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Risk of recurrence after laparoscopy-assisted radical gastrectomy for gastric cancer performed by a single surgeon

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Abstract
Background The risk of recurrence after laparoscopy-assisted radical gastrectomy (LAG) was investigated.
Materials and methods Clinical data of 398 consecutive patients who underwent radical gastrectomy with R0 resection for gastric cancer at Gyeongsang National University Hospital between January 2005 and December 2007 were reviewed retrospectively.
Results Of the patients, 65.4% ($n = 261$) and 34.6% ($n = 138$) underwent LAG and open radical gastrectomy (OG), respectively. Of the LAG cases, 73.2% ($n = 192$), 10.7% ($n = 28$), 12.6% ($n = 33$), and 3.1% ($n = 8$) had stage I, II, III, and IV gastric cancer, respectively. All patients were followed up for a mean of 36.8 ± 13.7 months, and 14.6% ($n = 58$) had recurrence during the follow-up period. Univariate analysis revealed that tumor size, tumor–node–metastasis (TNM) stage, method of approach (LAG versus OG), and operation type were associated significantly with recurrence. Multivariate analysis revealed that only high TNM stage was significantly associated with recurrence ($P = 0.00$). While patients who underwent OG had higher incidence of recurrence than patients who underwent LAG, OG was not significantly associated with recurrence on multivariate analysis ($P = 0.06$).
Conclusions LAG and OG did not differ significantly in terms of recurrence, even when used in advanced gastric cancer cases. Multivariate analysis revealed that high TNM stage was significantly associated with recurrence. Thus, LAG appears to be a safe and feasible procedure that has the potential to be an alternative to open surgery, even for advanced gastric cancer.

Keywords Stomach neoplasm · Recurrence · Laparoscopy · Laparoscopic gastrectomy · Laparoscopy-assisted gastrectomy

Gastric cancer is the fourth most common type of cancer and the second leading cause of cancer-related death in the world. Nearly one million new cases are diagnosed each year. In most parts of the world, the 5-year survival rate is less than 20%; however, in Japan, the survival rate is approximately 60% [1, 2]. Although the incidence of gastric cancer and the mortality associated with this disease have decreased gradually in Japan and Korea, it remains the second most frequent cause of death in Korea [3].

Kitano et al. first described laparoscopy-assisted distal gastrectomy (LAG) in 1991 [4]. Since then, this procedure has become the standard treatment for early gastric cancer in Korea and Japan. Relative to open surgery, laparoscopic surgery is associated with a significant improvement in quality of life, since pain is reduced, recovery is faster, hospital stay is shorter, and cosmetic outcome is better

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[5–11]. Recently, the inclusion criteria for LAG have expanded, which has led to an increase in the number of publications describing laparoscopic treatment of advanced gastric cancer (AGC) [12–17]. The aim of this study is to evaluate the risk of recurrence in patients undergoing radical LAG.

Patients and methods

Clinical data of 398 consecutive patients who underwent radical gastrectomy with R0 resection for gastric cancer at Gyeongsang National University Hospital between January 2005 and December 2007 were analyzed retrospectively. All open gastrectomy (OG) and LAG procedures were performed by an experienced surgeon (Y.-J.L.) who had previously performed 50 LAG procedures between 2001 and 2004. The decision to undergo OG or LAG was ultimately made by the patient after sufficient information was provided. However, we recommended LAG to all patients who fulfilled the following indications: presence of adenocarcinoma proven by histopathological analysis of biopsy material, tumor less than 5 cm in diameter, and preoperative computed tomography (CT) or endoscopic ultrasound (EUS) revealing clinical stage below T3N1 [defined according to the American Joint Committee on Cancer (AJCC) TNM 6th edition]. Patients who fulfilled the following exclusion criteria were excluded from this study: those with preoperative examinations revealing evidence of distant metastasis (liver, lung, bone, para-aortic lymph node, subclavian lymph node, rectal shelf), or those with history of another organ cancer. The study was approved by the local institutional review board. The retrospectively collected data were as follows: patient characteristics (age, sex), operative factors (operation time, open versus laparoscopy, reconstruction, and combined resection), and morbidity. Data were collected by reviewing medical charts and by conducting telephone interviews (01/12/2009 to 31/12/2009). In case of death, death was confirmed and causes of death were determined by searching the micro-data services of the National Statistical Office. Recurrence-related parameters, namely recurrence rate, site of recurrence, diagnostic tests that detected the recurrence, treatment of the recurrence, and survival time, were obtained by reviewing medical records. Statistical analyses were performed by using SPSS 12.0 (SPSS Inc., Chicago, IL) for Windows. Data are presented as mean ± standard deviation (SD). To determine the significance of differences, χ^2 test, Student's t test, binary logistic regression test, and the Kaplan–Meier method were used. A P value of <0.05 was considered to be statistically significant.

