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Original Article

Long-term follow-up after laparoscopic versus open distal gastrectomy for advanced gastric cancer

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Abstract: This study aimed to compare the long-term outcomes of laparoscopic and open distal gastrectomy for advanced gastric cancer. Between January 2007 and December 2014, patients with advanced gastric cancer underwent distal gastrectomy by laparoscopic or open approach were identified. Patients in both groups were selected after being matched by age, gender, American Society of Anesthesiologists (ASA) class and clinical TNM stage using propensity score method, to create two comparable groups: laparoscopy and open groups, and prognosis were compared between these two groups. After the patients were matched, 86 patients in each group were selected for analysis. There were no significant differences in the clinicopathological features between the two groups. There were significant differences between the laparoscopy and open groups in terms of blood loss, duration of surgery, and hospital stay. The 5-year overall survival rate was 59% in laparoscopy group, and 56% in open group (P=0.523). The 5-year disease-free survival rate was 52% and 46%, respectively (P=0.362). According to the univariate and multivariate analysis, this type of surgical approach was not a prognostic factor for long-term outcomes. The current results indicated that laparoscopic distal gastrectomy is associated with similar overall survival and disease-free survival for advanced gastric cancer.

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

Introduction

Gastric carcinoma is the leading cause of cancer-related deaths worldwide. Surgical resection of gastric cancer in patients without metastasis to other organs may provide an acceptable long-term survival benefit compared with nonsurgical therapies [1-5]. Seigo Kitano first described laparoscopic distal gastrectomy for early gastric cancer in 1994 [6]. After years of controversy and discussion, this technique is widely accepted by most surgeons because when compared with open distal gastrectomy for early gastric cancer, laparoscopic distal gastrectomy results in less intraoperative blood loss, less pain, more rapid return to normal activities, shorter length of stay and earlier ability to receive adjuvant therapy, and higher postoperative quality of life [7-14]. The latest Japanese gastric cancer treatment guidelines consider laparoscopic distal gastrectomy to be a reasonable method for the treatment of early gastric cancer with experienced hands. Its long-term outcome is similar to that of the traditional open resection while it has obvious advantages of minimally invasive surgery [15]. However, for advanced gastric cancer, laparoscopic distal gastrectomy is difficult because D2 lymphadenectomy is difficult laparoscopically [16].

We started performing laparoscopic distal gastrectomy in selected patients with early gastric cancer in 2006. After an initial learning curve period, we also started performing this procedure in patients with advanced gastric cancer, as we believed that the outcomes would not be inferior to those after open resection. This study compared the long-term survival outcomes after laparoscopic distal gastrectomy versus open resection for advanced gastric cancer, and evaluated the current concerns in these groups of patients.

Patients and methods

This study complied with the Declaration of Helsinki. This retrospective research was

Table 1. Patients' clinicopathological features of each group

	Laparoscopy (*n*=86)	Open (*n*=86)	*P* value
Age (y)	62 (49-78)	61 (51-75)	0.850
Gender (Male:Female)	57:29	61:25	0.511
Clinical stage (7th AJCC-UICC)			0.522
IB	9	10	
IIA	36	39	
IIB	30	28	
IIIA	11	9	
ASA score			0.981
I	54	53	
II	23	26	
III	9	7	
Lauren classification			0.299
Intestinal type	54	60	
Diffuse type	19	17	
Unclassified type	13	9	

Table 2. Postoperative complications of each group

	Laparoscopy (*n*=86)	Open (*n*=86)	*P* value
Post-operative complications (%)	9 (10.5)	13 (15.1)	0.361
Severity of complications			-
Major (3b, 4a, 4b and 5)			-
Anastomosis leakage	1	1	
Intra-abdominal bleeding	1	1	
Intra-abdominal abscess	0	1	
Minor (1, 2 and 3a)			-
Pancreatic fistula	2	2	
Ileus	2	3	
Pneumonia	1	3	
Atelectasis	2	2	

approved by our local ethics committees. The need for informed consent from patients was waived because of its retrospective nature.

Between January 2007 and December 2014, medical records of patients, who underwent radical distal gastrectomy for advanced gastric cancer in our institute, were retrospectively reviewed. We determined the tumor stage according to the 7th Edition of TNM staging system of gastric cancer, which was suggested by Union for International Cancer Control (UICC), Japanese Gastric Cancer Association (JGCA) and American Joint Committee on Cancer (AJCC) [17]. For those of the patients operated before 2010, their staging was recalculated to match the latest TNM classification by UICC, JGCA and AJCC.

