TABLE 1 Comparison of the patients' backgrounds

	ODG (n = 13)	LADG (n = 13)	P value
Age, years (median, range)	67 (45–76)	62 (38–79)	0.801
Sex ratio (M:F)	7/6	7/6	1.000
Performance status (0:1)	14/0	13/0	–
Total body weight, kg (median, range)	60.0 (39.8–75.5)	61.6 (42.2–66.9)	0.96
Lean body mass, kg (median, range)	48.3 (35.4–60.3)	46.6 (33.2–61.5)	0.88
Tumor site (body/antrum)	5/8	8/5	0.239
Pathological type (diff/undiff)	4/9	3/10	0.658
Clinical T factor (m/sm/mp)	4/4/5	7/2/4	0.45
Clinical N factor (0/1/2-)	13/0/0	12/1/0	0.308
Total protein, mg/dl (median, range)	7.5 (6.8–8.0)	7.4 (6.5–7.9)	0.65
Albumin, mg/dl (median, range)	4.6 (4.1–4.8)	4.5 (4.1–4.8)	0.545
Prealbumin, mg/dl (median, range)	26.6 (18.3–37.4)	27.6 (16.5–41.1)	0.801
WBC, μL (median, range)	4,800 (3,200–6,800)	5,800 (3,800–8,100)	0.072
Lymphocyte count, μL (median, range)	1,624 (1,095–2,713)	1,419 (946–2,639)	0.406
CRP, mg/dl (median, range)	0.045 (0.02–0.11)	0.06 (0.02–3.22)	0.11
IL-6, pg/ml (median, range)	0.8 (0.4–2.5)	1.5 (0.4–5.8)	0.091

TABLE 2 Surgical and pathological outcomes

	ODG (n = 13)	LADG (n = 13)	P value
Lymph node dissection (D1+/D2)	8/5	9/4	0.680
Reconstruction (Billroth-1/Roux-en-Y)	11/2	12/1	0.593
Bleeding, g (median, range)	190 (50–475)	40 (5–270)	0.009
Operation time, min (median, range)	154 (85–276)	267 (168–360)	0.005
Transfusion (no/yes)	14/0	13/0	–
Number of harvested lymph nodes (median, range)	43 (26–89)	40.5 (25–69)	0.938
Pathological T factor (m/sm/mp/ss/se)	6/6/0/0/1	7/4/2/0/0	0.324
Pathological N factor (N0/N1/N2)	10/3/0	11/1/1	0.359

or more anastomotic stenosis after surgery. No patients required additional nutritional support or additional hospitalization due to reduced food intake.

In both groups, the 12 patients who did not develop surgical morbidities were discharged 8–10 days after surgery following the ERAS protocol without variance.

Surgical Stress

The median WBC count (range) increased from 4,800 μL (3,200–6,800) to 7,100 μL (3,600–10,100) in the ODG group and from 5,800 μL (3,800–8,100) to 7,700 μL (4,800–13,200) in the LADG group. The median IL-6 (range) level increased from 0.8 pg/dl (0.4–2.5) to 36.3 pg/dl (14.4–405.0) in the ODG group and from 1.5 pg/dl (0.4–5.8) to 53.3 pg/dl (24.1–217.0) in the LADG group (Fig. 2). When comparing the WBC count and the IL-6 level before and after surgery between the groups, no significant differences were observed ($P = 0.375$ and $P = 0.545$, respectively). Furthermore, the median CRP (range) level increased from 0.045 mg/dl (0.02–0.11) to 1.9 mg/dl (0.2–12.93) at day 7 after surgery in the ODG group and from 0.06 mg/dl (0.02–3.22) to 1.38 mg/dl (0.3–10.19) at day 7 after surgery in the LADG group. There was no significant difference between two groups ($P = 0.626$).

Nutritional Status

The median total body weight (range) decreased from 60.0 kg (39.8–75.5) to 56.7 kg (40.7–75.4) in the ODG group and from 61.6 kg (42.2–66.9) to 58.6 kg (41.8–64.7) in the LADG group, whereas the median lean body mass (range) decreased from 48.3 kg (33.5–57.2) to 46.8 kg (35.4–57.6) in the ODG group and from 46.6 kg

(33.2–61.5) to 46.0 kg (33.2–57.8) in the LADG group (Fig. 3). When comparing the total body weight and lean body mass before and after surgery between the groups, no significant differences were observed ($P = 0.687$ and $P = 0.88$).

The median prealbumin (range) level decreased from 26.6 mg/dl (18.3–37.4) to 17.7 mg/dl (13.7–23.7) in the ODG group and from 27.6 mg/dl (16.5–41.1) to 18.3 mg/dl (10.5–28.7) in the LADG group, which was not statistically significant ($P = 0.88$). The median lymphocyte count (range) decreased from 1,624 µL (1,095–2,713) to 1,075 µL (886–1,721) in the ODG group and from 1,419 µL (946–2,639) to 1,440 µL (828–2,005) in the LADG group, which was not statistically significant ($P = 0.406$).

TABLE 3 Comparison of morbidity and mortality between the ODG and LADG groups

	ODG ($n = 13$)	LADG ($n = 13$)	P value
Any complications (≥grade 2)	1	1	1.000
Anatomic leakage	0	0	–
Anatomic stenosis	0	0	–
Pancreatic fistula	1 (grade 3A)	0	0.326
Abdominal abscess	0	0	–
Pneumonia	0	0	–
Small-bowel obstruction	0	0	–
Transient ischemic attack	0	1 (grade 2)	0.326
Morbidity	0	0	–

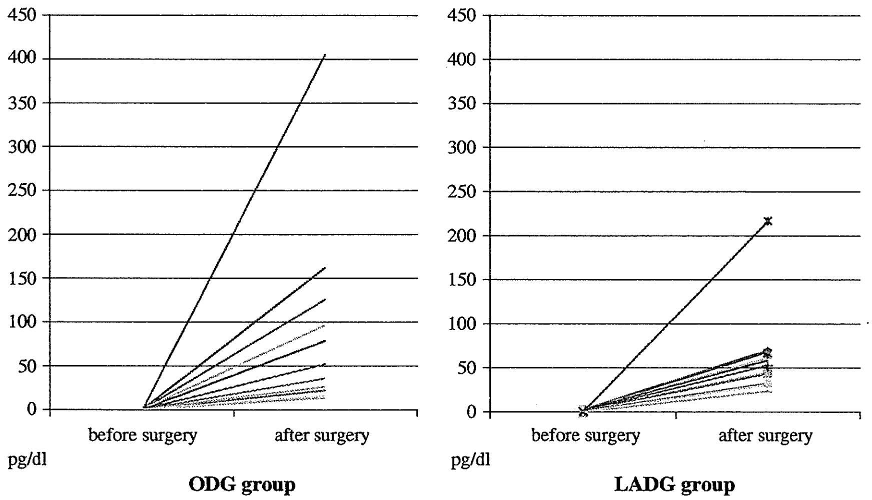

FIG. 2 Comparison of the changes in IL-6 between the laparoscopy-assisted distal gastrectomy group and the open distal gastrectomy group

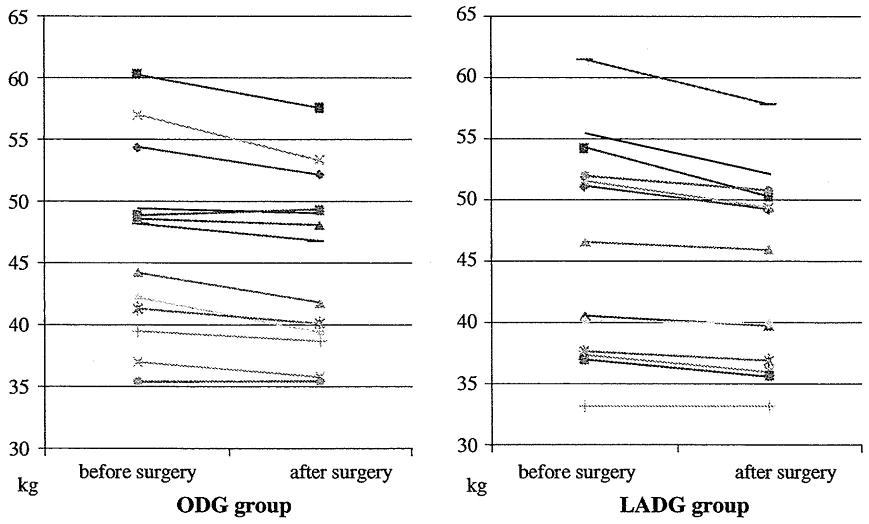

FIG. 3 Comparison of the changes in lean body mass between the laparoscopy-assisted distal gastrectomy group and the open distal gastrectomy group

Analyses Excluding the Patients who Developed Surgical Morbidities

Further analyses were performed after excluding two patients who developed surgical morbidities and were dropped from the ERAS protocol. The median WBC count and IL-6 level before and after surgery were not statistically significant ($P = 0.347$ and $P = 0.378$, respectively). The median total body weight and lean body mass also were not statistically significant ($P = 0.551$ and $P = 0.932$, respectively).

