

## Original Article

# Laparoscopic gastrectomy for locally advanced gastric carcinoma: long-term survival outcomes and prognostic factors

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**Abstract:** The purpose of this study was to evaluate the long-term outcomes of laparoscopic gastrectomy for patients with locally advanced gastric carcinoma. Of the 113 patients with locally advanced gastric carcinoma, 89 patients underwent laparoscopic total gastrectomy, while 24 patients underwent laparoscopic distal gastrectomy. There were no intraoperative or postoperative 30-day death occurred. The 3-, and 5-year overall survival rates were 64% and 57% respectively. Univariate analysis revealed that pathological T status, pathological N status, tumor size and cancer cell differentiation status were statistically significant factors affecting overall survival. Earlier pathological T status and earlier pathological N status were significantly predictive for longer overall survival by multivariate analysis. In summary, laparoscopic gastrectomy can be considered as an alternative to traditional incision in patients with locally advanced gastric carcinoma. A prospective randomized controlled study on a larger scale is required to reach definitive conclusions regarding the efficacy of laparoscopic gastrectomy relative to other techniques.

**Keywords:** Gastric carcinoma, laparoscopic gastrectomy, minimally invasive surgery, prognosis

## Introduction

Gastrectomy to treat early stage gastric carcinoma (cT1) using laparoscopy was first described in 1994 by Japanese general surgeon [1]. Compared with open gastrectomy, the benefits of laparoscopic gastrectomy for early stage gastric carcinoma stem primarily from its less traumatic approach and include reduced postoperative pain and impairment in abdominal muscle, lower cytokine production, and improved immune surveillance [2-10]. Various literatures have reported laparoscopic gastrectomy for early stage gastric carcinoma to be a safe procedure with acceptable long-term outcomes [11-14]. Prospective, multi-institutional studies have examined the feasibility of laparoscopic gastrectomy for early stage gastric carcinoma and demonstrated that laparoscopic gastrectomy is associated with low complication rate and faster recovery [15-17]. However, laparoscopic gastrectomy is still not practiced in locally advanced gastric carcinoma due to difficult technology and complexity of D2 lymph node dissection by laparoscopy. There are only

limited reports of laparoscopic gastrectomy for locally advanced gastric carcinoma [18-21]. Our institution has accumulated significant experience with laparoscopic surgery for early stage gastric carcinoma; therefore, we have expanded the indications for using laparoscopic surgery in patients with locally advanced gastric carcinoma. The purpose of this study was to evaluate the long-term survival outcomes of laparoscopic gastrectomy in 113 patients with locally advanced gastric carcinoma. This study also aimed to determine the significant prognostic factors predicting clinical outcome based on the seventh edition of tumor-node-metastasis (TNM) classification for gastric carcinoma proposed by Union for International Cancer Control (UICC), Japanese Gastric Cancer Association (JGCA) and American Joint Committee on Cancer (AJCC) [22-25].

## Patients and methods

This study complied with the Declaration of Helsinki. This retrospective research was approved by our local ethics committees. The need

**Table 1.** Patient characteristics (n=113)

Characteristics	n (%)
Age, years (range)	60 (40-77)
Sex	
Male	68 (%)
Female	45 (%)
ASA score	
I	91 (%)
II	19 (%)
III	3 (%)
Comorbidity	
None	91 (%)
Present	22 (%)
Liver cirrhosis	3 (%)
Hypertension	8 (%)
Type 2 diabetes mellitus	5 (%)
Stable angina	1 (%)
Chronic arrhythmia	3 (%)
Chronic heart failure	2 (%)
Clinical TNM stage (7th AJCC-UICC)	
IB	48 (%)
IIA	36 (%)
IIB	29 (%)

**Table 2.** Surgical and pathological data

Data	n (%)
Type of resection	
Laparoscopic total gastrectomy	89 (%)
Laparoscopic distal gastrectomy	24 (%)
Operative time (min)	190 (range 160-270)
Blood loss (ml)	150 (range 120-300)
Postoperative stay (days)	9 (range 7-35)
Retrieved lymph nodes	18 (range 17-26)
Pathological TNM stage (7th AJCC-UICC)	
IB	29 (%)
IIA	28 (%)
IIB	26 (%)
IIIA	11 (%)
IIIB	12 (%)
IIIC	7 (%)
Surgical margin (R0/R1/R2)	113/0/0
Histological type	
Differentiated	58 (%)
Undifferentiated	55 (%)

for informed consent from patients was waived because of its retrospective nature.

