of 12 SILS for gastric SMT at a single institution (July 2009–April 2013)

				Preoperative diagnosis			
Case no.	Age (years)	Gender	BMI (kg/m^2)	Growth appearance	Location		Tumor (mm)
1	49	Male	22.4	Exogastric	Middle	Greater curvature	30
2	55	Male	19.1	Exogastric	Middle	Anterior wall	25
3	60	Male	25.9	Exogastric	Upper	Greater curvature	30
4	69	Male	22.7	Intramural	Middle	Anterior wall	25
5	65	Male	17.8	Exogastric	Upper	Anterior wall	20
6	54	Male	20.7	Exogastric	Upper	Greater curvature	30
7	60	Male	25.4	Exogastric	Upper	Greater curvature	35
8	63	Male	25.0	Exogastric	Upper	Greater curvature	30
9	50	Female	21.5	Exogastric	Middle	Posterior wall	24
10	64	Male	22.5	Intramural	Upper	Greater curvature	28
11	47	Male	15.6	Exogastric	Middle	Anterior wall	35
12	80	Male	22.4	Exogastric	Middle	Greater curvature	30

SMT, submucosal tumor.

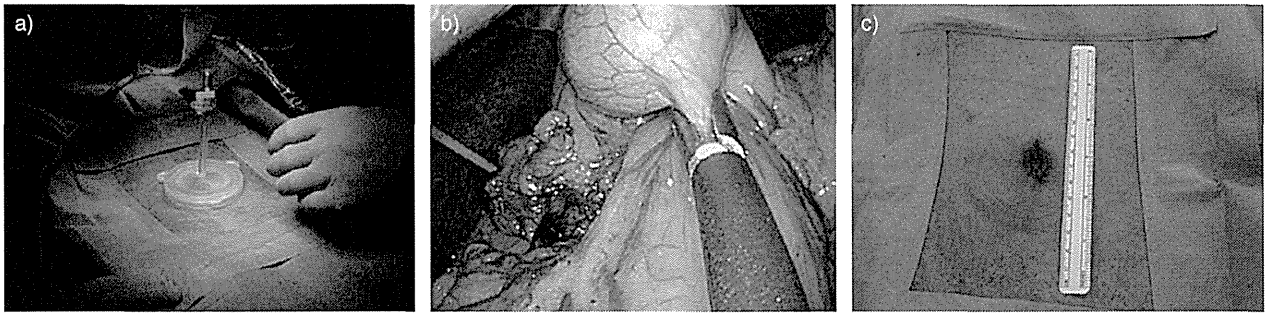

Figure 1 (a) An infraumbilical incision was made by pulling out the umbilicus. The peritoneum was incised, an EZ Access port (HAKKO) was inserted, and 5-mm trocars were then inserted through the port. (b) The stomach was clamped on the resection line, and intraoperative endoscopy was simultaneously performed. (c) The wound was closed with absorbable sutures.

Materials and Methods

Patients

For 12 consecutive patients with gastric SMT, SILS partial gastrectomy was offered as an alternative to conventional multiport laparoscopic partial gastrectomy between July 2009 and April 2013. All patients met our inclusion criteria for SILS partial gastrectomy: (i) tumor size less than 5 cm; (ii) exogastric/intramural tumor growth; (iii) no lesser curvature involvement; and (iv) lesions not adjacent to the cardia or pylorus. There were 11 men and 1 woman, with a median age of 60 years (Table 1). All patients underwent preoperative work-up using esophagogastroduodenoscopy and CT, which confirmed size, location and growth pattern of the tumors. Fine-needle aspiration cytology was performed on two patients with preoperative diagnosis of gastrointestinal stromal tumor (GIST).

Surgical technique

A single, vertical, 25-mm transumbilical incision was made by pulling out the umbilicus. A commercially available access device for SILS (EZ Access, HAKKO, Nagano, Japan) was assembled, and carbon dioxide pneumoperitoneum was created, with intra-abdominal pressure of 12 mmHg (Figure 1a). Three 5-mm trocars were used for the flexible 5-mm laparoscope (LTF TYPE VP, Olympus Medical Systems, Tokyo, Japan) and laparoscopic graspers.