DISCUSSION

This is the first study to compare the use of LADG and ODG in a randomized setting using the same perioperative care of fast-track surgery. In this study, the nutritional status after surgery was not significantly different between the LADG and ODG groups. Moreover, the level of surgical stress measured according to the WBC count and the IL-6 level was not significantly different between the two groups. Our results suggest that the level of surgical stress and the nutritional status were similar between the ODG and LADG groups in a randomized comparison using the same perioperative care of fast-track surgery.

The short-term nutritional status after surgery is affected not only by surgical stress, but also by the preoperative nutritional status and calorie intake after surgery. In the present study, none of the patients were cachexia before surgery and all had a strong nutritional status. Furthermore, all patients consumed a similar level of intake, as controlled by our protocol. Therefore, it is unlikely that the preoperative nutritional status or amount of oral intake after surgery roughly affected our results among the patients who did not develop surgical morbidities. Conversely, the level of surgical stress, as measured according to the WBC count and the IL-6 level, was similar between the groups. These findings suggest that the short-term nutritional status after surgery was similar between the ODG and LADG groups, because the level of surgical stress and the preoperative nutritional status were similar, at least in the analyses excluding the patients who developed morbidities.

Why did the level of surgical stress not differ between the LADG and ODG groups? The first possible reason is the differences in operative time. In the present study, the operative time was significantly longer in the LADG group than in the ODG group, which may have reduced the less invasive effects of LADG.[17] The second possibility is the effect of peritoneal CO_2 on peritoneal and systemic immunity. CO_2 insufflation is an essential element of laparoscopic procedures; however, it provokes local and systemic reactions, either due to the CO_2 itself or the pressure used, which may substantially increase the intra-abdominal pressure.[18] Moreover, the dissolution of CO_2 in plasma and tissue can cause cardiopulmonary dysfunction, acid–base imbalances, thromboembolic complications, organ necrosis, and disorders of the liver, kidneys, or neuroendocrine organs.[18] The peritoneum is a crucial element of local defense.[19] The first line of defense within the abdominal cavity is maintained by macrophages, which are the predominant cells in peritoneal fluid.[20] In animal studies, CO_2 insufflation has been found to reduce the macrophage intracellular pH and function.[21] Moreover, macrophages, monocytes, peritoneal mesothelial cells, fibroblasts, and leukocytes are all capable of producing large numbers of cytokines, such as IL-1, IL-6, and TNF, and these molecules are major regulators of local and systemic immune responses.[22] The secretion of proinflammatory cytokines takes place primarily in the peritoneum, and a transient increase in peritoneal interleukin production occurs after surgery.[20] The function of peritoneal immune cells after LADG is substantially diminished during the immediate postoperative period.[17] The third possibility is that the creation of the wound incision contributed to a smaller induced surgical stress response. Both surgical approaches have similar procedures for performing visceral dissection, mobilization, and anastomosis, with the exception of the length of the skin incision. It is possible that systemic immunity is not affected by the skin incision only.

On the other hands, Hayashi et al. evaluated surgical stress, such as IL-6, CRP, and WBC in LADG ($n = 14$) and ODG ($n = 14$) in a randomized study and demonstrated that surgical stress was significantly higher in ODG than LADG.[23] However, there are some differences between the present study and Hayashi's one. First, surgical results were different. Although operation time was significantly longer in the LADG group than in the ODG group in both studies, operation times of ODG and LADG in Hayashi's study were longer than in the present study. Furthermore, the blood loss was both high, more than 300 g both in the LADG and ODG in Hayashi's study, which was higher than ODG of the present study. Second, the perioperative course was different. All patients received ERAS protocol in the present study, which may reduce surgical stress. Third, value of IL-6 was different. In Hayashi's study, IL-6 was both high; >80 pg/ml in LADG and 190 mg/ml in ODG just after surgery and >70 pg/ml in LADG and >140 mg/ml in ODG 24 h after surgery. On the other hand, IL-6 was 53.3 pg/ml in LADG and 36.6 pg/ml in ODG 12 h after surgery in the present study. Considering operation time, blood loss, perioperative care, and IL-6 value, surgical stress of both procedures is considered to be higher in Hayashi's study than in the present study. Laparoscopic surgery may reduce high surgical stress, but the effect may disappear in the surgery with low surgical stress.

In the field of colon cancer surgery, some randomized studies comparing laparoscopic and open surgery have been reported especially on surgical stress. Leung et al. found that systemic cytokine response was less after laparoscopic resection than after open resection.[24] On the other hands, Tang et al.[25] and Dunker et al.[26] reported that there was no difference in the systemic immune response. Thus, it remains a controversial issue whether the laparoscopic surgery has really less surgical stress compared with open surgery.

There are some limitations in this study. First, the sample size may not have been large enough to lead to definitive conclusions, although the current results were obtained based on a randomized comparison with the use of the same perioperative care of fast-track surgery. Previously, Kiyama et al.[16]reported that weight change from preoperative status to 14 days after surgery was 2.5 ± 0.9 kg in LAG ($n = 22$) and 3.5 ± 1.8 kg in ODG ($n = 34$), which was statistically significant ($P = 0.039$). The postoperative observation period for the weight change was slightly longer in their report than our study: 14 days in their study but 8 or 9 days in our study. Considering the short-term period in our study, weight change would be smaller than their study. If we estimated the weight change as 2.0 ± 1.0 kg in laparoscopic surgery and 3.0 ± 1.0 kg in open surgery in this study, we could calculate the sample size as 25 with one sided alpha of 0.05 and statistical power of 0.8. Although our study was not the clinical trial based on this assumption, our sample size of 26 would not be too small to confirm the results of the previous report. Second, it is possible that the level of surgical stress was not accurately evaluated. Following a previous report,[27] the IL-6 level was measured 12 h after surgery but not at any other point. The peak values of IL-6 were unclear in this study. More, although the level of IL-6 is known to correlate with the level of operative stress, other cytokines and hormones, such as IL-1, TNF, IFN-γ, catecholamine, and corticosteroids, also are related to surgical stress. However, we did not measure these cytokines.

CONCLUSIONS

The level of surgical stress and the nutritional status were found to be similar between the ODG and LADG groups in a randomized comparison using the same perioperative care of fast-track surgery. The benefits of LADG, other than cosmetic advantages, should be clarified and discussed in the future.

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CONFLICT OF INTEREST Toru Aoyama, Takaki Yoshikawa, Tsutomu Hayashi, Shinichi Hasegawa, Kazuhito Tsuchida, Takanobu Yamada, Haruhiko Cho, Takashi Ogata, Hirohito Fujikawa, Norio Yukawa, Takashi Oshima, Yasushi Rino, and Munetaka Masuda declare no conflicts of interest.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Diagnostic Value of Computed Tomography for Staging of Clinical T1 Gastric Cancer

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ABSTRACT

Background. T1 gastric cancer can be diagnosed only by endoscopy and is almost curable by local treatment. It has been unclear how a multidetector-row computed tomography (CT) evaluation is valuable for clinical T1 patients.

Methods. Patients with clinical T1 disease, as diagnosed by endoscopy and treated with endoscopic submucosal dissection (ESD) or surgery between October 2000 and October 2007, were examined. The efficacy of CT was evaluated by the reversal rate of endoscopic T1 by CT, the incidence of clinical M1 disease, and the accuracy of diagnosing pathological N+ disease in patients who received surgery. To confirm metachronous distant and nodal metastases, the disease-free survival (DFS) also was evaluated.