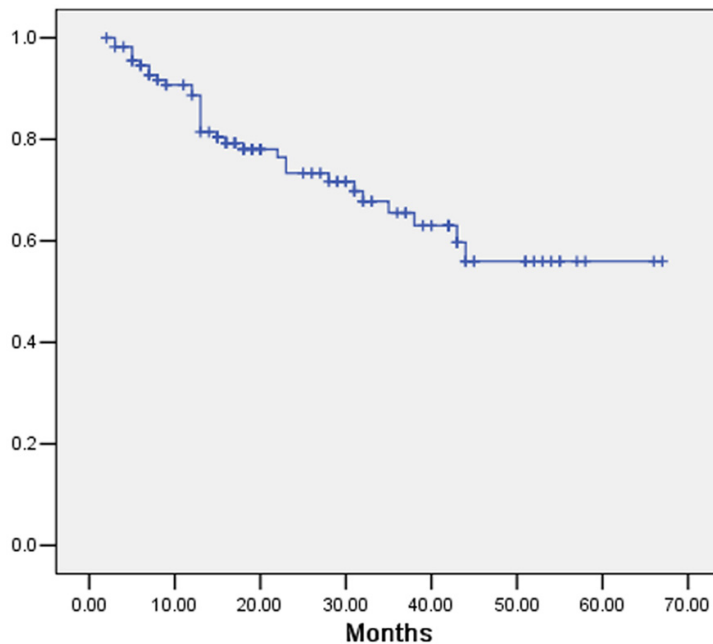
Between January 2010 and September 2015, 113 patients with clinical T2-3N0-1M0 gastric carcinoma who underwent complete removal of the primary tumor together with D2 lymph node dissection formed the basis of this retrospective research. Patients who had evidence distant metastasis were excluded from this retrospective research. TNM staging was carried out according to the seventh edition TNM Classification of gastric carcinoma by the UICC, JGCA and AJCC [22-25].

The preoperative workup included upper gastrointestinal endoscopy, endoscopic ultrasonography, computed tomographic scans of brain, chest, and abdomen, ultrasonography of abdomen. Positron emission tomography-computerized tomography (PET-CT), staging laparoscopy and bone scanning were performed if clinically indicated [26-28]. All patients underwent real-time video staging by laparoscopy before radical operation.

The technical aspects of laparoscopic gastrectomy with D2 lymph node dissection for locally advanced gastric carcinoma have been described previously [21]. The lymph nodes map was proposed by latest JGCA guideline [25]. Patients were placed in the supine position with legs apart, and were under general anesthesia. Carbon dioxide pneumoperitoneum was established at 15 mmHg after a 12-mm trocar was introduced through an umbilical incision. Two 12-mm trocars were introduced in the left and right lower quadrants, and two 5-mm trocars were inserted in the left and right upper quadrants. For distal gastrectomy, the D2 lymph nodes dissected were as follows: right cardiac lymph nodes (No. 1 station), lesser curvature lymph nodes (No. 3 station), lymph nodes along the left gastroepiploic vessels (No. 4sb station), lymph nodes along the right gastroepiploic vessels (No. 4d station), suprapyloric lymph nodes (No. 5 station), infrapyloric lymph nodes (No. 6 station), left gastric

**Table 3.** Postoperative 30-day complications

Data	n (%)
Cardiovascular complications	
Atrial fibrillation	4 (%)
Heart failure	2 (%)
Gastrointestinal complications	
Anastomotic leak	6 (%)
Intra-abdominal bleeding	2 (%)
Intra-abdominal abscess	3 (%)
Pancreatic fistula	3 (%)
Others	
Urinary system infection	3 (%)
Total	22
Major complications	3 (%)
Minor complications	19 (%)
Mortality (deaths within 30 postoperative days)	0

