ORIGINAL

Risk factors for recurrence of gastric cancer after curative laparoscopic gastrectomy

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Abstract : *Introduction* : Curative laparoscopic gastrectomy (LG) is associated with good outcomes when performed for early gastric cancers. The aim of this study was to identify risk factors for recurrence after LG. *Methods* : 212 patients with gastric cancer who underwent gastrectomy were enrolled (LG : 143, open gastrectomy, OG : 69). Univariate analysis was used to assess overall (OS) and disease-free survival (DFS) in LG and OG group. Multivariate analysis was used to assess risk factors for recurrence after LG. *Results* : In LG, six cases of recurrence were observed (liver : 2, peritoneum : 4). Neither lymph node nor port-site recurrences were evident after LG. The 5-year DFS after LG was 91.4%. Based on univariate analysis of 5-year DFS, three negative prognostic factors-lymph node metastasis, lymphatic invasion, and venous invasion-were identified. The independent risk factor for recurrence of LG was lymph node metastasis. LG and OG showed no significant differences in 5-year DFS among Stage IA, IB, IIA, and IIB groups. Independent risk factors for recurrence after LG or OG were tumor invasion≥muscularis mucosa and lymph node metastasis. *Conclusions* : DFS following LG is comparable to that following OG. Lymph node metastasis is an independent risk factor for gastric cancer recurrence after LG. J. Med. Invest. 64 : 79-84, February, 2017

Keywords **:** *Laparoscopic gastrectomy, Recurrence, Lymph node metastasis*

INTRODUCTION

Since laparoscopic gastrectomy (LG) for gastric cancer was introduced by Kitano *et al.* in 1994, the number of patients undergoing LG for gastric cancer has continued to increase rapidly (1). LG has four major advantages when compared with conventional open gastrectomy (OG) : 1) less intra-operative blood loss, 2) less post-operative pain, 3) less respiratory dysfunction, and 4) shorter hospital stays (2, 3). In Japan, patients with early gastric T1N0 cancer, which is characterized by invasion of the mucosa and submucosa and the absence of lymph node metastasis, have under gone LG with D1 or D1+ lymph node dissection. Recently, LG with extended lymph node dissection (D2) has been the prevailing treatment for advanced gastric cancer in some institutions (4). However, the Gastric Cancer Treatment Guidelines (3rd edition) state that indications for LG should be determined following additional clinical trials involving randomized control studies (5). Therefore, LG for advanced gastric cancer remains controversial.

Notably, a case involving port-site recurrence after LG (7). Therefore, indicators of disease recurrence after LG remain unclear because laparoscopic surgery has specific recurrences that are different than open gastrectomy (OG). The aim of this study was to identify risk factors for disease recurrence following LG and compared these risks with those identified for OG.

PATIENTS AND METHODS

From January 2004 through December 2010, 212 patients (132 men, 80 women ; mean age 68 years ; age range 35-91 years) were referred to our institution for treatment of gastric cancer. To match the backgrounds of the patients in the LG group with those of patients in the OG group, the OG group included only patients with fStage I or II cancer.

Eligibility criteria for laparoscopic versus open surgery

Of the 212 patients, 143 (85 men, 58 women ; mean age=66 years ; age range=40-89 years) underwent laparoscopic procedures. Written informed consent was provided by each patient before surgery. LG with D1 or D1+ lymph node dissection were performed for clinical stage IA cancers ; LAG with D2 dissection were performed for stage IB (T2N0) cancers ; all cancer staging was based on the Japanese Gastric Cancer Treatment Guidelines 2010 (5). Of the 212 patients, 69 (47 men, 22 women ; mean age=72 years ; age range=35-91 years) underwent OG (Table 1). OG with D1 or D1+ or OG with D2 were performed for cases involving clinical stage IB (T1N1) or stage II cancers or for cases in which LG was not indicated for non-oncological reasons.

Lymph node dissection strategy of LAG

In the Japanese Gastric Cancer Treatment Guidelines 2010 (5), LG has been categorized as appropriate for clinical trials in cases involving clinical stage IA or IB cancers. Therefore, according to the treatment plan, LG with lymph node dissection (D1 or D1+) was performed for T1N0 disease and LG with lymph node dissection (D2) was performed for cT2N0 disease. However, limited lymph node dissection was performed for the elderly patients or patients with severe comorbidities. All cancer staging was based on the Japanese Classification of Gastric Carcinoma (JCGC) (3rd English edition, corresponds to the Japanese 14th edition) (6).