Results. A total of 761 patients, 236 treated by ESD and 525 treated with surgery, were examined. None of the patients had an endoscopic diagnosis of clinical T1 reversed by CT. No clinical M1 disease was found. Among the 525 patients who underwent surgery, 8 showed clinical N+ disease (1.5 %), while 47 demonstrated pathological N+ disease (8.9 %). The accuracy, sensitivity, specificity, positive predictive value, and negative predictive values were 90.3, 4.3, 98.7, 25, and 91.3 %, respectively. The 5-year DFS rate was 93.6 % (95 % confidence interval 91.4–95.8 %).

Conclusions. The present study suggests that diagnostic value of CT is limited for staging of clinical T1 gastric cancer patients, because the reversal rate of endoscopic T1 by CT was very low, clinical M1 disease was rare, the diagnosis of N+ status was unreliable, and metachronous M1 and N+ findings were rare.

Gastric cancer is the fourth most commonly diagnosed cancer, the second most common cause of cancer-related death worldwide, and remains the most common malignancy in Japan.[1–3] The treatment for gastric cancer is determined based on the clinical TNM stage.[4] Among these, the top priority is to determine the M (metastasis) factor, because curative resection is essential for the cure of gastric cancer and is not applicable for M1 disease. The next priority is to determine the N factor. Some mucosal gastric cancer without nodal disease can be cured by endoscopic resection alone. When patients have early gastric cancer without nodal disease, limited dissection of D1 or D1+ gastrectomy is recommended.[4] When patients have T2–4 or nodal disease, D2 surgery is the standard of care.[4] Peri- or postoperative adjuvant chemotherapy also is recommended for such patients.[4] Thus, determining the M and N factors is essential to select the appropriate treatment and is the basis of every guideline for gastric cancer.[5–7] Multidetector-row computed tomography (CT) plays a central role not only in determining the M factor, but also the T and N factors.[5]

Because gastric cancer has no specific symptoms, the initial diagnosis is determined by upper gastrointestinal tract endoscopy, which also can determine the depth of invasion (T1 or non-T1). Subsequently, patients receive CT regardless of the depth of the tumor invasion to determine the N and M factors. However, we believe that it should be reconsidered whether CT for T1 disease is necessary,

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because accuracy to diagnose T1 is high only by endoscopy.[8] T1 disease has low metastatic potential and is almost curable by local treatment. Many previous studies reported that the 5-year survival rate of T1 patients was more than 90 % after only local treatment.[9–11] Nodal metastasis is pathologically found in 2.2 % of T1a and 17.9 % of T1b cases among the nodes dissected, but rarely forms a mass detectable by CT.[12]

Based on this background, we hypothesized that diagnostic value of CT is limited for staging of T1 disease. To confirm this hypothesis, we evaluated the reversal rate of endoscopic T1 by CT, incidence of synchronous distant metastasis, the reliability to diagnose nodal disease, and metachronous distant and nodal metastases after initial treatment in clinical T1 gastric cancer.

MATERIALS AND METHODS

Patients

Patients were selected from the prospective consecutive database of Kanagawa Cancer Center between October 2000 and October 2007 based on the following criteria: (1) histologically proven adenocarcinoma of the stomach, confirmed by endoscopic biopsy, (2) patients were diagnosed with clinical T1 (M, SM) by upper gastrointestinal endoscopy, (3) patients received CT, (4) patients received no prior treatment before the initial staging, and (5) patients received endoscopic submucosal dissection (ESD) or radical surgery with D1 or more lymphadenectomy as a primary treatment.

Diagnosis of Clinical T1

The primary tumors were endoscopically evaluated by experienced physicians, which has been shown to have a diagnostic accuracy of 95 % for T1a (M) and T1b (SM).[8] T1 (macroscopic type 0) or non-T1 (macroscopic types 1–5) classification was principally determined by the distensibility. T1 tumors are endoscopically diagnosed by the presence of an area of the mucosa that is slightly discolored (more pale or more red), an irregular microvascular network, or a slight elevation or depression.[13] Type 0 tumors were then subdivided into five categories: 0–1 for the protruding type, 0–2a for the superficially elevated type, 0–2b for the superficially spreading type, 0–2c for the superficially depressed type, and 0–3 for the depressed type.

CT Protocol

Patients received CT as described in our previous paper.[14] Patients were instructed to fast for at least 6 h before the examination. Each patient was given 400 ml of tap water orally to distend the stomach just before scanning. CT was performed using an 8-detector row CT scanner (Aquilion8; Toshiba) between October 2000 and July 2004 and 16-detector row CT scanner (Aquilion16; Toshiba) between August 2004 and October 2007. After undergoing unenhanced CT, a total of 100 ml of nonionic iodinated contrast material (Iopamiron 300, Iopamidol, Nihon Schering, Osaka, Japan) was injected intravenously at a rate of 1.5 ml/s using a power injector. Scanning was started 90 s after intravenous injection of the contrast material. The CT parameters used for both scanners were as follows: slice thickness of 1.00 mm, gantry rotation time of 0.5 s, tube voltage of 120 kVp, tube current–time product of 125 mA, and table feed per rotation of 15 mm. Using these raw data sets, we obtained a transverse image with a slice thickness of 7 mm and an interval of 7 mm.

Assessment by CT

At least one experienced radiologist who was blinded to the endoscopic findings evaluated the T, N, and M staging before treatment. We defined the evaluation criteria for the depth of tumor invasion (T stage) and nodal metastasis (N stage), as described previously.[14] T1 tumors were defined as those that could not be found on the images or those with focal thickening of the inner layer with a visible outer layer of the gastric wall and a clear fat plane around the tumor. T2 tumors were defined as those with focal or diffuse thickening of the gastric wall with transmural involvement and a smooth outer border of the wall or only a few small linear strands of soft tissue extending into the fat plane involving less than one-third of the tumor extent. T3 tumors were defined as transmural tumors with obvious blurring of at least one-third of the tumor extent or wide reticular strands surrounding the outer border of the tumor. T4 tumors were defined as those with obliteration of the fat plane between the gastric tumor and the adjacent organ or invasion of an adjacent organ. The regional lymph nodes were considered to be involved by metastases if they were larger than 8 mm in the short-axis diameter.[15]

Treatments

Principally, ESD was selected for patients with gastric cancer, which was predicted to have few lymph node metastases. The current Japanese guidelines recommend ESD for mucosal tumors with differentiated histology that are <2 cm in diameter without ulceration.[4] Following the guidelines, ESD was judged to be curative when *en bloc* excision was achieved and the resected specimen pathologically showed no lymphatic or vessel invasion, no tumor cells at the resection margin vertically or horizontally, and one of the following conditions: (1) mucosal tumors with a

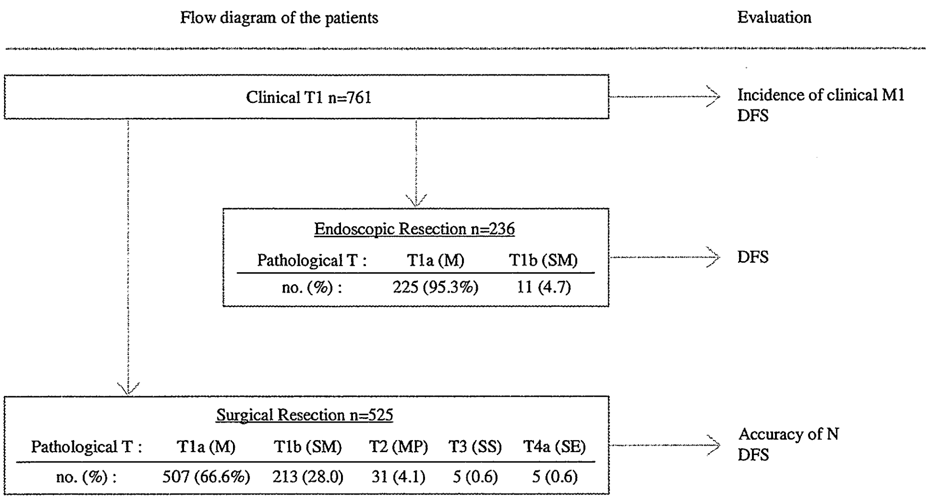

FIG. 1 Flow diagram of 761 patients who had a diagnosis of clinical T1 (M, SM)

differentiated type without ulceration, (2) mucosal tumors with a differentiated type <3 cm with ulceration, (3) mucosal tumors with undifferentiated histology <2 cm without ulceration, and (4) tumors invading the submucosal layer up to 500 μm with differentiated type. Basically, D1, D1+, or D2 gastrectomy was selected following the Japanese guidelines.[4]

Statistical Analysis

The efficacy of CT was evaluated by the reversal rate of endoscopic T1 by CT, the incidence of clinical M1, and the accuracy of diagnosing pathological N+ disease in patients who received surgery. Accuracy was expressed as the rate with 95 % confidence interval (95 % CI).