**Figure 1.** Cumulative Kaplan-Meier overall survival curves for patients with locally advanced gastric carcinoma.

artery lymph nodes (No. 7 station), common hepatic artery lymph nodes of anterosuperior group (No. 8a station), coeliac artery lymph nodes (No. 9 station), lymph nodes along the proximal splenic artery (No. 11p station) and lymph nodes in the hepatoduodenal ligament (No. 12a station). For total gastrectomy, the D2 lymph nodes dissected were as follows: the lymph nodes dissected in distal gastrectomy,

lesser curvature lymph nodes (No. 3 station), lymph nodes along the short gastric vessels (No. 4sa station), lymph nodes at the splenic hilum (No. 10 station) and lymph nodes along the distal splenic artery (No. 11d station) [21].

The length of postoperative hospital stay, all major and minor postoperative 30-day complications, and postoperative 30-day death were recorded from the medical database. Severity of postoperative 30-day complications was classified using Clavien-Dindo classification. The definition of Clavien-Dindo system was as follows: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death related to surgical complication. Major complications were classified as grades 3, 4 and 5. Minor complications were defined as 1 and 2 [29]. All slides were checked by two pathologists with proven experience in gastrointestinal tumor. The adjuvant chemotherapy was decided by internists with proven experience in gastric carcinoma and the general performance status of the patients after gastric resection [30, 31]. Adjuvant radiation therapy was not used in our series.

Follow-up data were obtained from outpatient clinic visits. Disease recurrence was defined as locoregional, peritoneal or distant metastasis proven by radiology or pathology, when available [32-34]. Follow-up of patients was ended in April 2015. The overall survival was assessed from the date of surgery until the last follow up or death of any cause. The disease-free survival was calculated from the date of surgery until

**Table 4.** Univariate analysis of overall survival

Characteristics	Five-year overall survival rate (%)	P value
Sex		0.325
Male	61	
Female	55	
Age		0.201
<65 years	63	
≥65 years	52	
Medical comorbidity		0.092
No	69	
Yes	53	
Type of resection		0.145
Total gastrectomy	54	
Distal gastrectomy	64	
Pathological T status		0.001
T <sub>2</sub>	74	
T <sub>3</sub>	56	
T <sub>4</sub>	46	
pathological N status		0.002
N <sub>0</sub>	84	
N <sub>1</sub>	61	
N <sub>2</sub>	31	
N <sub>3</sub>	23	
Tumor size		0.035
<5 cm	69	
≥5 cm	48	
Cell differentiation status		0.028
Differentiated	62	
Undifferentiated	45	
Vascular invasion		0.112
No	59	
Yes	48	

the date of cancer recurrence or death from any cause.

Variables were presented as mean and standard deviations for variables following normal distribution. For variables following non-normal distribution, data were expressed as median and range. Survival was calculated by the Kaplan-Meier method, and differences in survival were determined by log-rank analysis. Possible prognostic factors associated with survival probability at a significance level of 0.10 or less were considered in a multivariable Cox's proportional hazard regression analysis. Conversions from laparoscopic to laparotomy were analyzed in the laparoscopy cohort by the

“intent-to-treat” method. Analysis was performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, with the threshold of significance set at  $P < 0.05$  level.

## Results

Patient baseline characteristics are summarized in **Table 1**. The study cohort consisted of 68 men and 45 women with a median age of 60 years (range, 40-77 years). The type of resection and pathological diagnoses for these 113 patients are listed in **Table 2**. The median operating time was 190 min (range, 160-270 min) and median blood loss was 150 ml (range, 120-300 ml). The median number of dissected lymph nodes was 18 (range, 17-26). Four (3.5%) patients required conversion to open resection due to intra-operative complications such as adhesions ( $n=2$ ) and severe bleeding ( $n=2$ ). These cases were included in the analysis by the “intent-to-treat” analysis. The median length of postoperative hospital stay was 8 days (range, 7-35 days).