Parameters

General clinical and clinicopathological data from each eligible patient were retrieved from medical reports ; all data was reviewed

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Table 1. Clinicopathological characteristics in LG and OG group.

Factors	LAG (n=143)	OG (n=69)	p-value
Age (median)	40-89 (66)	35-91 (72)	N.S.
Gender : male/female	85/58	47/22	N.S.
Gastrectomy : Distal/Total/Proximal/Other	107/33/1/2	31/31/1/6	N.S.
Lymph node dissection : D1,D1+/2	113/30	32/37	<0.05
Number of dissected lymph nodes (Median)	25	27	N.S.
Differentiation : Differentiation/Undifferentiation	88/55	40/29	N.S
fT (T1/T2/T3)	120/21/2	33/32/4	<0.05
fN (N(-)/N(+))	118/25	50/19	N.S.
fStage (I/II/III)	129/11/3	50/19/0	N.S.
ly (+/-)	42/101	27/42	N.S.
v (+/-)	16/127	25/44	<0.05

retrospectively. LG and OG groups were compared with regard to six variables, pathological stage (which was based on JCGC staging), operative procedures, extent of lymph node dissection, number of dissected lymph nodes, postoperative morbidities, and postoperative mortalities.

Evaluation of curability

The JCGC staging and the gastric cancer clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) both define three criteria used to determine whether a gastric cancer indicates curative resection : 1) no involvement of the proximal and distal margins, 2) proximal and distal distances of no less than 10 mm, and 3) sufficient lymph node dissection with no fewer than 15 lymph nodes dissected (7). Each eligible patient was evaluated using these criteria. The LG and OG groups were compared with regard to recurrence site and long-term disease-free survival (DFS).

Follow-up schedule

Follow-ups were scheduled on a 6-month basis for 10 years ; each follow-up included a clinical examination ; monitoring of serum CEA, CA19-9, and CA125 cancer antigen levels ; endoscopy ; abdominal CT scan ; or some combination thereof.

Statistical analysis

The unpaired Student's t-test or the Mann-Whitney U test was used statistical analysis of continuous variables ; the χ^2 test was used for categorical variables. For all three tests, $p < 0.05$ was interpreted as significant. Values for each continuous variable are expressed as a mean±the standard deviation (SD). Long-term prognosis was determined by the Kaplan-Meier method using JMP 8 software (SAS Institute, Cary, NC, USA). The log-rank test was used to assess the significance of differences in DFS between the LG and OG groups.

RESULTS

The clinicopathological characteristics of patients in the LG and OG groups are shown in Table 1. The percentage of D1 and D1+ lymph node dissections was higher for the LG group than the OG group. Similarly the percentage of cases involving T1 cancers, which invaded only the mucosa or submucosa, but no venous invasion, was higher for the LG group than the OG group.

DFS following LG and risk factors for disease recurrence following LG

A comparison between cStage (clinical Stage) and fStage (final Stage) cancers is presented in Table 2. Indications for LG were limited to cT2 and cN0 cancers, which invaded only up to the mucosal plate and did not involve lymph node metastasis ; therefore, the proportion of IA and IB cancers among the cStage cancers was 71.3% and 28.7%, respectively. Among fStage cancers, the proportions of IA, IB, IIA, IIB, and IIIA were 74.1%, 16.1%, 6.3%, 1.4%, and 2.1%, respectively. The proportion of overdiagnosis (≧fStage II) was 9.8%.

Table 2. Comparison between cStage and fStage in LG

Stage	cStage (n=143)	fStage (n=143)
IA	102 (71.3%)	106 (74.1%)
IB	41 (28.7%)	23 (16.1%)
IIA	0 (0%)	9 (6.3%)
IIB	0 (0%)	2 (1.4%)
IIIA	0 (0%)	3 (2.1%)

The 5-year OS and DFS rates for the LG were 94.1% and 91.4%, respectively (Figures 1a and 1b). Based on univariate analyses, four factors-lymph node metastasis, JGCA stage, lymphatic invasion, and venous invasion-were each significant negative indicators for DFS in LG (Table 3). The rate of recurrence after LG was higher for cancers with more lymph node metastases (recurrence rate ; fN0 1.7%, fN1 14.3%, fN2 ≦25%, data not shown). Based on a multivariate analysis, the only independent risk factor for disease recurrence after LG was fN (+) (Table 4).