After the tumor was located, the greater omentum was divided using ultrasonic coagulating shears. We always performed wide mobilization while retracting the stomach around the tumor without grasping the tumor itself. The resection line was designed by provisional clamping (Figure 1b). At this point, intraoperative endoscopy was performed to exclude gastric passage distur-

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Table 2 Postperative characteristics of 10 SILS for gastric SMT at a single institution (July 2009–April 2013)

Case no.	Growth appearance	Location		Tumor (mm)	Operating time (min)	Blood loss (mL)	Pathological diagnosis	Ancillary use
1	Exogastric	Middle	Greater curvature	30 × 25 × 25	65.0	10.0	GIST	None
2	Exogastric	Middle	Anterior wall	27 × 25 × 23	59.0	Neg	GIST	None
3	Exogastric	Upper	Greater curvature	31 × 25 × 23	110.0	Neg	Schwannoma	Done
4	Intramural	Middle	Anterior wall	25 × 20 × 20	102.0	Neg	GIST	Done
5	Exogastric	Upper	Anterior wall	18 × 16 × 15	57.0	Neg	GIST	None
6	Exogastric	Upper	Greater curvature	30 × 25 × 17	134.0	10.0	GIST	Done
7	Exogastric	Upper	Greater curvature	38 × 35 × 28	123.0	30.0	GIST	Done
8	Exogastric	Upper	Greater curvature	30 × 24 × 19	104.0	Neg	GIST	Done
9	Exogastric	Middle	Posterior wall	24 × 20 × 18	129.0	15.0	Schwannoma	None
10	Intragastric	Upper	Greater curvature	28 × 22 × 15	91.0	10.0	GIST	Done
11	Exogastric	Middle	Anterior wall	36 × 25 × 15	66.0	5.0	GIST	Done
12	Exogastric	Middle	Greater curvature	30 × 25 × 25	83.0	10.0	GIST	None

GIST, gastrointestinal stromal tumor; neg, negligible amount; SMT, submucosal tumor.

bance and/or any extreme deformity of the gastric remnant. One of the 5-mm trocars was then exchanged for a 12-mm trocar, and stapled-resection was performed using endoscopic linear staplers. The specimen was isolated in a specimen bag and retrieved via the umbilical wound. The wound was closed with absorbable sutures (Figure 1c).

Results

Table 2 depicts the surgical results. SILS partial gastrectomy was completed in all patients without addition of ports. In 7 of 12 cases, we elevated the left lateral segment of the liver with a 2-mm loop-type retracting device (Mini-Loop Retractor II, Covidien, Norwalk, USA) to fully expose the lesion. Median operating time was 96.5 min (range, 57.0–134.0 min), and the median blood loss was 7.5 mL (range, 0.0–30.0 mL). The median tumor size was 30 mm (18–38 mm). In all cases, the postoperative course was rapid and uneventful.

For 10 of 12 patients, gastric GIST was confirmed by immunohistochemistry. In all patients, the margins were free of disease. According to Fletcher's classification, there was 1 patient with "very low risk," 10 with "low risk," and 1 patient with "intermediate risk." Two cases of gastric schwannoma were also confirmed. During a median follow-up of 12 months (range, 1–41 months), there were neither tumor recurrences nor metastases. Although one patient continued to need H_2 receptor antagonist to resolve his preexisting reflux symptom, other patients had no postoperative complaints, such as anorexia, dyspepsia, or epigastric discomfort. On esophagogastroduodenoscopy 1-year after surgery (eight patients), there was no food residue and/or bile reflux in the remnant stomach. The function of the gastric remnant was considered well preserved in this series.