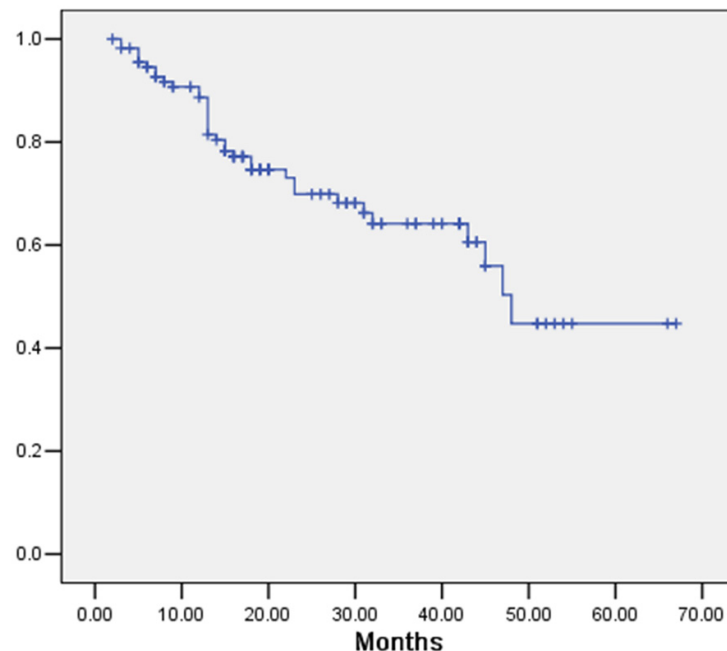
There were no intra-operative deaths. There were no deaths within 30 postoperative days. There were no postoperative 30-day complications in 94 patients (%). The remaining 19 patients (%) had one or more postoperative 30-day complications, which are listed in **Table 3**.

The median follow-up time was 39 months (range, 3-67 months). The 3- and 5-year overall survival rates were 64% and 57% respectively (**Figure 1**). Univariate analysis by log-rank test indicated that pathological T status, pathological N status, tumor size and cancer cell differentiation status were statistically significant for overall survival (**Table 4**). Earlier pathological T status and earlier pathological N status were significantly predictive for longer overall survival by multivariate analysis (**Table 5**).

The 3- and 5-year disease-free survival rates were 62% and 43% respectively (**Figure 2**). Univariate analysis by log-rank test indicated that pathological T status, pathological N status and vascular invasion status were statistically significant for disease-free survival (**Table 6**). Earlier pathological T status and earlier pathological N status were significantly predic-

**Table 5.** Multivariate analysis of overall survival

Characteristics	HR (95% CI)	P value
Medical comorbidity		0.120
No	Reference group	
Yes	1.253 (0.751-1.402)	
Pathological T status		0.008
T <sub>2</sub>	Reference group	
T <sub>3</sub>	1.654 (0.900-1.981)	
T <sub>4</sub>	3.214 (1.254-5.241)	
pathological N status		0.001
N <sub>0</sub>	Reference group	
N <sub>1</sub>	1.058 (0.654-1.325)	
N <sub>2</sub>	2.540 (1.025-3.005)	
N <sub>3</sub>	3.445 (2.021-4.450)	
Tumor size		0.121
<5 cm	Reference group	
≥5 cm	1.541 (0.741-1.695)	
Cell differentiation status		0.297
Differentiated	Reference group	
Undifferentiated	1.301 (0.589-1.510)	

**Figure 2.** Cumulative Kaplan-Meier disease-free survival curves for patients with locally advanced gastric carcinoma.

tive for longer disease-free survival by multivariate analysis (**Table 7**).

### Discussion

Since the use of laparoscopic gastrectomy for early gastric carcinoma was first reported in 1990s [35], this minimally invasive gastrecto-

my has been performed with increasing frequency. Advocates of laparoscopic gastrectomy emphasize the benefit in terms of less tissue trauma, decreased postoperative pain, reduced cytokine release, less postoperative complication rates, and shorter hospital stay. Previous series suggested that laparoscopic gastrectomy can be performed with low morbidity and mortality rates [3-8]. Randomized clinical trials evaluated the technical feasibility and safety of laparoscopic gastrectomy for early stage gastric carcinoma and demonstrated that the procedure is associated with faster recovery [15-17]. Recent meta-analysis of nonrandomized trials evaluating the safety and efficacy of laparoscopic gastrectomy for locally advanced gastric carcinoma demonstrated that laparoscopic gastrectomy may become a valid alternative to open surgery if performed in qualified centers though no randomized clinical trials reporting [1, 6, 20].