Surgical procedures

In all OG cases, conventional gastrectomy, total omentectomy, and D2 lymph node dissection were performed. Lymph node station numbers were scored according to the Japanese Classification of Gastric Carcinoma from 1998 [18]. The gastric resection and determination of the resection area of the lymph node stations were performed by following the Japanese Gastric Cancer Association (JGCA) guidelines from 2002 [19].

With regard to LAG for mid- and low-body cancer, when preoperative diagnosis using gastrofiberoscopy and spiral computed tomography (CT) scans revealed early gastric cancer (EGC), subtotal gastrectomy, partial omentectomy, and D1 + β lymph node dissection (D1 + 7, 8a, 9) were performed. However, if AGC was detected, total omentectomy and D2 lymph node dissection (1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a, 14v) were performed. For reconstruction, extracorporeal Billroth I (54.8%) or extracorporeal Billroth II (19.2%) using upper midline or right subcostal minilaparotomy was performed. When performing the Billroth I method, while an extracorporeal anastomosis was made initially, the intracorporeal Billroth I stapled anastomosis was created by using a hand-access device as described in 2007 [20]. This method improves the operative view without compromising the minimal invasiveness of LAG.

With regard to LAG for upper-body cancer, when preoperative diagnosis using gastrofiberoscopy and spiral CT scans revealed EGC, proximal gastrectomy (15, 5.7%) or total gastrectomy (46, 17.6%), partial omentectomy, and D1 + β lymph node dissection (D1 + 7, 8a, 9) were performed; esophagogastrostomy was achieved by using a circular stapler in extracorporeal end-to-side fashion. In cases of AGC, total gastrectomy, omentectomy, and D2 lymph node dissection were performed, and reconstruction involved an extracorporeal end-to-side Roux-en-Y esophagojejunostomy generated by using the circular stapler through an upper minilaparotomy [21].

Results

Patient demographics

Mean patient age was 61.8 years. The male-to-female ratio was 2.1:1. The most frequent location of tumors was the lower body (n = 272, 68.3%), followed by the mid body (n = 83, 20.9%) and the high body (n = 43, 10.7%). Mean tumor size, mean proximal resection margin, and mean distal resection margin were 4.0 ± 4 cm, 4.9 ± 3 cm, and 4.8 ± 4 cm, respectively. Analysis of TNM stage revealed that 69.3% (n = 276), 12.8% (n = 51), 13.6% (n = 54), and 4.3% (n = 17) of the patients had stage I, II, III, and IV disease, respectively. Mean operation time was 362 min. On average, first flatulence occurred 6.2 days (median 5 days) after the operation, and mean postoperative hospital stay was

17 days (median 13 days). In terms of approach, OG and LAG were used in 34.6% ($n = 138$) and 65.4% ($n = 261$) of cases, respectively. With regard to operation type, subtotal, total, and proximal gastrectomy was performed in 70.9%, 21.1%, and 5.8% of patients, respectively, with the remaining 2.3% receiving wedge resection. Combined organ resection was performed in 15.8% ($n = 63$) of all cases. The mean follow-up period was 36.8 ± 13.7 months. Recurrence was found in 14.6% ($n = 58$) of the cases; this was determined by reviewing the medical charts in 53 cases and by assessing National Statistical Office data in the remaining 5 cases.