Discussion

Complete gross tumor resection with preservation of organ function is a standard treatment for gastric GIST (8–12). Because GIST usually grows out from the primary organ instead of being diffusely infiltrating, the procedure does not require wide negative margins. In addition, lymph node dissection is not necessary because GIST rarely metastasizes to the lymph nodes (9,10). Under these circumstances, laparoscopic surgery is equivalent to traditional open surgery. Although in a retrospective study on dozens of cases, laparoscopic surgery for GIST and SMT was reported to be less invasive than open surgery, and the complications of both operations were equivalent (5,11–13). Moreover, it has been reported that laparoscopic resection of GIST <5 cm in diameter is as oncologically feasible as open surgery from medium- to long-term standpoints. The National Comprehensive Cancer Network Clinical Practice Guidelines and clinical practice guidelines for GIST in Japan recently suggested that experienced surgeons may consider the laparoscopic technique for tumors less than 5 cm in diameter (14,15). The stomach is a large organ centered in the abdomen, and in appropriate circumstances, the stomach can be partially resected with endoscopic stapling devices. As we previously reported, we aggressively apply laparoscopic resection to gastric GIST and achieve acceptable surgical results and oncologic outcomes (5).

SILS is a recent evolution in laparoscopic surgery that allows a number of forceps to be inserted via a single incision. The possible advantages of SILS include improved cosmesis and reduced tissue damage because fewer trans-abdominal ports are needed (16). In contrast, SILS has some disadvantages, most which are technical concerns: conflicts between the laparoscope and operating devices, in-line movement of instruments, limited

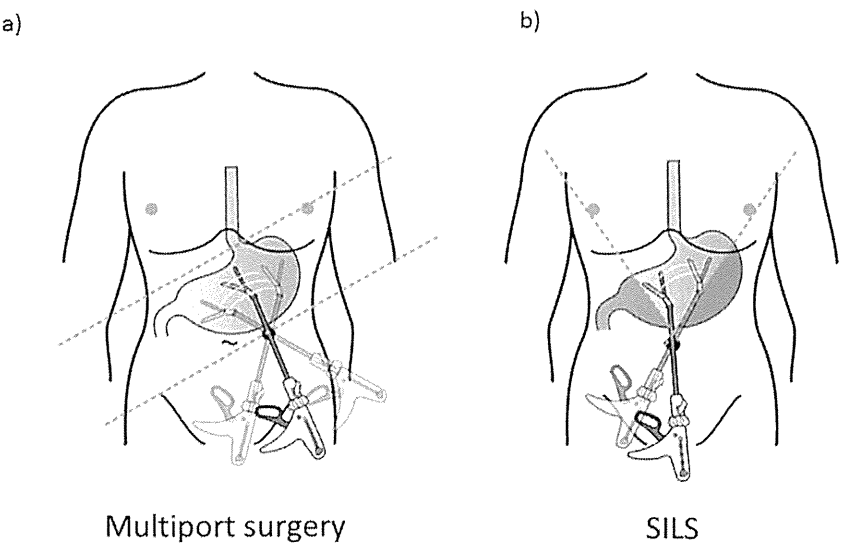

Figure 2 (a) In multiport laparoscopic surgery, a digital stapling device can be managed and is able to reach around the stomach. (b) However, in SILS, handling of a digital stapling device is circumscribed, and the device must be inserted in the direction of the long axis of the stomach.

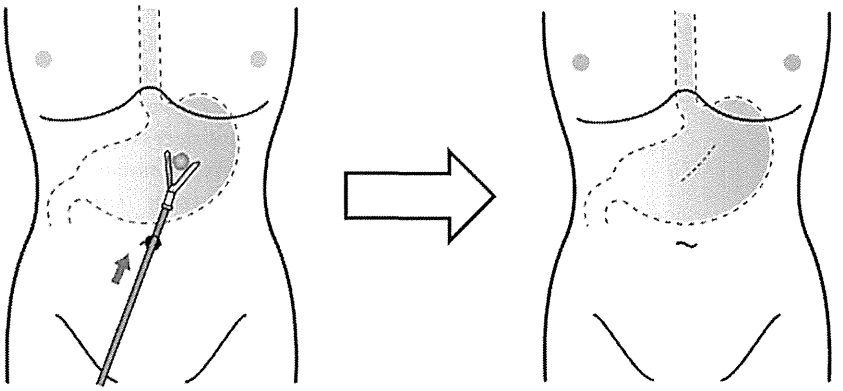

Figure 3 In SILS, the endoscopic stapling device can only be inserted in the direction of the long axis of the stomach.

organ retraction, and difficultly in tissue triangulation (17).

