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Long-term outcomes after laparoscopy-assisted gastrectomy for advanced gastric cancer: a large-scale multicenter retrospective study

Do Joong Park · Sang-Uk Han · Woo Jin Hyung · Min Chan Kim · Wook Kim · Seong Yeob Ryu · Seung-Wan Ryu · Kyo Young Song · Hyuk-Joon Lee · Gyu-Seok Cho · Hyung-Ho Kim · Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) Group

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Abstract

Background Recently, the number of laparoscopic procedures for gastric cancer has increased rapidly. Laparoscopic surgery is reported to have many advantages over open gastrectomy with oncologic safety in early gastric cancer. However, there were few reports on long-term outcomes of laparoscopy-assisted gastrectomy (LAG) for advanced gastric cancer (AGC). The aim of this study was to investigate long-term survival outcomes after LAG for AGC.

Methods The data of 1,485 patients who underwent LAG between April 1998 and December 2005 by ten surgeons at ten hospitals were collected retrospectively. Among them, 239 patients who were diagnosed with AGC on final pathologic examination were enrolled in the present study to investigate long-term clinical outcomes.

Results The ratio of male to female patients was 151:88 and the mean age was 57.1 years. One hundred ninety-three subtotal gastrectomies, 41 total gastrectomies, and 5 proximal gastrectomies were performed. D1 + α, D1 + β, and D2 lymph node dissections were performed for 14, 62, and 163 cases, respectively. The median follow-up period was 55.4 months. The overall 5-year survival rate of the 239 AGC patients was 78.8% and the disease-specific 5-year survival rate was 85.6%. The 5-year survival rates of the TNM staging system's (7th ed.) stages were 90.5% (stage Ib, $n = 86$), 86.4% (stage IIa, $n = 53$), 78.3% (stage IIb, $n = 44$), 52.8% (stage IIIa, $n = 24$), 52.9% (stage IIIb, $n = 24$), and 37.5% (stage IIIc, $n = 8$) ($p < 0.001$).

Conclusion The long-term survival outcome rates of LAG for AGC in the present study were comparable to those previously reported for open gastrectomy. Based on

D. J. Park · H.-H. Kim (✉)
Department of Surgery, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Gyeonggi-do, Seongnam-si, Korea
e-mail: hhkim@snubh.org

S.-U. Han
Department of Surgery, Ajou University College of Medicine, Suwon, Korea

W. J. Hyung
Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

M. C. Kim
Department of Surgery, Dong-A University College of Medicine, Busan, Korea

W. Kim
Department of Surgery, Holy Family Hospital, Catholic University of Korea, Bucheon, Korea

S. Y. Ryu
Department of Surgery, Chonnam National University School of Medicine, Gwangju, Korea

S.-W. Ryu
Department of Surgery, Keimyung University School of Medicine, Daegu, Korea

K. Y. Song
Department of Surgery, Kangnam St. Mary's Hospital, Catholic University of Korea, Seoul, Korea

H.-J. Lee · H.-H. Kim
Department of Surgery, Seoul National University College of Medicine, Seoul, Korea

G.-S. Cho
Department of Surgery, Soonchunhyang University College of Medicine, Seoul, Korea

the present results, a well-designed phase III trial comparing LAG and open gastrectomy for AGC will be needed to affirm the validity of LAG for AGC.

Keywords Laparoscopy-assisted gastrectomy · Advanced gastric cancer · Long-term survival

Gastric cancer is one of the life-threatening cancers in the world and is the most prevalent cancer in Korea. The most important treatment for gastric cancer is surgery. The definitive surgery for gastric cancer is subtotal or total gastrectomy with D2 lymph node dissection. However, because the incidence of early gastric cancer has increased due to a national health screening program in Korea and Japan, the concept of minimally invasive surgery such as endoscopic submucosal dissection or laparoscopic gastrectomy was introduced in the field of gastric cancer surgery [1]. Recently, the number of laparoscopic procedures for gastric cancer has increased rapidly [2]. Laparoscopic surgery is reported to have many advantages over open gastrectomy, with oncologic safety in early gastric cancer [3–8]. However, there were few reports on long-term outcomes of laparoscopy-assisted gastrectomy (LAG) for advanced gastric cancer (AGC) [9–11]. Therefore, we aimed to investigate the outcome of LAG for AGC. This multicenter retrospective study can be considered a basis for a prospective randomized controlled trial (RCT) of LAG for AGC in the future.