To confirm whether metachronous distant or nodal metastases occurred after initial treatment, disease-free survival (DFS) also was evaluated. DFS was defined as the date of the initial treatment to the date of any cause of death or the disease recurrence. DFS was calculated by Kaplan–Meier method. Five-year DFS rate was expressed with 95 % CI. The descriptions of T, N, and M followed the UICC-TNM classification, version 7.[16]

RESULTS

A total of 761 patients were entered into this study. Of these, 236 patients received ESD, whereas 525 underwent surgery (Fig. 1). Table 1 shows the background characteristics of all 761 patients. Overall, the most frequently diagnosed tumors were of the 0–2c type macroscopically,

TABLE 1 Characteristics of the 761 patients

Characteristics	Treated by ESD ($n = 236$)	Treated by surgery ($n = 525$)	Total ($n = 761$)
Age (years)			
Median	70	63	65
Range	47–90	26–85	26–90
Sex			
Male	175 (74.2)	364 (69.3)	539 (70.8)
Female	61 (25.8)	161 (30.7)	222 (29.2)
Tumor location			
Upper third of stomach	16 (6.8)	94 (17.9)	110 (14.5)
Middle third of stomach	105 (44.5)	244 (46.5)	349 (45.8)
Lower third of stomach	115 (48.7)	187 (35.6)	302 (39.7)
Maximum tumor diameter			
0–20 mm	176 (74.6)	195 (37.1)	371 (48.8)
>21 mm	60 (25.4)	330 (62.9)	390 (51.2)
Median (mm)	15	26.5	22
Range	3–54	2–170	3–170
Macroscopic types			
0–1	8 (3.4)	17 (3.2)	25 (3.3)
0–2a	147 (62.3)	63 (12)	210 (27.6)
0–2b	1 (0.4)	10 (1.9)	11 (1.4)
0–2c	80 (33.9)	431 (82.1)	511 (67.1)
0–3	0	4 (0.8)	4 (0.5)
Histologic types			
Differentiated	234 (99.2)	294 (56)	528 (69.4)
Undifferentiated	2 (0.8)	231 (44)	233 (30.6)

Data are numbers with percentages in parentheses unless otherwise indicated

TABLE 2 Surgical and pathological results for the 525 patients who received surgery

Variables	Treated by surgery (*n* = 525)
Type of gastrectomy	
Total	133 (25.3)
Distal	347 (66.1)
Proximal	5 (1.0)
Local	40 (7.6)
Dissection	
Sentinel	40 (7.6)
D1+	241 (45.9)
D2	244 (46.5)
Harvested nodes	
Sentinel	
1–15	36 (90)
>16	4 (10)
Median	7
Range	1–18
D1+	
1–15	18 (7.5)
>16	223 (92.5)
Median	38
Range	10–112
D2	
1–15	3 (1.2)
>16	241 (98.8)
Median	44
Range	11–137

Data are numbers with percentages in parentheses unless otherwise indicated

differentiated type histologically, and located in the middle to the lower third of the stomach. Table 2 shows the surgical and pathological characteristics of 525 patients who received surgery. Most patients who proceeded to surgery underwent D1 or more lymphadenectomy, but 40 patients received sentinel-node basin dissection as an investigational treatment.

No patient showed that endoscopic diagnosis of clinical T1 was reversed by CT. No cM1 disease was found on CT in any of the 761 patients. After ESD or surgery, 720 patients were pathologically diagnosed with T1 (94.6 %), 36 with T2 (4.7 %), and 5 with T3 (0.6 %) disease (Fig. 1).

Among the 525 patients who underwent surgery, clinical N+ disease was observed in 8 patients (1.5 %), whereas pathological N+ was observed in 47 (8.9 %). The accuracy, sensitivity, specificity, positive-predictive value (PPV), and negative-predictive value (NPV) for nodal metastasis in all patients was 90.3 % (95 % CI 89.7–91.3 %), 4.3 % (95 % CI 1.2–9.9 %), 98.7 % (95 % CI 98.4–99.3 %), 25 % (95 % CI 7.2–58.3 %), and 91.3 % (95 % CI 91–91.8 %), respectively (Table 3).

TABLE 3 Accuracy of N staging by CT

	Pathological N0	Pathological N+	Total
Clinical N0	472	45	517
Clinical N+	6	2	8
Total	478	47	525

Clinical N N stage based on the CT findings, *Pathological N* N stage based on the histopathologic findings, *N0* node-negative, *N+* node-positive

When the patients were separated into clinical T1a and clinical T1b categories, the accuracy, sensitivity, specificity, PPV, and NPV in the clinical T1a group were 95.8 % (95 % CI 95.1–95.8 %), 9.1 % (95 % CI 1.9–9.1 %), 100 % (95 % CI 99.7–100 %), 100 % (95 % CI 20.9–100 %) and 95.8 % (95 % CI 95.4–95.8 %), respectively, and those in the clinical T1b group were 85.7 % (95 % CI 85.1–87.5 %), 2.8 % (95 % CI 0.5–9.8 %), 97.6 % (95 % CI 97.3–98.6 %), 14.3 % (95 % CI 2.6–50.2 %), and 87.5 % (95 % CI 87.2–88.4 %), respectively.

Figure 2 shows DFS curve. The median follow-up period (range) was 51 (range 1–145 months). Five-year DFS rate was 93.6 % (95 % CI 91.4–95.8 %) in all 761 patients, 95 % (95 % CI 90.5–99.5 %) in 236 patients who received ESD, and 93.4 % (95 % CI 91.0–95.8 %) in 525 patients who received surgery. Event for the DFS was found in 12 patients: 1 patient in the primary lesion of the stomach after ESD and 2 patients in the remnant stomach, 2 in the peritoneum, and 7 in the distant organs (lung, liver, and bone) after surgery.

DISCUSSION

To the best of our knowledge, this is the first study to focus on the necessity of CT for clinical T1 gastric cancer. The major finding of this study was that the reversal rate of endoscopic T1 by CT was rare, clinical M1 was rare, the nodal diagnosis by CT was unreliable, and metachronous distant and nodal metastases after initial treatment were rare. The present results strongly suggested that diagnostic value of CT is limited for staging of clinical T1 disease.

The top priority of staging is to determine the M factor, because M1 status indicates incurable disease. However, there was no role for CT in determining the M factor in clinical T1 disease, because none of our patients had M1 disease. Moreover, only nine patients developed metachronous distant metastasis after initial treatment in this study, although the metachronous distant tumors were not detectable by initial CT. Previously, there were only three sporadic case reports showing M1 status in patients with clinical T1 disease: two from Japan and one from Korea. The metastatic sites included distant lymph nodes, the

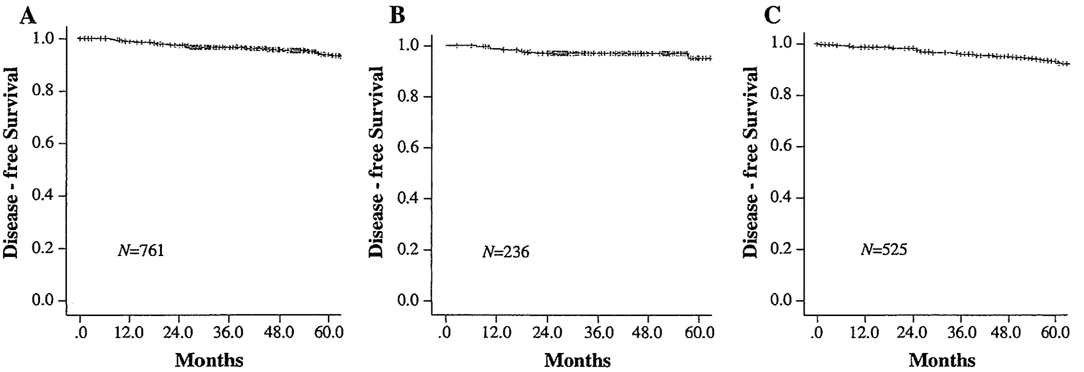

FIG. 2 Kaplan–Meier estimates of disease-free survival, **a** all 761 patients, **b** 236 patients who received ESD, and **c** 525 patients who received surgery

liver, and an ovary (Krukenberg tumor).[17–19] Considering the occurrence of T1 gastric cancer in Japan, incidence of M1 is considered to be extremely rare.