Although there are some reports that SILS has been safely performed for GIST (6,7,18,19), they did not deal with any technical issues (e.g. difficulty handling the endoscopic linear stapler) or how they were resolved. In the present series, the conflict among transumbilical devices was partially resolved by using a SILS access device, which allowed more flexible port placement. By ensuring that there was distance between each port, we could obtain a practical working angle between left-handed and right-handed instruments. As a result, most laparoscopic dissection could be completed with the conventional parallel technique. We also resolved the retraction issue by using a 2-mm loop retracting device. By carefully including the diaphragmatic fascia in the loop, we effectively retracted the left lateral segment of the liver. This retraction was robust and the surgical exposure was stabilized throughout the procedure.

One remaining challenge specific to single-incision laparoscopic partial gastrectomy, was transumbilical surgical stapling. In conventional multiport laparoscopic surgery, the stapling device is inserted via the left mid-abdomen. This allows for an adjustable staple line formation for virtually all lesions in the stomach (Figure 2). In SILS, the stapler is inserted via the umbilicus, so the insertion direction of the stapling device is almost always parallel to the organoaxial of the stomach (Figure 3). The stapling becomes further complicated as a result of the limited handling of the stapling device in the crowed transumbilical instruments. To accomplish appropriate gastric stapling in such adverse condition, we adopted the "move the ground" technique (Figure 4). Trying to adjust the staple line by moving the stapler is almost always unsuccessful. Instead of moving the stapler, we brought the lesion to the staple by using an articulated grasper. Although this technique requires prior wide mobilization of the stomach, it is extremely useful in SILS gastrectomy where handling of the stapling device is limited.

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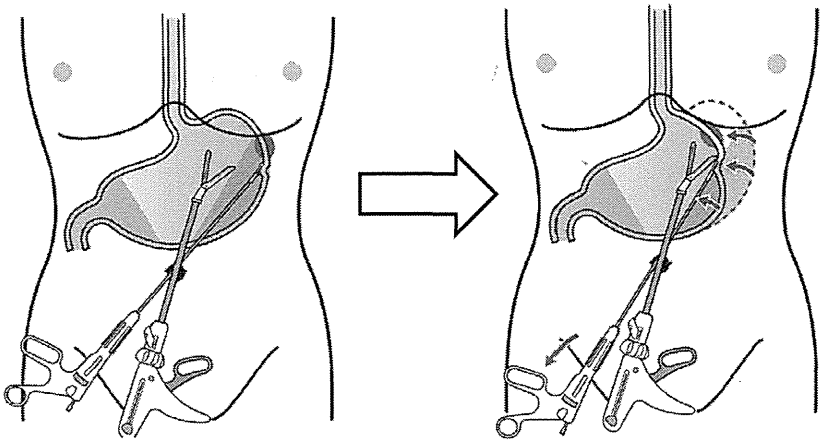

Figure 4 In a stapled resection, adjusting the stapling line by moving the stapler is almost always unsuccessful. Instead of moving the stapler, we brought the lesion to the stapler.

Any type of surgical approach for gastric SMT should be validated in terms of oncologic clearance and gastric remnant function. SILS is still a new technology, and therefore, we should carefully select candidates until we obtain conclusive data regarding oncologic and functional outcomes. At this time, we restrict the application of SILS to lesions on the anterior gastric wall or greater curvature that can be resected with a stapling device. Extended follow-up is mandatory to validate oncologic appropriateness for this small group of patients.

SILS is feasible, safe and reasonable for gastric SMT, without compromising transumbilical gastric stapling. This technique is an attractive and practical alternative to conventional multiport laparoscopy in carefully selected patients, and it offers improved cosmetic outcomes.