To create two comparable groups, we conducted propensity score analysis using nearest neighbor matching method of covariates without replacement. Verified independent variables are age, gender, ASA (American Society of Anesthesiologists) score and clinical TNM stage (7th). The short- and long-term outcomes were compared between these two groups.

The decision to perform either laparoscopic or open distal gastrectomy was made by the individual two surgeons in our institution and patients. Candidates for laparoscopic distal gastrectomy were patients with clinical T2-3N0-2M0 disease before operation, tumors located in the lower third of the stomach, without neoadjuvant therapy, and no extended resection. 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 in selected cases.

A detailed procedure of radical laparoscopic or open distal gastrectomy with D2 lymphadenectomy has been described elsewhere [18]. The lymph nodes harvested 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 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)

Table 3. Surgical outcomes of each group

	Laparoscopy (*n*=86)	Open (*n*=86)	*P* value
Operative time (min)	210 (170-260)	180 (160-230)	0.001
Blood loss (ml)	200 (120-360)	260 (200-350)	0.003
Post-operative hospital stay (d)	8 (6-16)	12 (8-23)	0.010
Retrieved lymph nodes	20 (16-23)	21 (17-23)	0.580
Pathological stage			0.912
IB	5	4	
IIA	23	25	
IIB	29	31	
IIIA	17	14	
IIIB	9	10	
IIIC	3	2	
Residual tumor (R0/R1/R2)	86/0/0	86/0/0	1.000

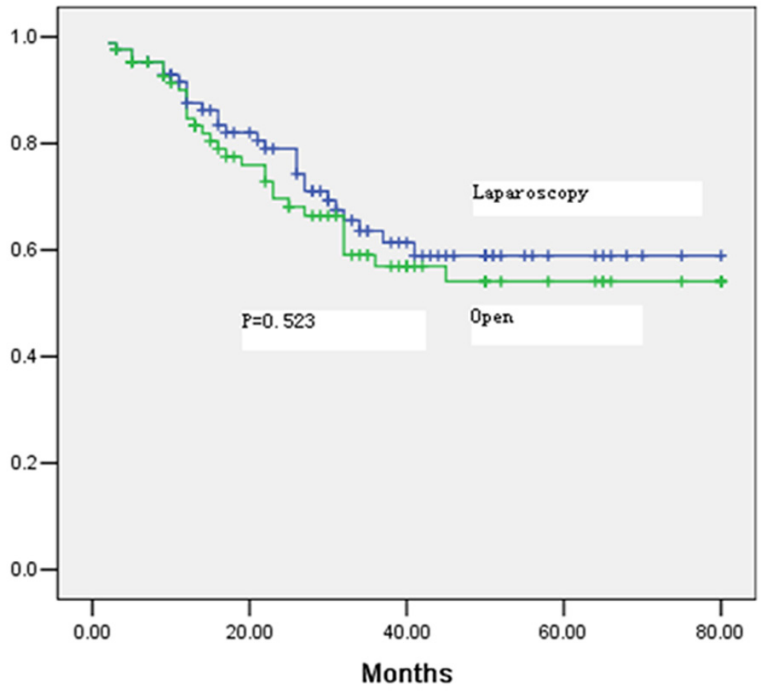

Figure 1. Five-year overall survival curve was shown. The 5-year overall survival were 59% in laparoscopy group and 56% in open group (*P*=0.523).

and lymph nodes in the hepatoduodenal ligament (No. 12a station). The lymph nodes mapping was based on the Japanese classification of gastric carcinoma proposed by JGCA [17].

Follow-up data were obtained through outpatient clinic visits. The overall survival was assessed from the date of gastrectomy until the last follow up or death of any cause. The disease-free survival was calculated from the date of gastrectomy until the date of cancer recurrence or death of any cause. Disease recurrence was defined as locoregional or distant metastasis proven by radiology or pathology. The last follow up was January 2015.

For statistical analysis, data were presented as mean and standard deviations for variables following normal distribution and were analyzed by *t* test. For variables following non-normal distribution, results were expressed as median and range and were compared by nonparametric test. Differences of semi-quantitative results were analyzed by Mann–Whitney *U*-test. Differences of qualitative results were analyzed by chi-square tests or Fisher exact test as appropriate. Survival rates were analyzed using the Kaplan-Meier method; differences between the two groups were analyzed with the log-rank test. Univariate analyses were performed to identify prognostic variables related to overall survival. Univariate variables with probability values less than 0.05 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted odds ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. $P<0.05$ was considered statistically significant using SPSS 14.0 for windows (SPSS Inc., Chicago, IL, USA).