In the 236 patients who received ESD, CT identified no lymph node metastasis. Moreover, no metachronous distant and nodal metastases were observed after ESD. These results strongly suggested that these 236 patients had neither nodal metastasis nor distant metastasis.

Different from the patients who were treated with ESD, the patients who received surgery had a risk of nodal metastasis. Previously, it has been reported that submucosal tumors had nodal metastasis of 10–20 % and mucosa tumors had that of 3–5 %.[12] In fact, nodal metastasis was found in 8.9 % in 525 patients who received surgery in this study. However, sensitivity to diagnose nodal disease by CT was only 4.3 % (8 among 525 patients). Moreover, only two of eight patients were truly diagnosed with nodal disease pathologically. Thus, nodal diagnosis by CT was unreliable in patients who are candidate for gastrectomy. Moreover, metachronous regional nodal disease was not found after gastrectomy with appropriate nodal dissection, suggesting that nodal evaluation by CT is limited for patients who receive radical gastrectomy with nodal dissection.

A misdiagnosis of nodal disease is associated with several risks. When patients are diagnosed with clinical N0 but are pathological N+ (false negative), such patients lose the chance to receive D2 surgery. As a result, their survival might be decreased. When patients are diagnosed with clinical N+ but are pathological N0 (false-positive), such patients receive unnecessary D2 surgery instead of endoscopic mucosal dissection or D1 surgery. As a result, the patient might suffer from surgical morbidity or gastrectomy-related symptoms. D2 resection is technically difficult and risky when performed by inexperienced surgeons. The morbidity and mortality rates due to D2 resection were reportedly 46 and 13 %, respectively, in the MRC trial of UK, and 43 and 10 % in a Dutch trial.[20,21]

CT identified 6 patients who were false-positives and 45 false-negative in the 525 patients who received surgery. Thus, CT for clinical T1 is not only limited in the diagnostic value, it is actually hazardous when considering the risk.

On the other hand, the benefit of CT is that it can suggest the need for D2 surgery when patients are diagnosed to have clinical N+ and pathological N+ disease. However, there were only two such cases (0.4 %) among the 525 patients who underwent surgery in our study. Thus, the number of patients who benefitted from CT was very small, and smaller than the number harmed due to an inappropriate treatment. Thus, CT for staging should not be recommended for clinical T1 gastric cancer after considering the benefits and risks.

There may be other benefits to CT than staging. Some investigators reported that CT provided useful information about the surgical anatomy, especially in cases with anomalies.[22] Synchronous malignancies of abdominal organs might also be found accidentally. Our report does not deny these values of CT.

The present results could have been affected by the diagnostic accuracy of the tumor depth. No patient showed that endoscopic diagnosis of clinical T1 was reversed by CT. The diagnostic accuracy of T1 was 94.6 % in this study, which is almost equivalent to that in the previous reports.[8] However, such a high diagnostic accuracy might not be available in other countries. Nodal metastasis is present in less than 10 % of cases of pathological T1 disease, but the rates are as high as 30–50 % in patients with pathological T2 or pathological T3 disease, and more than 70 % in pathological T4 disease.[23] When T2–4 tumors contaminate the clinical T1 classification, the proportion of nodal disease would be much higher. We previously reported that the accuracy, sensitivity, and specificity for the nodal diagnosis of advanced tumors were 81.3, 46.6, and 96.8 %, respectively.[14] The sensitivity was higher, but the accuracy was lower, in that study than the present results. It is likely that the clinical value of CT is increased when the diagnostic accuracy for T1 is low.

In conclusion, diagnostic value of CT is limited for staging of clinical T1 gastric cancer, because the reversal rate of endoscopic T1 by CT was rare, clinical M1 disease is rare, the diagnosis of N+ is unreliable, and metachronous distant or nodal metastases are rare.

CONFLICT OF INTEREST None declared.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Randomized Comparison of Surgical Stress and the Nutritional Status Between Laparoscopy-Assisted and Open Distal Gastrectomy for Gastric Cancer

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ABSTRACT

Background. Laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer may prevent the development of an impaired nutritional status due to reduced surgical stress compared with open distal gastrectomy (ODG).

Methods. This study was performed as an exploratory analysis of a phase III trial comparing LADG and ODG for stage I gastric cancer during the period between May and December of 2011. All patients received the same perioperative care via fast-track surgery. The level of surgical stress was evaluated based on the white blood cell count and the interleukin-6 (IL-6) level. The nutritional status was measured according to the total body weight, amount of lean body mass, lymphocyte count, and prealbumin level.

Results. Twenty-six patients were randomized to receive ODG (13 patients) or LADG (13 patients). The baseline characteristics and surgical outcomes were similar between the two groups. The median IL-6 level increased from 0.8 to 36.3 pg/dl in the ODG group and from 1.5 to 53.3 pg/dl in the LADG group. The median amount of lean body mass decreased from 48.3 to 46.8 kg in the ODG group and from 46.6 to 46.0 kg in the LADG group. There are no significant differences between two groups.

Conclusions. The level of surgical stress and the nutritional status were found to be similar between the ODG and LADG groups in a randomized comparison using the same perioperative care of fast-track surgery.

The use of laparoscopy-assisted distal gastrectomy (LADG) to treat gastric cancer was first described by Kitano.[1] Since then, the number of cases of gastric cancer treated with LADG has been increasing gradually. The advantages of this procedure, compared with open distal gastrectomy (ODG), include reduced amounts of operative blood loss and pain, earlier recovery of bowel activity, and resumption of oral intake and shorter hospital stays.[2,3] Adachi et al.[4] evaluated 102 early gastric cancer patients and compared the level of surgical stress between patients undergoing ODG and those undergoing LADG. The authors reported lower levels of surgical stress and a lower incidence of impaired nutrition in the LADG group than in the ODG group.

Once surgical stress occurs, immune cells produce cytokines that act as mediators of both immune and systemic responses to injury.[5] Interleukin (IL)-6, IL-1, tumor necrosis factor (TNF), and interferon gamma (IFN-γ) are important mediators of the integrated host response.[6] These cytokines are synthesized from amino acids supplied by muscle catabolism. In addition, the response of skeletal muscle during critical illness is characterized by a rapid decrease in protein content and accelerated amino acid release.[7,8] Low relative muscularity and/or low overall levels of lean body mass are reportedly related to a poor quality of life and the severity of toxicity induced by chemotherapy.[9,10] Theoretically, less invasive surgical

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procedures inhibit muscle catabolism during surgery, which may reduce the incidence of an impaired nutritional status and improve the quality of life after surgery.

Based on this background, we hypothesized that the use of LADG reduces the incidence of an impaired nutritional status, including decreases in lean body mass, induced by surgical stress. To confirm our hypothesis, we evaluated the levels of surgical stress and the nutritional status after surgery in a randomized comparison of patients undergoing ODG and LADG. To minimize variability in perioperative care, all patients received the same fast-track surgery program in this study.

PATIENTS AND METHODS

This study was performed as an exploratory analysis of the Surgical Invasion and Nutrition in ERAS protocol after Gastrectomy (SINEG) study and the Japan Clinical Oncology Group (JCOG)-0912 trial. The SINEG is an in-house prospective cohort study performed to evaluate surgical stress and nutrition in patients who undergo gastrectomy for gastric cancer and receive perioperative care based on the enhanced recovery after surgery (ERAS) protocol at Kanagawa Cancer Center. The details of the perioperative ERAS protocol have been previously described.[11] The SINEG study was initiated in May 2011 and terminated in December 2011. The JCOG-0912 trial is a multicenter phase III trial comparing ODG and LADG for clinical stage I gastric cancer disease diagnosed according to the 14th edition of the general rules for gastric cancer published by the Japanese Gastric Cancer Association (UMIN-ID 000003319).[12] The details of the JCOG-0912 trial have been previously reported.[13] The JCOG-0912 trial was initiated in March 2010 and is currently ongoing. The institution was selected as a stratification factor for randomization in the JCOG-0912 trial. The institutional review board of our hospital approved both the SINEG and JCOG-0912 studies. The primary investigators of the JCOG-0912 trial, the representative director of the JCOG Gastric Cancer Study Group and the chairman of the JCOG, approved the exploratory study of the JCOG-0912 trial. The primary investigator of the SINEG trial also approved this study.