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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Determinants of Response to Neoadjuvant Chemotherapy for Esophageal Cancer Using ^{18}F-fluorodeoxiglucose Positron Emission Tomography (^{18}F-FDG-PET)

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ABSTRACT

Background. ^{18}F-FDG-PET is potentially useful for evaluating response to neoadjuvant therapy for esophageal cancer. However, the optimal ^{18}F-FDG-PET parameter for evaluating the response to therapy and survival has not been established. This study aimed to select the best of the two parameters of fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography (PET): decreased ratio of maximal standardized uptake (SUV_{max}-DR) or absolute value of posttreatment SUV_{max} (post-SUV_{max}), in predicting response and survival of patients with esophageal cancer who underwent neoadjuvant chemotherapy.

Methods. The study subjects were 211 consecutive patients with esophageal cancer who received neoadjuvant chemotherapy followed by surgery. ^{18}F-FDG-PET was performed before and 2–3 weeks after completion of neoadjuvant chemotherapy in assessment with pretreatment SUV_{max} (pre-SUV_{max}), post-SUV_{max} and SUV_{max}-DR.

Results. The mean SUV_{max} decreased during neoadjuvant chemotherapy from 11.4 to 5.8, and the mean SUV_{max}-DR was 49.4 %. Both post-SUV_{max} and SUV_{max}-DR correlated significantly with pathological response, although neither post-SUV_{max} nor SUV_{max}-DR could distinguish pathological complete response from pathological good response. The 5-year survival rate was significantly higher in patients with SUV_{max}-DR of >50 % than those with <50 % (56.5 vs. 39.6 %, $p = 0.0137$), and also significantly higher in patients with post-SUV_{max} of <3.5 than those with >3.5 (62.2 vs. 35.1 %, $p < 0.0001$). Multivariate analysis identified post-SUV_{max} value, but not SUV_{max}-DR, as an independent prognostic factor in patients who underwent neoadjuvant chemotherapy.

Conclusions. Post-SUV_{max} is more useful for predicting survival of patients with esophageal cancer who undergo neoadjuvant therapy followed by surgery, although both SUV_{max}-DR and post-SUV_{max} equally correlate with pathological response.

Esophageal cancer is one of the most aggressive gastrointestinal cancers. Esophagectomy is the standard treatment for advanced esophageal cancer, but the reported 5-year survival rates rarely exceed 35 % even though curative resection is performed.[1,2] To improve prognosis, neoadjuvant therapy such as chemoradiotherapy or chemotherapy followed by surgery is widely accepted as treatment for advanced esophageal cancer.[3–8] However, only patients who experience good response to neoadjuvant therapy experience survival benefit from it.[9–11]

Fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography (PET) is a well-established functional imaging modality and used for the diagnosis and staging of esophageal cancer.[12–14] In addition, there is increasing evidence that ^{18}F-FDG-PET is useful for evaluation of the response to neoadjuvant therapy in patients with esophageal cancer.[15,16] Several studies have demonstrated that decrease in FDG uptake ratio early during neoadjuvant therapy can predict pathological response and survival.[17–19] Other studies have demonstrated that a decrease in FDG uptake ratio after completion of neoadjuvant therapy correlates well with

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pathological response and survival.[20–22] Thus, decrease in FDG uptake is used to evaluate the response to therapy and survival of patients who undergo neoadjuvant therapy followed by surgery. The absolute value of FDG uptake after completion of neoadjuvant therapy has also been used for assessment of response to such therapy and prognosis. Several studies demonstrated that posttreatment FDG uptake could predict the response to neoadjuvant therapy and survival.[23,24] Thus, to evaluate the response to therapy and survival of patients with esophageal cancer who undergo neoadjuvant therapy followed by surgery, both a decrease in FDG uptake and posttreatment FDG uptake have been used. However, which is a more valuable method to predict response and survival—that is, decrease in FDG uptake or absolute value of FDG uptake after neoadjuvant therapy—is not clear at present.