Table 1 Differences in clinicopathologic characteristics of patients undergoing open gastrectomy (OG) or laparoscopy-assisted gastrectomy (LAG)

	OG	LAG	*P*-value
Tumor location			
Upper	17	26	0.49
Mid	27	56	0.79
Low	93	179	0.91
Tumor size (cm)	4.6 ± 2.9	3.7 ± 2.5	**0.00**
Retrieved nodes	30 ± 14	25 ± 13	**0.00**
Metastatic nodes	3.0 ± 5.7	2.1 ± 5.3	0.10
TNM stage			
I	84 (61.3%)	192 (73.6)	**0.01**
II	23 (16.8%)	28 (10.7)	0.11
III	21 (15.3%)	33 (12.6)	0.44
IV	9 (6.6)	8 (3.1)	0.11
Tumor-free resection margin (cm)			
Proximal margin	5.3 ± 3.2	4.6 ± 2.9	**0.03**
Distal margin	4.2 ± 3.8	5.0 ± 4.1	0.07
Operation time (min)	287 ± 91	401 ± 101	**0.00**
Time to first flatulence (days)	6.1 ± 3.1	6.3 ± 2.9	0.57
Hospital stay (days)	18 ± 16	16.5 ± 14	0.34
Combined organ resection	34 (24.8%)	29 (11.1)	**0.00**
Operation type			
Subtotal gastrectomy	89 (64.9%)	193 (74%)	**0.03**
Total gastrectomy	39 (28.5%)	46 (17.4%)	**0.00**
Proximal gastrectomy	8 (5.8%)	15 (5.7%)	1.0
Wedge resection	1 (0.7%)	7 (2.7%)	0.27
Morbidity rate			
EGC	14/61 (23%)	17/152 (11.2%)	**0.03**
AGC	15/76 (19.7%)	29/109 (26.6%)	0.29
Cancer recurrence			
EGC	2/61 (3.3%)	2/152 (1.3%)	0.32
AGC	28/76 (36.8%)	26/109 (23.9)	0.07

Comparison of the OG and LAG groups

The OG and LAG groups differed significantly in terms of tumor size, number of retrieved nodes, number of stage I tumors, operation time, the first day of flatulence, rate of combined organ resection, morbidity rate associated with EGC, and number of subtotal and total gastrectomies ($P < 0.05$). The two groups did not differ significantly with regard to tumor location, tumor-free resection margin, hospital stay, morbidity rate associated with AGC or cancer recurrence rate. With regard to recurrence, when the OG and LAG groups were divided according to EGC and AGC, the EGC-OG subgroup did not differ from the EGC-LAG subgroup, and the same was true for the AGC-OG and AGC-LAG subgroups ($P > 0.05$) (Table 1).

Demographics of the patients with recurrence

Average age of patients with recurrence was 58 years. The ratio of males to females was 2.4:1. Mean tumor size was 6 cm, mean number of retrieved lymph nodes (LN) was 33, and mean number of metastatic nodes was 9.3. In terms of TNM stage, the most common stage was stage III (47.1%, $n = 24$), and 29.4% ($n = 15$), 13.7% ($n = 7$), and 9.8% ($n = 5$) had stage II, IV, and I disease, respectively. The OG and LAG groups did not differ significantly in terms of site of recurrence ($P > 0.05$), with the most common recurrence sites being the liver (25.5%) and peritoneum (23.5%) (Table 2). The tool that was most frequently used to detect the site of recurrence was spiral CT scanning (64.2%, $n = 34$); other methods used were gastrofiberoscopy (15.1%, $n = 8$), magnetic resonance imaging (3.8%,

Table 2 Differences in site of recurrence between patients undergoing open gastrectomy (OG) and laparoscopy-assisted gastrectomy (LAG)