Results

After the patients were matched by age, gender, ASA score and clinical TNM stage, 172 patients were eligible for analysis, and 86 patients in each group. Distribution of clinicopathological features of the patients was compared, and there was no significant difference in these variables between the two groups (**Table 1**).

In the two matching groups, there was no in-hospital mortality or morbidity occurring within

Table 4. Multivariate Cox regression analyses of overall survival

Regression variables	Adjusted hazared ratio	95% CI	*P* value
Pathological T stage			
T_2	1.00		
T_3	2.35	0.48-2.94	0.210
T_{4a}	4.69	2.26-6.58	0.030
Pathological N stage			
N_0	1.00		
N_1	1.58	0.54-1.88	0.501
N_2/N_3	4.50	3.11-5.18	0.003
Differentiation grade			
Differentiated	1.00		
Undifferentiated	4.30	2.36- 6.58	0.004

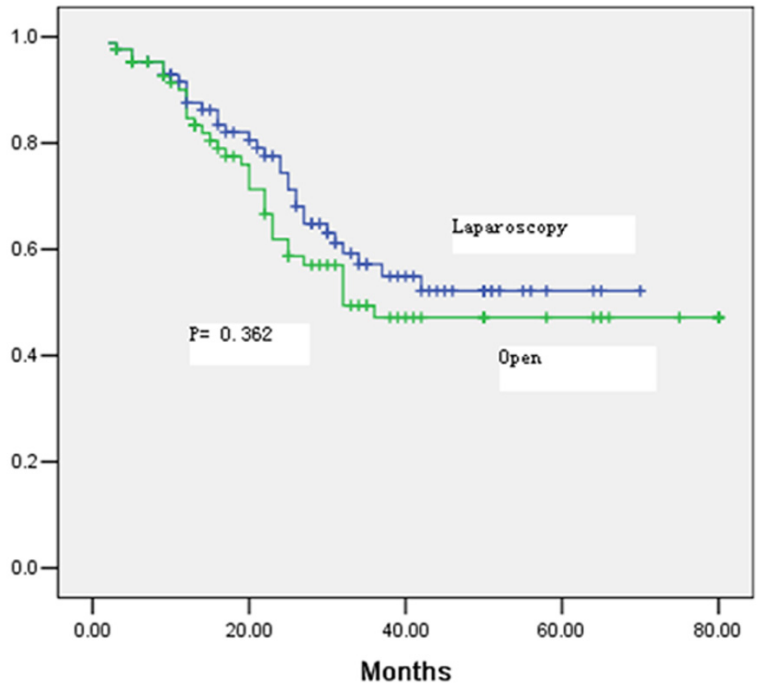

Figure 2. Five-year disease-free survival was shown. The 5-year disease-free were 52% in laparoscopy group and 46% in open group (*P*=0.362).

30 postoperative days occurred. There was no statistical difference in postoperative complications between the two groups (*P*>0.05). **Table 2** shows the details of complications in each group. The severity of complications was graded according to the Clavien-Dindo classification, being major and minor complications. Major complications were defined as grades 3b, 4a, 4b and 5. Minor complications were classified as 1, 2 and 3a [19, 20].

Though duration of surgery was longer in the laparoscopy group (*P*<0.05), the blood loss and length of postoperative hospital stay of the patients who underwent laparoscopic distal gastrectomy was significantly shorter than that of open group (*P*<0.05) (**Table 3**).

The median follow-up period of open group and laparoscopy group were 38 months and 40 months, respectively. The 5-year overall survival was 59% in laparoscopy and 56% in open groups. There was no significant survival difference between the two groups (*P*=0.523) (**Figure 1**). Multivariate Cox regression analysis of overall survival of all patients in the whole cohort was also performed. Significant predictors of worse overall survival were advanced pathologic T4 stage, pathologic N2 or N3 disease, and tumors with undifferentiated histological type (**Table 4**). Surgical approach by laparoscopic surgery was not found to be a significant predictor for overall survival by univariate analysis and multivariate analysis.