Materials and methods

The data of 1,485 patients who underwent LAG for gastric cancer between April 1998 and December 2005 performed by ten surgeons at ten hospitals were collected retrospectively. Preoperative indications were cT1N0M0 (not suitable for endoscopic submucosal dissection), cT1N1M0, or cT2N0M0 (according to the 7th American Joint Committee on Cancer staging system) [12]. LAG, such as laparoscopy-assisted distal gastrectomy, laparoscopy-assisted proximal gastrectomy, and laparoscopy-assisted total gastrectomy, was performed as previously reported [13]. All patients underwent D1 + α, D1 + β, or D2 lymph node dissection [14, 15]. Among them, 239 patients who were diagnosed as AGC on final pathologic examination were enrolled in the present study. Patient demographics, postoperative complications, overall survival, disease-specific survival, and recurrences were investigated. The last follow-up month was December 2009. Follow-up information came from medical records, telephone calls, and the Korean National Statistical Office survey.

Survival rates were evaluated using the Kaplan–Meier method. Prognostic factors for overall survival after LAG for AGC were analyzed with the Cox regression model and $p < 0.05$ was regarded as significant. SPSS for Windows v13.0 (SPSS, Inc., Chicago, IL, USA) was used for the analysis.

Results

The data of 239 patients who underwent LAG from May 1998 to December 2005 was used in this study. Patient demographics are given in Table 1. The ratio of males to females was 151:88 and the mean age was 57.1 ± 12.5 years. One hundred ninety-three subtotal gastrectomies, 41 total gastrectomies, and 5 proximal gastrectomies were performed. D1 + α, D1 + β, and D2 lymph node

Table 1 Patient characteristics

Variables	*N*	%
M/F	151/88	
Age (mean ± SD) (years)	57.1 ± 12.5	
BMI (mean ± SD) (kg/m^2)	23.2 ± 3.1	
Comorbidity	99	41.4
Type of operation		
Distal gastrectomy	193	80.8
Total gastrectomy	41	17.2
Proximal gastrectomy	5	2.1
Lymph node dissection		
D1 + α	14	5.9
D1 + β	62	25.9
D2	163	68.2
Operation time (mean ± SD) (min)	235.4 ± 87.6	
Tumor size (mean ± SD) (cm)	3.5 ± 1.7	
Number of retrieved lymph nodes (mean ± SD)	33.6 ± 14.0	
T stage		
T2	130	54.4
T3	63	26.4
T4	46	19.2
N stage		
N0	128	53.6
N1	47	19.7
N2	41	17.2
N3	23	9.6
Stage		
Ib	86	36.0
IIa	53	22.2
IIb	44	18.4
IIIa	24	10.0
IIIb	24	10.0
IIIc	8	3.3
Adjuvant chemotherapy	124	51.9

SD standard deviation

dissections were performed for 14, 62, and 163 cases, respectively. The stages were as follows: Ib, 86 (36.0%); IIa, 53 (22.2%); IIb, 44 (18.4%); IIIa, 24 (10.0%); IIIb, 24 (10.0%); and IIIc, 8 (3.3%) cases.

Morbidity and mortality

The morbidity rate was 15.9% (38 of 239 patients) and mortality rate was 0.8% (2 of 239 patients). The types of complications encountered are listed in Table 2.

Follow-up results

The follow-up end point was December 30, 2009. The mean follow-up period was 53.5 ± 18.4 (range = 1–127) months. Median follow-up duration was 55.4 months. There were 40 (16.7%) recurrences during follow-up period (Table 3). The patterns of recurrences are listed in Table 4.

Survival and prognostic factors for survival

The overall 5-year survival rate of 239 AGC patients was 78.8% and the disease-specific 5-year survival rate was 85.6% (Fig. 1). There were statistically significant differences of overall survival according to T stage ($p < 0.001$) and N stage ($p < 0.001$) (Fig. 2). Significant differences of

Table 2 Complications after LAG for AGC

	Number ($n = 239$)	Percentage (%)
Morbidity	38	15.9
Wound problem	12	5
Fluid collection	4	1.7
Bleeding, intra-abdominal	1	0.4
Bleeding, intraluminal	3	1.3
Ileus	2	0.8
Stenosis	2	0.8
Leakage	4	1.7
Pulmonary	2	0.8
Hepatic	2	0.8
Others	6	2.5
Mortality	2	0.8

Table 3 Follow-up results of the patients

	Patients	%
Total	239	100
Alive	189	79.1
Dead	50	20.9
Gastric cancer-related	33	13.8
Others	17	7.1
Loss to follow-up	9	3.8
Recurrence	40	16.7

Table 4 Recurrences after LAG for AGC ($n = 40$)

	Ib	IIa	IIb	IIIa	IIIb	IIIc
Remnant			1		1	1
Lymph node			3	2	5	1
Liver	2	1	4		2	1
Peritoneum	2		3	4	1	3
Bone	1			1	5	1
Lung				1		
Ovary				1	1	1
Total number of patients	3	1	9	7	14	6