A total of 26 patients who were enrolled into both the SINEG and JCOG-0912 studies were examined in this study. The 26 patients were randomly assigned to undergo either ODG or LADG and received the same perioperative care based on the ERAS protocol.

Surgical Procedure

All patients received distal gastrectomy with nodal dissection. D1 or more nodal dissection was applied for clinical stage IA tumors and D2 dissection was applied for clinical stage IB tumors, regardless of the approach.

For the laparoscopic surgery, one of two certified laparoscopic staff surgeons was responsible for the surgical quality following the protocol of the JCOG-0912 trial. Five or six ports were used. Lymph node dissection was performed in the laparoscopic field. The omentum was preserved except where resection was necessary for lymph node dissection along the right gastroepiploic artery. A small abdominal incision ($\leq$6 cm) was made in the upper abdomen for removal of the specimen and reconstruction. In principle, reconstruction was performed using Billroth-I gastroduodenostomy and all reconstruction procedures were performed extracorporeally using circular staplers.[14]

For the open surgical procedure, an upper abdominal median incision extending from the xiphoid to the navel was created. The nodal dissection and reconstruction procedure was the same as that used in the laparoscopic approach.

For the both procedure, in principal, no drain was used in both laparoscopy and open distal gastrectomy. If the surgeon need drain placement for postoperative bleeding or pancreatitis, a low-vacuum drainage system was left in the subhepatic area for peritoneal fluid collection.

Perioperative Care

The patients received ERAS protocol after both ODG and LADG. Figure 1 shows the details of this protocol, which have been previously reported.[11] In brief, the patients were allowed to eat until midnight on the day before the surgery and were required to drink the contents of two 500-ml plastic bottles containing oral rehydration solution until 3 h before surgery. The nasogastric tube was removed immediately after surgery. Oral intake was initiated on POD 2, beginning with water and an oral nutritional supplement. The patients began to eat solid food on POD 3, starting with rice gruel and soft food on POD 3 and advancing in three steps to regular food intake on POD 7. The patients were discharged when they had achieved adequate pain relief and soft food intake, had returned to their preoperative mobility level, and exhibited normal laboratory data on POD 7.

Evaluation of Operative Morbidity and Mortality

The surgical and nonsurgical complications were assessed prospectively and classified according to the Clavien–Dindo classification.[15] Operative mortality was defined as postoperative death from any cause within 30 days after surgery or during the same hospital stay.

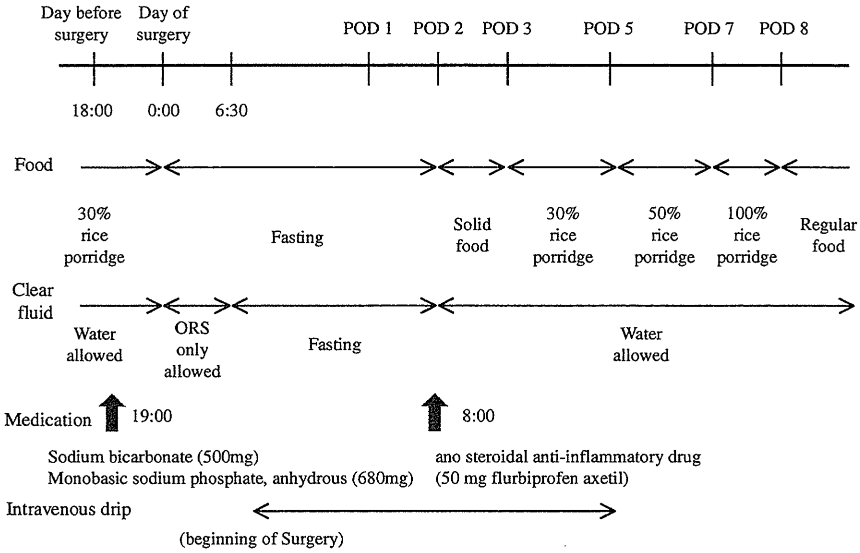

FIG. 1 Details of enhanced recovery after surgery protocol used in this study

Surgical Stress and Nutritional Status

The response induced by systemic surgical stress was assessed by measuring the white blood cell (WBC) count and IL-6 levels. The nutritional status was assessed by measuring the serum prealbumin level, lymphocyte count, and body composition. The segmental body composition was analyzed using the Tanita MC-190EM bioelectrical impedance analyzer (Tanita, Tokyo, Japan), which provides relative information regarding the amount of lean and fat tissue in the trunk area and each limb, as well as the overall body composition and hydration status.

The body composition was measured 3–4 days before and 8 or 9 days after surgery. Previous, Kiyama et al.[16] clarified that body composition dramatically changed during the immediate postoperative period of only 14 days. Although the period for the weight change was only 8 or 9 days in this study, we considered that the change of the body weight or body composition could be detectable. The IL-6 level was measured before surgery and 12 h after surgery. The WBC count was examined before and on the day after surgery. The prealbumin level and lymphocyte count also were evaluated before and 7 days after surgery. Rapid-turnover protein of prealbumin was considered to be a marker for the nutritional status of the short-term period, because half-life of prealbumin was only 2 days. We considered that the change of prealbumin could be detectable before the change of the body weight or composition. We measured total lymphocyte count as one of the general marker for the nutritional status. We considered that total lymphocyte count might be different if weight loss is different.

Evaluation and Statistical Analyses

The values are expressed as the median and range. The statistical analyses were performed using the χ^2 test or the Wilcoxon signed-rank test. $P < 0.05$ was considered to indicate statistical significance. The SPSS software package (v12.0 J Win, SPSS, Chicago, IL) was used for all statistical analyses.

RESULTS

Background

Among the 26 patients, 13 were assigned to receive ODG and 13 were assigned to receive LADG. The background characteristics and baseline data were well randomized to both groups (Table 1). No patients had any history of weight loss, appetite loss, or food intake loss before surgery. No patients had a past history of diabetes mellitus or metabolic or mental disorders.

Surgical and Pathological Outcomes

No patients assigned to receive LADG underwent conversion to open surgery The median duration of surgery was significantly longer in the LADG group than in the ODG group ($P = 0.005$). On the other hand, the median amount of bleeding was significantly less in the LADG group than in the ODG group ($P = 0.009$; Table 2). No differences were observed between the groups in terms of pathological outcomes.

No mortalities occurred in either group. The surgical morbidities are shown in Table 3. No patients had grade 1

TABLE 1 Comparison of the patients' backgrounds

	ODG ($n = 13$)	LADG ($n = 13$)	P value
Age, years (median, range)	67 (45–76)	62 (38–79)	0.801
Sex ratio (M:F)	7/6	7/6	1.000
Performance status (0:1)	14/0	13/0	–
Total body weight, kg (median, range)	60.0 (39.8–75.5)	61.6 (42.2–66.9)	0.96
Lean body mass, kg (median, range)	48.3 (35.4–60.3)	46.6 (33.2–61.5)	0.88
Tumor site (body/antrum)	5/8	8/5	0.239
Pathological type (diff/undiff)	4/9	3/10	0.658
Clinical T factor (m/sm/mp)	4/4/5	7/2/4	0.45
Clinical N factor (0/1/2-)	13/0/0	12/1/0	0.308
Total protein, mg/dl (median, range)	7.5 (6.8–8.0)	7.4 (6.5–7.9)	0.65
Albumin, mg/dl (median, range)	4.6 (4.1–4.8)	4.5 (4.1–4.8)	0.545
Prealbumin, mg/dl (median, range)	26.6 (18.3–37.4)	27.6 (16.5–41.1)	0.801
WBC, μL (median, range)	4,800 (3,200–6,800)	5,800 (3,800–8,100)	0.072
Lymphocyte count, μL (median, range)	1,624 (1,095–2,713)	1,419 (946–2,639)	0.406
CRP, mg/dl (median, range)	0.045 (0.02–0.11)	0.06 (0.02–3.22)	0.11
IL-6, pg/ml (median, range)	0.8 (0.4–2.5)	1.5 (0.4–5.8)	0.091

TABLE 2 Surgical and pathological outcomes

	ODG ($n = 13$)	LADG ($n = 13$)	P value
Lymph node dissection (D1+/D2)	8/5	9/4	0.680
Reconstruction (Billroth-1/Roux-en-Y)	11/2	12/1	0.593
Bleeding, g (median, range)	190 (50–475)	40 (5–270)	0.009
Operation time, min (median, range)	154 (85–276)	267 (168–360)	0.005
Transfusion (no/yes)	14/0	13/0	–
Number of harvested lymph nodes (median, range)	43 (26–89)	40.5 (25–69)	0.938
Pathological T factor (m/sm/mp/ss/se)	6/6/0/0/1	7/4/2/0/0	0.324
Pathological N factor (N0/N1/N2)	10/3/0	11/1/1	0.359

or more anastomotic stenosis after surgery. No patients required additional nutritional support or additional hospitalization due to reduced food intake.