Five-year disease-free survival was 52% in laparoscopy group and 46% in open group. There was no significant difference in recurrence between the two groups (*P*= 0.362, **Figure 2**). Multivariate Cox regression analysis of disease-free survival showed that significant predictors of worse disease-free survival were advanced pathologic T4 stage, pathologic N3 disease and poor tumor differentiation (**Table 5**). The laparoscopic surgery was not found to be a significant predictor for decreased disease-free survival.

Discussion

Although laparoscopic surgery has many advantages, the laparoscopic technique for advanced gastric cancer is not yet a commonly accepted

Table 5. Multivariate Cox regression analyses of disease-free survival

Regression variables	Adjusted hazared ratio	95% CI	*P* value
Pathological T stage			
T_2	1.00		
T_3	158	0.35-2.52	0.858
T_{4a}	3.08	2.30-5.04	0.012
Pathological N stage			
N_0	1.00		
N_1	1.45	0.42-1.88	0.240
N_2/N_3	4.87	2.55-6.77	0.009
Angiolymphatic invasion			
No	1.00		
Yes	3.88	2.58-2.85	0.015

approach, and it is currently performed in only experienced centers [21]. This study showed that the open and laparoscopic distal gastrectomies for advanced gastric cancer did not differ significantly in terms of oncologic and survival time outcomes. However, laparoscopic distal gastrectomy for advanced gastric cancer was associated with significantly less blood loss, better cosmetic results and shorter hospital stay.

Previous studies on distal gastrectomy showed that open and laparoscopic distal gastrectomy had similar surgical outcomes [22-25]. Some of these retrospective reports also found that laparoscopic distal gastrectomy had similar or superior oncologic outcomes, such as rates of R0 resection and lymphadenectomy results [22-25]. However, previous studies have shown mixed and insufficient results on surgical outcomes and oncologic feasibility of laparoscopic distal gastrectomy for advanced gastric cancer, partly because differences in patient distributions were not comparable between the 2 groups [15, 19, 22-25].

In this study, we reported our experiences with all patients who were treated by either open or laparoscopic distal gastrectomy for advanced gastric cancer. Laparoscopic resection seemed to associate with an early return to ordinary and social activities because the laparoscopic distal gastrectomy patients had shorter hospital stays, and acceptable postoperative complications compared with the open resection patients.

Previous analyses of the long-term outcomes of all unmatched patients may suggest that laparoscopic distal gastrectomy for advanced gastric cancer has comparable or superior long-term outcomes to open resection [15, 19, 22-25]. However, such interpretation must be done with care because there are significant differences in terms of baseline clinicopathological features between laparoscopy and open groups, which may be a result of selection bias. To assess the true value of laparoscopic gastrectomy for gastric cancer, a randomized clinical trial would yield the most meaningful and powerful results. However, such trials are limited mainly by technical difficulty of D2 lymphadenectomy and the patients unwilling to receive open resection. Therefore, to reduce the impact of selection bias, we adjusted for their differences by using propensity score matching.

The most important indicators in evaluating efficacy of a new surgical approach are the postoperative outcome and long-term outcomes [26]. In the current study, the rates of recurrence were similar between the two groups. Kaplan-Meier survival curves showed that there was no significant difference in overall survival and disease-free survival. So, initial fears regarding the oncologic equivalence of the laparoscopic and open techniques do not seem to berealized. This demonstrates that laparoscopic gastrectomy produces oncologically similar results to the open resection. This finding is in accordance with other reports who have hypothesized that the reduced inflammatory response associated with minimally invasive radical cancer resection may be associated with equivalent or even improved long-term survival [26].

The propensity score-matched analysis had some limitations. First, although it was performed to reduce the impact of selection bias in terms of clinicopathological features, which was created by the nature of retrospective design, it controlled and adjusted only for factors that were actually measured or observed. Therefore, selection biases in terms of unmeasured or unobserved features were likely to remain and could have influenced the long-term outcomes of the study. Second, follow-up duration was not very long. So, later cancer recurrence was not observed. Very longer-term survival data may be necessary to verify our hypothesis.

In conclusion, the results of the current study showed the laparoscopic distal gastectomy for locally advanced gastric cancer appears to be an oncologcially equivalent operation to open resection. Although laparoscopic distal gastectomy is a more difficult surgical procedure than open resection, it will be used extensively for removing advanced tumors, thus enhancement surgical experience, improvement of surgical skills and the innovation of new surgical instruments.

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Disclosure of conflict of interest

None.

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