Sites of recurrence and DFS following LG or OG

The recurrence rates in the LG and OG groups were 4% and 9%, respectively, and this difference was statistically significant ($p < 0.05$). Among the 143 patients who underwent LG, two developed post-operative liver metastasis, and four developed peritoneal disseminations. Neither port-site recurrence nor lymph node metastasis was observed (data not shown).

DFS following LG was significantly better than that following OG (5-year-DFS ; LG 91.4% vs. OG 77.5%, $p < 0.01$) (Figure 2). Among the cases involving fStage cancers, 5-year DFS following resection

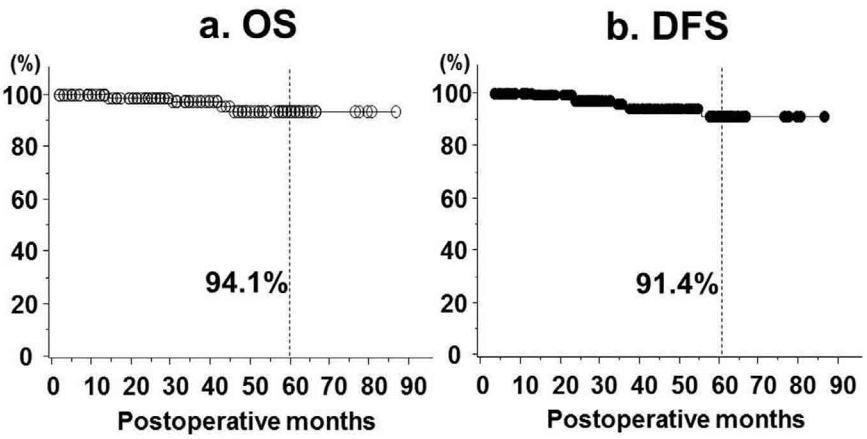

Figure 1a, b : OS and DFS curves for the LG group.

Table 3. Univariate analysis of 5-year DFS in LG.

Factors	5-year DFS (%)	p value
Age (≦65/65<)	95.4/85.8	0.26
Gender (male/female)	95.5/82.5	0.44
Lymph node dissection (D1, D1+/D2)	95.6/74.2	0.05
Differentiation : (Differentiation/Undifferentiation)	95.4/87.0	0.65
fT (T1/T2≦)	93.3/84.6	0.05
fN (-/+)	96.8/63.3	<0.01
fStage (I/II, III)	94.0/75.0	<0.01
ly (-/+)	97.7/77.4	<0.01
v (-/+)	92.8/83.1	<0.05

Table 4. Multivariate analysis of 5-year DFS in LG.

Factors	HR (95%CI)	p value
Age (65<)	3.009 (0.490-18.47)	0.72
Gender (female)	0.680 (0.083-5.606)	0.68
Lymph node dissection (D2)	0.961 (0.097-9.490)	0.97
Differentiation (Undifferentiation)	0.727 (0.091-5.814)	0.76
fT (fT2≦)	2.387 (0.323-17.62)	0.39
fN (+)	6.277 (0.700-56.29)	<0.05

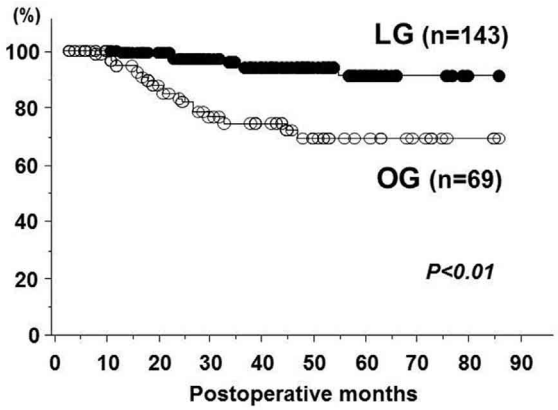

Figure 2 : Respective DFS curves for the LG and OG groups.

of fStage IA, IB, or II cancers was not different between the LG and OG groups (LG vs. OG ; IA 97.8% vs. 100%, IB 75.6% vs. 84.9%, II 79.5% vs. 43.1%) (Figure 3a, b, c).