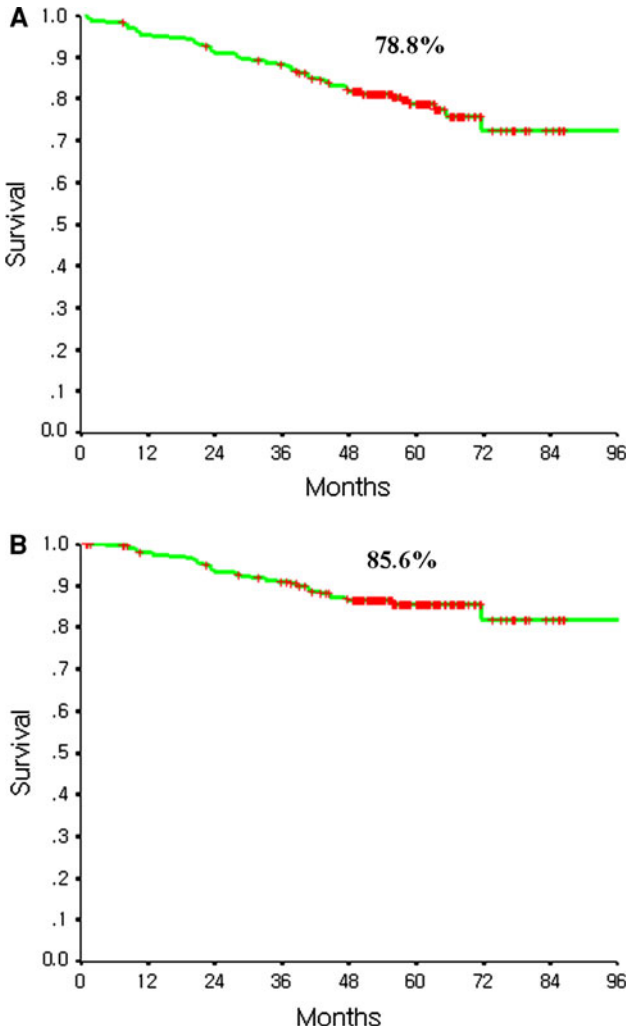

Fig. 1 Survival of patients after LAG for AGC ($n = 239$). The overall (**A**) and disease-specific (**B**) 5-year survival rates of all patients were 78.8 and 85.6%, respectively

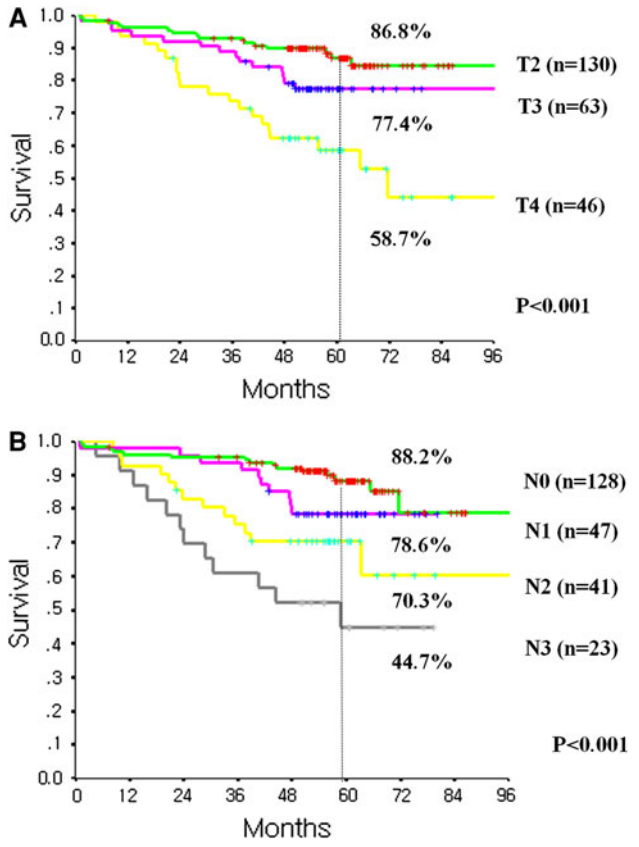

Fig. 2 Comparison of overall survival for patients after LAG for AGC according to T stage (**A**) and N stage (**B**)