Recurrence site	OG	LAG	Total *N*	%	*P*-value
Peritoneal seeding	6	6	12	23.5	1.0
Gastric bed	2	5	7	13.7	0.42
Remnant stomach	3	4	7	13.7	1.0
Liver	8	5	13	25.5	0.35
Lung	3	3	6	9.8	1.0
Bone	1	1	2	3.9	1.0
Brain and meningeal	0	2	2	3.8	0.49
Intra-abdominal organ	6	3	9	17.3	0.46
Ovary	1	2	3	5.7	1.0
Ext abdominal LN	0	3	3	5.7	0.23
Trocar site, skin	0	1	1	1.9	1.0

$n = 2$), and chest posteroanterior X-ray ($n = 2$). Half of the patients with recurrence were treated by chemotherapy (56.6%, $n = 30$), while the others were treated by curative resection (11.3%, $n = 6$), palliative procedures (such as bypass surgery and percutaneous transhepatic biliary drainage, 11.3%, $n = 6$), and supportive care only ($n = 20.8\%$, $n = 11$).

Table 3 Clinicopathologic features and univariate analysis of risk factors for recurrence in gastric cancer

	Value	Recurrence (%)	*P*-value	OR
Age				
<60 years	142	24 (16.9%)	0.08	
≥60 years	256	27 (10.5%)		
Sex				
Male	263	37 (13.9%)	0.42	
Female	131	14 (10.7%)		
Tumor location				
Upper	43	9 (20.9%)	0.14	
Mid	83	7 (8.4%)		
Low	272	42 (15.4%)		
Tumor size				
<4 cm	214	14 (6.5%)	**0.00**	1
≥4 cm	184	44(23.9%)		4.4
TNM stage				
I	276	5 (1.8%)	**0.00**	1
II	51	15 (29.4%)		23
III	54	24 (44.4%)		48
IV	17	7 (41.2%)		39
WHO				
Well differentiated	81	5 (6.2%)	0.18	
Moderate differentiated	115	15 (13%)		
Poor differentiated	119	20 (16.8%)		
Undifferentiated	70	11 (15.7%)		
Approach				
Open	137	25 (18.2%)	**0.02**	1
Laparoscopy assisted	261	26 (10%)		0.4
Operation type				
Subtotal gastrectomy	282	28 (9.9%)	**0.03**	1
Total gastrectomy	84	19 (22.4%)		2.6
Proximal gastrectomy	23	4 (17.4%)		1.9
Wedge resection	8	0 (0%)		0
BMI				
<25 kg/m^2	310	45 (14.5%)	0.09	
≥25 kg/m^2	85	6 (7.1%)		
Underlying disease				
No	231	34 (14.7%)	0.22	
Yes	167	17 (10.2%)		

OR odds ratio, *BMI* body mass index, *WHO* World Health Organization

Univariate and multivariate analysis of the risk factors of cancer recurrence

Univariate analysis revealed that tumor size, TNM stage, approach, and operation type were significantly associated with cancer recurrence (Table 3, $P < 0.05$). When multivariate analysis was performed, only high TNM stage

Table 4 Multivariate analysis of risk factors for recurrence in gastric cancer

	Value	Recurrence (%)	*P*-value	OR
Tumor size				
<4 cm	214	14 (6.5%)	0.35	
≥4 cm	184	44 (23.9%)		
TNM stage				
I	276	5 (1.8%)	**0.00**	1
II	51	15 (29.4%)		13.3
III	54	24 (44.4%)		26.3
IV	17	7 (41.2%)		31.3
Approach				
LAG	261	26 (10%)	0.06	1
OG	137	25 (18.2%)		1.9
Operation type				
Subtotal gastrectomy	282	28 (9.9%)	0.40	
Total gastrectomy	84	19 (22.4%)		
Proximal gastrectomy	23	4 (17.4%)		
Wedge resection	8	0 (0%)		