In both groups, the 12 patients who did not develop surgical morbidities were discharged 8–10 days after surgery following the ERAS protocol without variance.

Surgical Stress

The median WBC count (range) increased from 4,800 μL (3,200–6,800) to 7,100 μL (3,600–10,100) in the ODG group and from 5,800 μL (3,800–8,100) to 7,700 μL (4,800–13,200) in the LADG group. The median IL-6 (range) level increased from 0.8 pg/dl (0.4–2.5) to 36.3 pg/dl (14.4–405.0) in the ODG group and from 1.5 pg/dl (0.4–5.8) to 53.3 pg/dl (24.1–217.0) in the LADG group (Fig. 2). When comparing the WBC count and the IL-6 level before and after surgery between the groups, no significant differences were observed ($P = 0.375$ and $P = 0.545$, respectively). Furthermore, the median CRP (range) level increased from 0.045 mg/dl (0.02–0.11) to 1.9 mg/dl (0.2–12.93) at day 7 after surgery in the ODG group and from 0.06 mg/dl (0.02–3.22) to 1.38 mg/dl (0.3–10.19) at day 7 after surgery in the LADG group. There was no significant difference between two groups ($P = 0.626$).

Nutritional Status

The median total body weight (range) decreased from 60.0 kg (39.8–75.5) to 56.7 kg (40.7–75.4) in the ODG group and from 61.6 kg (42.2–66.9) to 58.6 kg (41.8–64.7) in the LADG group, whereas the median lean body mass (range) decreased from 48.3 kg (33.5–57.2) to 46.8 kg (35.4–57.6) in the ODG group and from 46.6 kg

TABLE 3 Comparison of morbidity and mortality between the ODG and LADG groups

	ODG ($n = 13$)	LADG ($n = 13$)	P value
Any complications (≥grade 2)	1	1	1.000
Anatomic leakage	0	0	–
Anatomic stenosis	0	0	–
Pancreatic fistula	1 (grade 3A)	0	0.326
Abdominal abscess	0	0	–
Pneumonia	0	0	–
Small-bowel obstruction	0	0	–
Transient ischemic attack	0	1 (grade 2)	0.326
Morbidity	0	0	–

(33.2–61.5) to 46.0 kg (33.2–57.8) in the LADG group (Fig. 3). When comparing the total body weight and lean body mass before and after surgery between the groups, no significant differences were observed ($P = 0.687$ and $P = 0.88$).

The median prealbumin (range) level decreased from 26.6 mg/dl (18.3–37.4) to 17.7 mg/dl (13.7–23.7) in the ODG group and from 27.6 mg/dl (16.5–41.1) to 18.3 mg/dl (10.5–28.7) in the LADG group, which was not statistically significant ($P = 0.88$). The median lymphocyte count (range) decreased from 1,624 μL (1,095–2,713) to 1,075 μL (886–1,721) in the ODG group and from 1,419 μL (946–2,639) to 1,440 μL (828–2,005) in the LADG group, which was not statistically significant ($P = 0.406$).

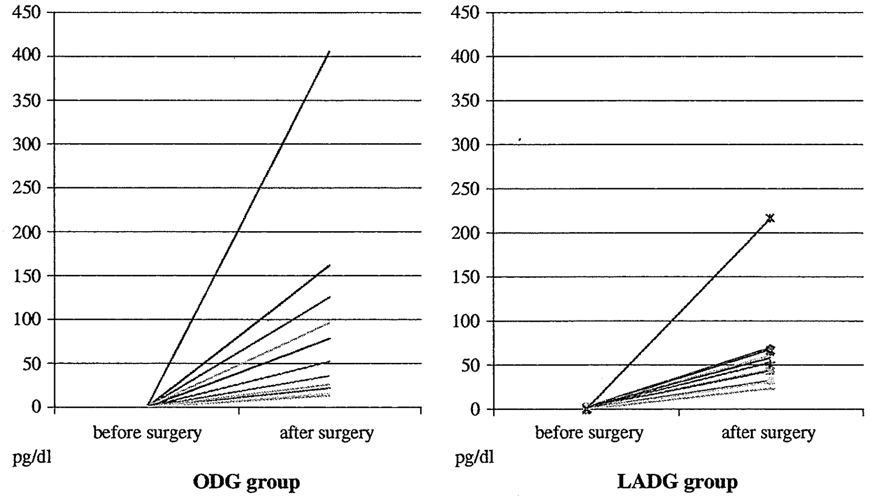

FIG. 2 Comparison of the changes in IL-6 between the laparoscopy-assisted distal gastrectomy group and the open distal gastrectomy group

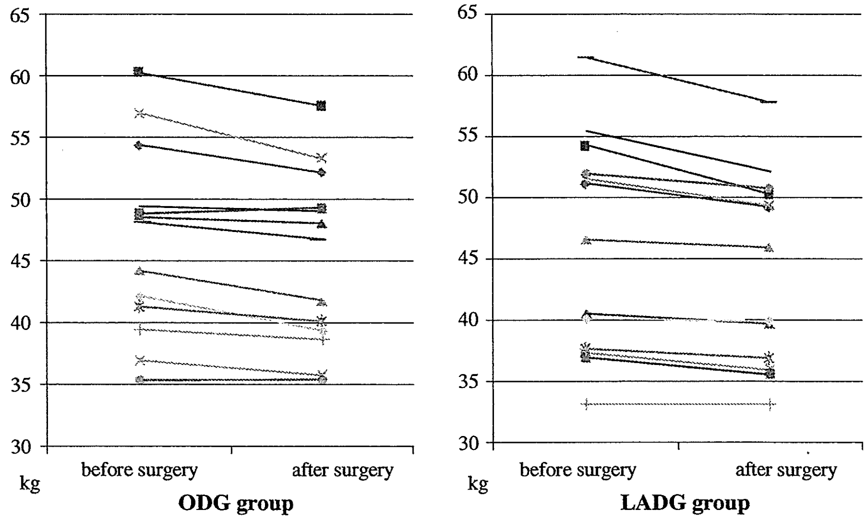

FIG. 3 Comparison of the changes in lean body mass between the laparoscopy-assisted distal gastrectomy group and the open distal gastrectomy group

Analyses Excluding the Patients who Developed Surgical Morbidities

Further analyses were performed after excluding two patients who developed surgical morbidities and were dropped from the ERAS protocol. The median WBC count and IL-6 level before and after surgery were not statistically significant ($P = 0.347$ and $P = 0.378$, respectively). The median total body weight and lean body mass also were not statistically significant ($P = 0.551$ and $P = 0.932$, respectively).

DISCUSSION

This is the first study to compare the use of LADG and ODG in a randomized setting using the same perioperative care of fast-track surgery. In this study, the nutritional status after surgery was not significantly different between the LADG and ODG groups. Moreover, the level of surgical stress measured according to the WBC count and the IL-6 level was not significantly different between the two groups. Our results suggest that the level of surgical stress and the nutritional status were similar between the ODG and LADG groups in a randomized comparison using the same perioperative care of fast-track surgery.

The short-term nutritional status after surgery is affected not only by surgical stress, but also by the preoperative nutritional status and calorie intake after surgery. In the present study, none of the patients were cachexia before surgery and all had a strong nutritional status. Furthermore, all patients consumed a similar level of intake, as controlled by our protocol. Therefore, it is unlikely that the preoperative nutritional status or amount of oral intake after surgery roughly affected our results among the patients who did not develop surgical morbidities. Conversely, the level of surgical stress, as measured according to the WBC count and the IL-6 level, was similar between the groups. These findings suggest that the short-term nutritional status after surgery was similar between the ODG and LADG groups, because the level of surgical stress and the preoperative nutritional status were similar, at least in the analyses excluding the patients who developed morbidities.