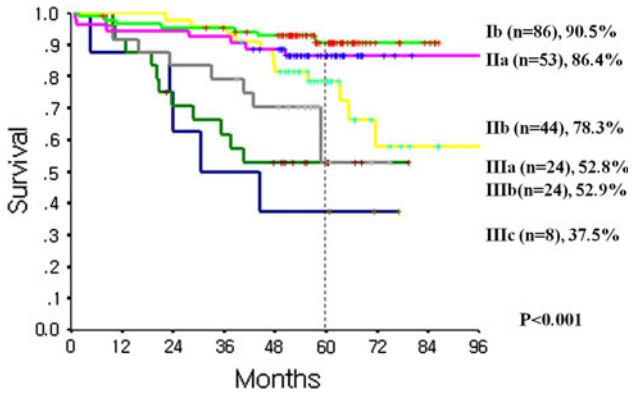

Fig. 3 Comparison of overall survival for patients after LAG for AGC according to stage

overall survivals also existed in staging ($p < 0.001$) (Fig. 3). In regard to prognostic factors for overall survival after LAG for AGC, age, operation time, T stage, and N stage were prognostic factors in univariate analysis, but age, T stage, and N stage were independent prognostic factors in multivariate analysis (Table 5).

Table 5 Prognostic factors for overall survival after LAG for AGC

Factors	Univariate *p*-value	Multivariate *p*-value
Age	0.016	<0.001
Sex	0.374	
BMI	0.081	
Operation time	0.015	
Extent of resection	0.591	
Extent of LN dissection	0.979	
Location	0.432	
Borrmann type	0.939	
Size	0.375	
Histology	0.507	
T stage	<0.001	0.006
N stage	<0.001	0.002
Adjuvant chemotherapy	0.007	

Discussion

Because of the many short-term advantages of laparoscopic surgery over open surgery, laparoscopic gastrectomy has rapidly gained its popularity for use in treating gastric cancer [3–7, 16]. Although the long-term results of the phase III KLASS trial are yet to be published, laparoscopic gastrectomy is considered to be accepted for early gastric cancer [17].

Application of laparoscopic gastrectomy for AGC remains controversial due to the technical difficulty of performing complete D2 lymphadenectomy and the few data available on the procedure's oncologic adequacy. One RCT and one retrospective case–control study including AGC showed that there was no significant difference between the two groups in terms of the number of resected lymph nodes, recurrence, or survival [9, 10]. One retrospective single-center study demonstrated that the 5-year overall and disease-free survival rates were 81.4% and 72.4%, respectively [11]. However, the number of cases was not large enough to prove the oncologic safety after LAG for AGC. Before conducting a large multicenter phase III RCT comparing laparoscopic gastrectomy with open gastrectomy for AGC, a large retrospective study on the long-term outcomes after LAG for AGC will be a good basis for such a prospective RCT.

In the present study, with a relatively large number of cases, laparoscopy-assisted distal gastrectomy with D2 dissection mainly was performed. The number of retrieved lymph nodes was considered to be oncologically acceptable. The complication rates and mortality rates in our study were also acceptable compared to previous reports [18, 19]. Thus, LAG for AGC can be regarded as technically feasible.

Table 6 Five-year overall survival rates after LAG for AGC compared to historical data

Stage	Present study (%)	SNUH [23] (%)	AJCC manual [12] (%)
IB	90.5	88.4	57.4
IIA	86.4	84.0	45.5
IIB	78.3	71.7	32.8
IIIA	52.8	58.4	19.8
IIIB	52.9	41.3	14.0
IIIC	37.5	26.1	9.2

SNUH Seoul National University Hospital; *AJCC* American Joint Committee on Cancer

In regard to recurrences after LAG for AGC, the recurrence rate in the present study was not higher than that of previous studies [20–22]. The majority of recurrences were distant metastases, which means that there was adequate local control by LAG. Most lymph node recurrences occurred around para-aortic and distant lymph nodes.

The present study's overall survival results stratified according to staging were comparable to historical data (Table 6) [12, 23]. Of course, the present study had two weak points: selection bias and a small number of cases in each stage. The retrospective data have selection bias in that the preoperative stage was cT2 or less than cT2 but the final pathologic stage was T2 or more than T2. Therefore, a prospective well-designed study for AGC should include cT2 or more than cT2 gastric cancers initially. Second, the sample size must be calculated appropriately to compare laparoscopic gastrectomy with open gastrectomy with good stratification of each stage.

Age, operation time, T stage, N stage, and adjuvant chemotherapy were prognostic factors for overall survival after LAG for AGC. However, multivariate analysis revealed that age, T stage, and N stage were the independent prognostic factors for overall survival. Unlike most studies on prognostic factors for survival in gastric cancer, age was one of the independent prognostic factors in the present study [24]. The cause of poorer prognosis in elderly gastric cancer patients might be that elderly patients have a weaker host-defense condition.

In conclusion, the long-term outcomes of LAG for AGC in the present study seem to be comparable to those previously reported for open gastrectomy. However, a well-designed prospective RCT will be needed to affirm the validity of LAG for AGC because the present study had selection bias and a small number of cases to stratify each stage.

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