Our results are comparable to previous reports [3-8, 36, 37]. In our series, postoperative mortality and morbidity rates were 1.3% and 9.1%, respectively. We have performed 113 laparoscopic gastrectomies for locally advanced gastric carcinoma during a relatively short period at a single institution; this may have resulted in a relatively homogeneous quality of perioperative management.

Despite these favorable short-term outcomes, the adequacy of laparoscopic gastrectomy for oncologic control still needs to be proven compared with standard open gastrectomy [38-42]. Concerns about the possibility of laparoscopy-related recurrence in laparoscopic gastrectomy when compared with open gastrectomy may be related to the possibilities of cancer dissemina-



**Table 6.** Univariate analysis of disease-free survival

Characteristics	Five-year disease-free survival rate	P value
Sex		0.320
Male	54	
Female	39	
Age		0.530
<65 years	51	
≥65 years	40	
Medical comorbidity		0.090
No	54	
Yes	39	
Type of resection		0.258
Total gastrectomy	49	
Distal gastrectomy	38	
Pathological T status		0.017
T <sub>2</sub>	63	
T <sub>3</sub>	51	
T <sub>4</sub>	40	
pathological N status		0.011
N <sub>0</sub>	84	
N <sub>1</sub>	58	
N <sub>2</sub>	30	
N <sub>3</sub>	18	
Tumor size		0.150
<5 cm	57	
≥5 cm	41	
Cell differentiation status		0.087
Differentiated	58	
Undifferentiated	39	
Vascular invasion		0.044
No	51	
Yes	32	

**Table 7.** Multivariate analysis of disease-free survival

Characteristics	Five-year disease-free survival rate	P value
Medical comorbidity		0.148
No	Reference group	
Yes	Reference group	
Pathological T status		0.002
T <sub>2</sub>	Reference group	
T <sub>3</sub>	1.369 (0.821-1.581)	
T <sub>4</sub>	2.287 (1.854-4.251)	
pathological N status		0.008
N <sub>0</sub>	Reference group	
N <sub>1</sub>	1.141 (0.547-1.897)	
N <sub>2</sub>	3.010 (2.325-4.256)	
N <sub>3</sub>	4.025 (2.014-5.019)	
Cell differentiation status		0.128
Differentiated	Reference group	
Undifferentiated	1.201 (0.700-1.420)	
Vascular invasion		0.218
No	Reference group	
Yes	1.518 (0.870-1.987)	

tion during laparoscopy manipulation, leaving residual tumor at the resection margin, and performing an insufficient D2 lymphadenectomy. In our series, overall survival and disease-free survival for patients were comparable to other reports [1-11]. This suggests that survival outcomes after laparoscopic gastrectomy for locally advanced gastric carcinoma compare favorably with those for standard open gastrectomy.

Several studies have reported conversion rates of laparoscopic gastrectomy to open gastrectomy ranging from 0% to 15.7% [1-14]. The conversion rate is influenced by the nature of the cases selected. Of our 113 cases, 4 (3.5%) patients required conversion of the intended procedure to open gastrectomy. In this study, there were no intra-operative deaths, and the 30-day mortality rate was zero. The 30-day complication rate was 16.8%, with the most common complications classified as minor complication.

There are several limitations of this study. Because this is a retrospective and non-comparative study, our results should be interpreted with caution. Prospective randomized controlled trials are required for more conclusive results. We chose to perform laparoscopic gastrectomy in selected patients with relative early stage. This may have predisposed the study population undergoing laparoscopic gastrectomy to experience favorable outcomes compared with those undergoing open gastrectomy.

In conclusion, these data suggest that in experienced

hands, laparoscopic gastrectomy can be considered as an alternative to traditional gastrectomy in patients with locally advanced gastric carcinoma. Lower pathological T status and pathological N status were significantly predictive for better overall survival and disease-free survival. A prospective randomized controlled study on a larger scale is required to reach definitive conclusions regarding the efficacy of laparoscopic gastrectomy relative to other techniques.

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## Discourse of conflict of interest

None.

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