Why did the level of surgical stress not differ between the LADG and ODG groups? The first possible reason is the differences in operative time. In the present study, the operative time was significantly longer in the LADG group than in the ODG group, which may have reduced the less invasive effects of LADG.[17] The second possibility is the effect of peritoneal CO_2 on peritoneal and systemic immunity. CO_2 insufflation is an essential element of laparoscopic procedures; however, it provokes local and systemic reactions, either due to the CO_2 itself or the pressure used, which may substantially increase the intra-abdominal pressure.[18] Moreover, the dissolution of CO_2 in plasma and tissue can cause cardiopulmonary dysfunction, acid–base imbalances, thromboembolic complications, organ necrosis, and disorders of the liver, kidneys, or neuroendocrine organs.[18] The peritoneum is a crucial element of local defense.[19] The first line of defense within the abdominal cavity is maintained by macrophages, which are the predominant cells in peritoneal fluid.[20] In animal studies, CO_2 insufflation has been found to reduce the macrophage intracellular pH and function.[21] Moreover, macrophages, monocytes, peritoneal mesothelial cells, fibroblasts, and leukocytes are all capable of producing large numbers of cytokines, such as IL-1, IL-6, and TNF, and these molecules are major regulators of local and systemic immune responses.[22] The secretion of proinflammatory cytokines takes place primarily in the peritoneum, and a transient increase in peritoneal interleukin production occurs after surgery.[20] The function of peritoneal immune cells after LADG is substantially diminished during the immediate postoperative period.[17] The third possibility is that the creation of the wound incision contributed to a smaller induced surgical stress response. Both surgical approaches have similar procedures for performing visceral dissection, mobilization, and anastomosis, with the exception of the length of the skin incision. It is possible that systemic immunity is not affected by the skin incision only.

On the other hands, Hayashi et al. evaluated surgical stress, such as IL-6, CRP, and WBC in LADG ($n = 14$) and ODG ($n = 14$) in a randomized study and demonstrated that surgical stress was significantly higher in ODG than LADG.[23] However, there are some differences between the present study and Hayashi's one. First, surgical results were different. Although operation time was significantly longer in the LADG group than in the ODG group in both studies, operation times of ODG and LADG in Hayashi's study were longer than in the present study. Furthermore, the blood loss was both high, more than 300 g both in the LADG and ODG in Hayashi's study, which was higher than ODG of the present study. Second, the perioperative course was different. All patients received ERAS protocol in the present study, which may reduce surgical stress. Third, value of IL-6 was different. In Hayashi's study, IL-6 was both high; >80 pg/ml in LADG and 190 mg/ml in ODG just after surgery and >70 pg/ml in LADG and >140 mg/ml in ODG 24 h after surgery. On the other hand, IL-6 was 53.3 pg/ml in LADG and 36.6 pg/ml in ODG 12 h after surgery in the present study. Considering operation time, blood loss, perioperative care, and IL-6 value, surgical stress of both procedures is considered to be higher in Hayashi's study than in the present study. Laparoscopic surgery may reduce high surgical stress, but the effect may disappear in the surgery with low surgical stress.

In the field of colon cancer surgery, some randomized studies comparing laparoscopic and open surgery have been reported especially on surgical stress. Leung et al. found that systemic cytokine response was less after laparoscopic resection than after open resection.[24] On the other hands, Tang et al.[25] and Dunker et al.[26] reported that there was no difference in the systemic immune response. Thus, it remains a controversial issue whether the laparoscopic surgery has really less surgical stress compared with open surgery.

There are some limitations in this study. First, the sample size may not have been large enough to lead to definitive conclusions, although the current results were obtained based on a randomized comparison with the use of the same perioperative care of fast-track surgery. Previously, Kiyama et al.[16]reported that weight change from preoperative status to 14 days after surgery was 2.5 ± 0.9 kg in LAG ($n = 22$) and 3.5 ± 1.8 kg in ODG ($n = 34$), which was statistically significant ($P = 0.039$). The postoperative observation period for the weight change was slightly longer in their report than our study: 14 days in their study but 8 or 9 days in our study. Considering the short-term period in our study, weight change would be smaller than their study. If we estimated the weight change as 2.0 ± 1.0 kg in laparoscopic surgery and 3.0 ± 1.0 kg in open surgery in this study, we could calculate the sample size as 25 with one sided alpha of 0.05 and statistical power of 0.8. Although our study was not the clinical trial based on this assumption, our sample size of 26 would not be too small to confirm the results of the previous report. Second, it is possible that the level of surgical stress was not accurately evaluated. Following a previous report,[27] the IL-6 level was measured 12 h after surgery but not at any other point. The peak values of IL-6 were unclear in this study. More, although the level of IL-6 is known to correlate with the level of operative stress, other cytokines and hormones, such as IL-1, TNF, IFN-γ, catecholamine, and corticosteroids, also are related to surgical stress. However, we did not measure these cytokines.

CONCLUSIONS

The level of surgical stress and the nutritional status were found to be similar between the ODG and LADG groups in a randomized comparison using the same perioperative care of fast-track surgery. The benefits of LADG, other than cosmetic advantages, should be clarified and discussed in the future.

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CONFLICT OF INTEREST Toru Aoyama, Takaki Yoshikawa, Tsutomu Hayashi, Shinichi Hasegawa, Kazuhito Tsuchida, Takanobu Yamada, Haruhiko Cho, Takashi Ogata, Hirohito Fujikawa, Norio Yukawa, Takashi Oshima, Yasushi Rino, and Munetaka Masuda declare no conflicts of interest.

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ORIGINAL ARTICLE

Application of reduced-port laparoscopic total gastrectomy in gastric cancer preserving the pancreas and spleen

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Abstract

Background The feasibility of using reduced-port laparoscopic total gastrectomy (RPLTG) for the treatment of gastric cancer remains unclear. This study aimed to address the potentially important advantages of this surgical technique.

Methods Between April 2002 and February 2014, 90 patients underwent laparoscopy-assisted total gastrectomies, performed by a single surgeon. Of these, 45 patients underwent RPLTG and 45 patients underwent conventional laparoscopy-assisted total gastrectomy (CLATG). Short-term outcomes were compared to evaluate the feasibility of RPLTG for gastric cancer.

Results There were several significant differences between the RPLTG and CLATG groups in short-term outcomes: the mean total operation durations were significantly longer in the RPLTG group (319.0 min) than in the CLATG group (259.0 min). However, the mean volume of blood loss, the degree of lymph node dissection, and the number of dissected lymph nodes did not differ between the two groups.

Conclusions We have shown that RPLTG could be an acceptable and satisfactory procedure for the treatment of gastric cancer requiring total gastrectomy for surgeons sufficiently experienced in CLATG.

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Keywords Gastric cancer · Laparoscopic total gastrectomy · Reduced-port gastrectomy

Introduction

Laparoscopy-assisted distal gastrectomy (LADG) for the treatment of gastric cancer has been widely accepted and is widely used in Japan and Korea. Previous studies have reported satisfactory short-term and long-term outcomes for LADG in patients with early gastric cancer [1–5]. Moreover, some recent studies have shown the feasibility of using LADG in advanced gastric cancer patients [6–8]. However, laparoscopy-assisted total gastrectomy (LATG) has not been widely used for the treatment of gastric cancer because of its technical difficulty and complexity, including the reconstruction required and its oncological safety. The most important issue that needs to be resolved is the technique used for the reconstruction of an esophagojejunostomy during LATG [9, 10].

Several studies of LATG in gastric cancer patients from large surgical oncology centers have reported favorable short-term and long-term outcomes [11–13], demonstrating that experienced laparoscopic surgeons can perform lymph node dissection and reconstruction as effectively during LATG as during LADG. We expect LATG to become the prevalent technique as surgical skills increase in the foreseeable future.

Recently, surgical outcomes for reduced-port laparoscopic gastrectomy have been reported by several institutions. We showed similar surgical outcomes in a previous study for a reduced-port laparoscopic distal gastrectomy (RPLDG) procedure, using a multiaccess port at the umbilicus plus one additional port, compared with conventional LADG (CLADG), using five ports plus a small,