In the present study, we determined the correlation between decrease in FDG uptake and absolute value of FDG uptake after neoadjuvant therapy and the response to such treatment and survival in patients with esophageal cancer who received neoadjuvant chemotherapy followed by surgery.

MATERIALS AND METHODS

Patients and Pretreatment Protocols

Between October 2000 and June 2011, a total of 570 patients with thoracic esophageal cancers underwent surgery at the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University. Among them, 292 patients underwent esophagectomy after neoadjuvant chemotherapy for thoracic esophageal cancer. Of these 292 patients, excluding 81 patients who did not undergo ^{18}F-FDG-PET scan before or after neoadjuvant treatment, 211 patients who underwent ^{18}F-FDG-PET scan before and after neoadjuvant treatment were included in the present study. All 211 patients were diagnosed with squamous cell carcinoma of the thoracic esophagus by pretreatment biopsy samples. Before treatment, all 211 patients were staged by CT and endoscopy, together with ^{18}F-FDG-PET scan. Lymph nodes were diagnosed as metastasis positive on CT scan if they were spherical and greater than 1.0 cm in maximum transverse diameter. Lymph nodes visible but smaller than 1.0 cm on the long axis on CT scan were regarded as metastasis-positive only if focal prominent 18-fluorodeoxy glucose (FDG) uptake, compared with normal mediastinal activity, was detected on the PET scan.

The neoadjuvant chemotherapy regimen in our hospital consists of 5-fluorouracil (5-FU) and cisplatin plus Adriamycin (ACF) or 5-FU and cisplatin plus docetaxel (DCF), as described previously.[25] In the ACF regimen, cisplatin was administered at 70 mg/m^2, Adriamycin at 35 mg/m^2 by rapid intravenous infusion on day 1, and 5-FU at 700 mg/m^2 administered by continuous intravenous infusion on days 1 through 7. Two courses of chemotherapy were used, separated by a 4-week interval. From July 2008, patients clinically diagnosed with T3–T4 tumors and/or cervical lymph node metastasis (M1lym) often received the DCF regimen instead of ACF. In the DCF regimen, cisplatin was administered at 70 mg/m^2, docetaxel at 70 mg/m^2 by rapid intravenous infusion on day 1, and 5-FU at 700 mg/m^2 administered by continuous intravenous infusion on days 1 through 5. Two courses of chemotherapy were used, separated by a 3-week interval.

The study protocol was approved by the Human Ethics Review Committee of the Osaka University Graduate School of Medicine.

Surgical Treatment

Surgical resection was performed 3–5 weeks after completion of the preoperative therapy. Our standard procedures consisted of subtotal esophagectomy with mediastinal lymphadenectomy via right thoracotomy, upper abdominal lymphadenectomy, reconstruction of a gastric tube, and anastomosis in the cervical incision. Of 211 patients, 89 underwent two-field lymphadenectomy and 122 patients underwent three-field lymphadenectomy. Of the 211 patients, 203 patients underwent curative resection (R0), whereas eight patients underwent noncurative resection (R1 or R2). Among 211 patients, operation-related death (within 30 days) occurred in one patient (0.5 %) who died of cardiac failure, and hospital death occurred in three patients (1.4 %), including two patients who died of recurrence during pulmonary complication and one patient who died of respiratory failure. All patients were included in the analysis.

Pathological Response to Chemotherapy

The degree of histopathological tumor regression in the surgical specimens was classified into five categories.[11,26,27] The extent of viable residual carcinoma at the primary site was assessed semiquantitatively on the basis of the estimated percentage of viable residual carcinoma in relation to the macroscopically identifiable tumor bed that was evaluated histopathologically. All specimens were examined independently by two observers (K.M. and K.T.) who were blinded to patient outcome and other clinical findings, and one pathologist (E.M.) confirmed their diagnosis. In case of a disagreement about a tumor grading, observers and the pathologist reviewed slides together and reached a consensus diagnosis. The percentage of viable