LAG laparoscopy-assisted gastrectomy, *OG* open gastrectomy

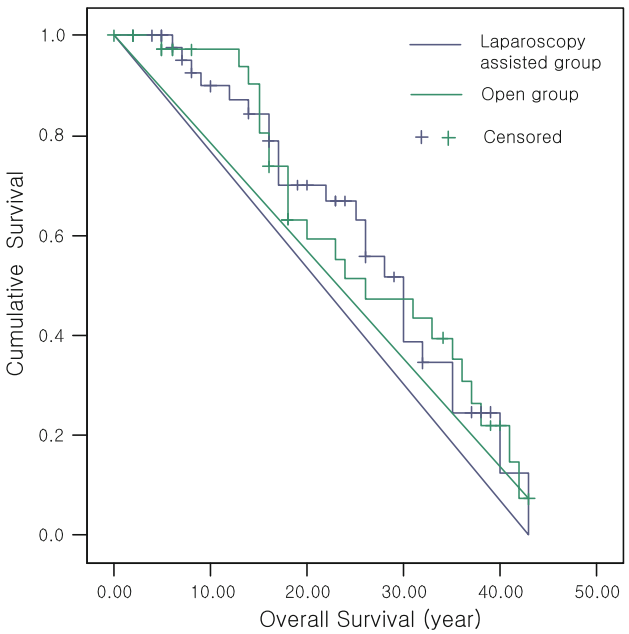

Fig. 1 Kaplan–Meier survival curve between open gastrectomy group and laparoscopy-assisted group

remained significantly associated with recurrence ($P = 0.00$). While OG was associated with higher incidence of recurrence than LAG on univariate analysis ($P = 0.02$), this was no longer statistically significant on multivariate analysis ($P = 0.06$) (Table 4).

Kaplan–Meier survival analysis

To compare the outcomes of OG and LAG, Kaplan–Meier survival analysis was performed. Median survival was 30 months, and the two groups did not differ significantly ($P = 0.96$) (Fig. 1).

Discussion

Use of LAG for AGC was first reported more than 10 years ago by Uyama et al., who described laparoscopy-assisted total gastrectomy with D2 LN dissection and distal pancreaticosplenectomy for advanced upper-third gastric cancer [8]. Subsequently, Goh et al. and Ziqiang et al. reported their early experiences with laparoscopic radical gastrectomy with D2 node dissection for AGC [22]. Those authors reported that, while LAG required longer operation time, it was also associated with lower blood loss, reduced need for pain control, and faster recovery. In 2007, Lee et al. reported the results of a phase II clinical trial that indicated the feasibility of laparoscopic D2 node dissection [14]. Thereafter, Song et al. and Tokunaga et al. reported that it is possible to perform radical subtotal gastrectomy with D2 LN dissection by laparoscopy; they also noted that operation times were longer for laparoscopic D2 dissection than for D1 + β, but that both had the same surgical outcome [15]. A number of reports have also been published recently on the surgical outcome of LAG in Korea. Hur et al. reported that LAG and OG did not differ in terms of 3-year overall survival or disease-free survival; they also suggested that the inclusion criteria for LAG could be expanded to include subserosa invasion [17]. Hwang et al. and Lee et al. reported that LAG is associated with good long-term survival, although their follow-up periods were relatively short (23.6 and 21.5 months, respectively) [12, 13].

In the present study, multivariate analysis showed that high TNM stage was a significant risk factor for recurrence. While univariate analysis found that operation type, method of approach, and larger tumor size (>4 cm) were also significantly associated with recurrence, this was not repeated on multivariate analysis. This discrepancy may relate to selection bias, since patients with high TNM stage were more likely to select open surgery and total gastrectomy rather than laparoscopy and subtotal gastrectomy.

The main aim of this study is to evaluate the risk of recurrence associated with LAG relative to OG. OG and LAG did not differ in terms of recurrence. Moreover, when they were divided into EGC and AGC subgroups, the EGC-OG subgroup did not differ from the EGC-LAG subgroup, and the same was true for the AGC-OG and AGC-LAG subgroups. Further supporting the safety of the LAG procedure is the pattern of recurrence. The most common recurrence sites were found to be the liver and peritoneum, which is suggestive of systemic metastasis; recurrence in the gastric bed occurred in only 14.2% of LAG cases. However, one case of trocar-site recurrence after LAG has been reported in the literature [23]. After this, specimens were removed more carefully en bloc; use of gloves when handling the trocar is also recommended when small specimens, such as separated lymph nodes, are delivered during LAG.