The univariate analysis of DFS for all 212 cases (LG and OG) is presented in Table 5. Differentiation, tumor invasion, lymph node metastasis, stage, lymphatic and venous invasion, approach were each significant factors for DFS. The multivariate analysis found that tumor invasion and lymph node metastasis were each independent risk factors for disease recurrence following LG (Table 6). OG, which was identified as a significant prognostic factor in the univariate analysis, was not an independent risk factor for recurrence based on the multivariate analysis.

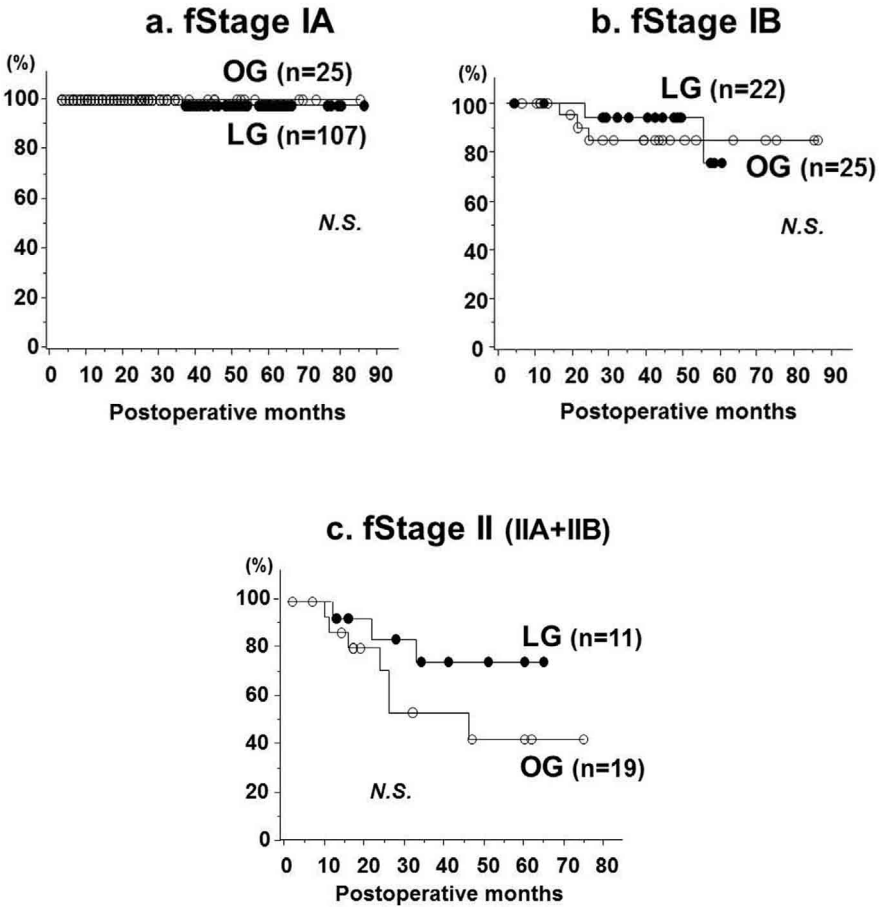

Figure 3a, b, c : DFS curves of LG and OG according to fStage.

Table 5. Univariate analysis of 5-year DFS in all cases (LG and OG).

Factors	5-year DFS (%)	p value
Age (≦65/65<)	87.2/77.7	0.19
Gender (male/female)	82.2/82.7	0.29
Lymph node dissection (D1, D1+/D2)	82.2/75.9	0.67
Differentiation : (Differentiation/Undifferentiation)	91.3/73.6	<0.05
fT (T1/T2≦)	93.5/65.7	<0.01
fN (-/+)	93.4/59.5	<0.01
fStage (I/II, III)	93.3/53.0	<0.01
ly (-/+)	94.4/64.3	<0.01
v (-/+)	90.0/60.3	<0.01
Approach (LG/OG)	91.4/69.0	<0.01

Table 6. Multivariate analysis of 5-year DFS in all cases (LG and OG).