Many studies have addressed the risk of recurrence in gastric cancer. Patient age, degree of tumor spread (which is related to depth of invasion and growth potential of the cancer cells), and extended lymph node dissection were all found to be closely associated with gastric cancer recurrence and poorer overall prognosis [24, 25]. Moreover, Bormann type III or IV, poorly differentiated tumors, as well as tumors with serosal invasion, adjacent tissue invasion, or free intraperitoneal cancer cells, have been reported to be associated with high risk of subsequent peritoneal spread [24, 26–28]. In EGC, Wu et al. reported high risk of recurrence in the elderly in cases associated with lymphatic and submucosal involvement and when a positive family history was present [29]. In addition, Lai et al. reported that male gender, elevated gross type, and presence of lymph node metastasis are related to early recurrence of EGC [30]. Deng et al. reported that limited lymphadenectomy, few dissected nodes, and serosal involvement are related to postoperative recurrence in lymph-node-negative gastric cancer patients [31]. The results of the present study are consistent with those of previous studies, since high TNM stage was found to be an independent factor for tumor recurrence.

With regard to diagnostic tools, the most useful diagnostic tool for detecting recurrence was spiral CT scan (64.2%), but few of these patients (8.8%, $n = 3$) were eligible for curative resection. While gastrofiberoscopy only detected 15% ($n = 8$) of the recurrences, half of these patients ($n = 4$) were eligible for curative resection; therefore, frequent endoscopy is recommended for not only young patients but also elderly patients who have good performance status. Small lung metastases were detected by chest posteroanterior X-ray in two cases, which makes this procedure a useful and cost-effective test.

Use of LAG to treat AGC is associated with several problems. First, exact preoperative staging is a difficult process. Ahn et al. reported that the predictive values of esophagogastroduodenoscopy, spiral CT, and EUS were

87.4%, 92.2%, and 94.1% for EGC [32]. The predictive values for negative nodes with spiral CT and EUS were 90.1% and 92.6%, respectively. Those authors reported that cancers located in the upper third of the stomach and larger tumors measuring more than 2 cm tend to be underestimated. Second, there is a degree of technical difficulty associated with this procedure; for example, in the present study, AGC cases were treated with total omentectomy and D2 node dissection, which proved to be quite difficult procedures, even for an experienced laparoscopic surgeon. In addition, for cancers located in the upper third of the stomach, the anastomosis of the esophagojejunostomy as well as the dissection of LN 11d and LN 10 have been reported to be difficult to perform [21]. These problems could be resolved by using a robotic operation system, but its high cost remains a problem. Although there is no evidence that laparoscopic D2 gastrectomy improves survival of patients with AGC, it is likely to attract an increasing number of patients in the future because of its apparent superiority in terms of early postoperative quality of life when compared with open D2 surgery [33]. Additional large-scale prospective randomized multicenter trials are needed to evaluate the safety of LAG for AGC.

The present study has several limitations. Firstly, it is a retrospective nonrandomized study. Secondly, only short-term follow-up could be used to evaluate overall survival. Thirdly, the LAG group only had a small number of cases with high TNM stage. Fourthly, although it has been reported that LAG is more strongly associated with better quality of life compared with OG [10, 11], our study found that LAG was associated with a shorter the first day of flatulence, than OG, which we could not find in hospital stay. The present study also has several advantages. Firstly, the procedures were performed by a single, expert laparoscopic surgeon, and the medical reports originated from one institution. Secondly, the study included a large group of patients with AGC whose T stages exceeded T2 (41.8%, $n = 109$). Thirdly, 91% of patients with recurrence were diagnosed at the institution where the study was carried out, which facilitated detailed research and analysis of the diagnostic tools and recurrence patterns.

In conclusion, the present study showed that LAG did not differ from OG in terms of recurrence, even for patients with AGC. In addition, high TNM stage was found to be significantly associated with recurrence on multivariate analysis. Therefore, it can be concluded that LAG is safe and feasible and could be an alternative to open surgery, even for patients with AGC.

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