Factors	HR (95%CI)	p value
Age (65<)	1.871 (0.772-4.537)	0.17
Gender (female)	1.787 (0.683-4.673)	0.24
Lymph node dissection (D2)	2.208 (0.780-6.250)	0.14
Differentiation (Undifferentiation)	2.208 (0.875-5.574)	0.09
fT (fT2≦)	5.170 (1.476-18.11)	<0.05
fN (+)	4.187 (0.695-11.25)	<0.01
Approach (OG)	2.171 (0.695-6.781)	0.18

DISCUSSION

This study was designed to investigate the risk factors for disease recurrence after curative LG for gastric cancer. In the LG group, the 5-year OS was 94.1% ; DFS was 91.4% ; the recurrence rate was 3%, and the sites of recurrence were liver (n=2) and peritoneum (n=4). In the entire group of 212 consecutive patients, neither port-site nor lymph-node recurrence were observed. Based on a univariate analysis of data from 143 patients who underwent curative LG, lymph node metastasis, lymphatic and venous invasion were each significant negative prognostic factors. Furthermore, lymph node metastasis was identified as an independent risk factor for recurrence. DFS in LG was comparable to that in OG of the same fStage. Among all patients who underwent gastrectomy (LG or OG), ≧fT2 and fN (+) were each independent risk factors for disease recurrence. A laparoscopic approach was not an independent risk factor for recurrence. However, the limitation of this study was totally retrospective study.

Based on several studies that included randomized controlled trials, LAG with D1/D1+ lymph node dissection results in acceptable short- and long-term outcomes when used as a treatment for early gastric cancer (9-14).

Nevertheless, LAG with D2 lymph node dissection has not been recognized as a standard surgical option for advanced gastric cancer. Hamabe *et al.* reported that LG with D2 lymph node dissection was acceptable in terms of long-term results for advanced gastric cancer cases (15). At our institution, LG with D2 lymph node dissection has been performed for T2N0 gastric cancer. Based on an analysis of the fStage cancers in our series, the LG and OG groups did not differ significantly with regard to 5-year DFS. If the difficulty of D2 lymph node dissection can be overcome, LG will be the indicated surgical option for treatment of advanced gastric cancer.

In our study, fN(+) was identified as an independent risk factor for disease recurrence after LG ; notably, fN(+) was also an independent risk factor following OG. T stage and N stage are each reportedly independent risk factors for disease recurrence after LG (16). Lee *et al.* reported that N1-3 in early gastric cancers and N2,3 in advanced gastric cancers according to lymph node dissection were the most potent risk factors for disease recurrence after LG (17). Laparoscopic surgery for gastric cancer has a demonstrably smaller effect than conventional surgery on the inflammatory factors that have been implicated in local recurrence and peritoneal metastasis because laparoscopic surgery results in smaller postoperative immune responses, both in the peritoneum and systemically (18). In the present study, the recurrence rate after LG was significantly lower than that after OG. Therefore, laparoscopic surgery for gastric cancer may contribute to the suppression of disease recurrence after a curative operation when compared with conventional open surgery.

Limitations of our study were totally retrospective study, and a selection bias in background of the two groups. Therefore, the prospective and double blind study will be needed.

In conclusion, the long-term outcomes associated with LG are acceptable when compared with those of OG. Lymph node metastasis was identified as an independent risk factor for disease recurrence after LG. Therefore, laparoscopic gastrectomy may be adaptable to advanced gastric cancer with no preoperative indication of lymph node metastasis.

FOOTNOTES

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ABBREVIATIONS

LG ; Laparoscopic gastrectomy
OG ; Open gastrectomy
OS ; Overall survival
DFS ; Disease-free survival
JCGC ; the Japanese Classification of Gastric Carcinoma
CEA ; Carcinoembryonic antigen
CA19-9 ; Carbohydrate antigen 19-9
CA125 ; Cancer Antigen 125
CT ; Computed Tomography

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All investigations on human subjects must include a statement that the subject gave informed consent and patient anonymity should be preserved.

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