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ORIGINAL ARTICLE

A propensity score-matched case-control comparative study of laparoscopic and open gastrectomy for locally advanced gastric carcinoma

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Summary

Purpose: *The aim of this study was to compare the surgical and long-term outcomes of laparoscopic and open gastrectomy with radical intent for locally advanced gastric carcinoma in case-controlled patient groups using the propensity score.*

Methods: *Between January 2009 and December 2014, 389 patients who underwent gastrectomy with radical intent for locally advanced gastric carcinoma were enrolled. These patients were divided into two groups according to the method of operation: the laparoscopy group (patients who underwent laparoscopic gastrectomy) and the open group (patients who underwent open gastrectomy). To correct different demographic and clinical factors in the two groups, a propensity score matching was used at a 1:1 ratio, and, finally, 184 patients were enrolled in this study, 92 patients in each group. Preoperative characteristics, surgical results, and long-term results were analyzed.*

Results: *Preoperative baseline variables were well balanced in both groups. There were no differences of the extent of surgery between the two groups. With the exception of shorter postoperative hospital stay and less blood loss in the laparoscopy group as compared with the open group, there were no significant differences in surgical, pathological, and long-term outcomes. The 5-year overall survival rates were 57% in the laparoscopy group and 50% in the open group (p=0.606). The 5-year disease-free survival rates were 48% in the laparoscopy group and 42% in the open group (p=0.515).*

Conclusion: *Laparoscopic gastrectomy for locally advanced gastric carcinoma is safe, and long-term outcomes were comparable to those who underwent open resection.*

Key words: *gastric carcinoma, gastrectomy, laparoscopic gastrectomy, minimally invasive surgery*

Introduction

Recently, because of technical refinements and improvements of instruments, applications of laparoscopic gastrectomy have been expanding in gastric carcinoma [1-3]. In particular, in the case of early gastric carcinoma (cT1), laparoscopic resection is considered as a standard practice in the latest guidelines. Most patients with gastric carcinoma are in advanced stage in China when diagnosed, and this makes laparoscopic gastrectomy more difficult because of D2 lymphadenectomy [4-6]. However, several short-term benefits of laparoscopic gastrectomy for advanced gastric carcinoma, such as better cosmetic results, less pain, less bleeding, less postoperative complications, and shorter hospital stay, have been reported [7-9]. However, the oncologic results of laparoscopic gastrectomy for locally advanced gastric carcinoma still remain a matter of debate.

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The purpose of this study was to compare the short-term and long-term outcomes of laparoscopic gastrectomy and open gastrectomy for locally advanced gastric carcinoma in groups of well-matched patients using propensity score matching.

Methods

This retrospective study complied with the Declaration of Helsinki rules and was approved by the Ethics Committee of Qingdao Hiser Medical Center. The need for informed consent from all patients was waived because this was retrospective study and not prospective study.

Between January 2009 and December 2014, 389 patients underwent gastrectomy with radical intent for locally advanced gastric carcinoma at Qingdao Hiser Medical Center. Among these patients, laparoscopic gastrectomy was performed in 95 patients. Those patients with previous treatment for gastric carcinoma, noncurative resection, and conversion to open resection during laparoscopic resection were excluded from study. The remaining 361 patients were enrolled, and were divided into two groups according to the method of operation: the laparoscopy group (N=92; laparoscopic resection) and the open group (N=269; open resection). To correct for different demographic and clinical factors in the two groups, propensity score matching was used at a 1:1 ratio, and, finally, 184 patients were enrolled in this study, 92 patients in each group. Propensity scores were generated with the baseline characteristics, including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, clinical TNM stage and extent of resection. The matching method was used for comparison.

To determine operative methods and extent of gastrectomy, all patients with gastric carcinoma were preoperatively assessed by upper endoscopy, endoscopic ultrasonography, computed tomographic scans of brain, chest, and abdomen, and abdominal ultrasonography. In selected patients, positron emission tomography-computerized tomography (PET-CT), staging laparoscopy and bone scanning were performed. These preoperative assessments and intraoperative staging delineated the location and type of gastrectomy [10]. The indication for laparoscopic gastrectomy was clinical stage T2-3N0-1M0 gastric carcinoma without need for multivisceral resections. The tumor stage of gastric cancer was based on the 7th edition of the TNM classification of gastric cancer, which was proposed by the Union International Contre le Cancer (UICC), Japanese Gastric Cancer Association (JGCA) and American Joint Committee on Cancer (AJCC) [10-12]. The lymph nodes staging was based on the 3rd English edition of Japanese classification of gastric carcinoma proposed by JGCA. For those patients operated before 2010, their staging was recalculated to match the latest TNM edition by UICC, JGCA and AJCC [11].

For distal gastrectomy, the range of D2 lymphadenectomy was 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) and lymph nodes in the hepatoduodenal ligament (No. 12a station). For total gastrectomy, the D2 lymphadenectomy was as follows: the lymph nodes dissected in distal gastrectomy as mentioned above, 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). The operative techniques for laparoscopic gastrectomy have been described elsewhere [12].

Postoperative complications were 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 defined as grades 3, 4 and 5. Minor complications were classified as 1 and 2 [13,14].

The routine follow-up program consisted of physical examination, upper gastrointestinal endoscopy, computed tomography, and laboratory tests every 3 months for the first 2 years and then every 6 months for the next 3 years, which then was done annually for patients who had neither recurrence nor metastasis. Recurrent disease was diagnosed based on the clinical, laboratory, diagnostic imaging and pathological findings when available [15,16]. The last follow up was March 2015. The overall survival was assessed from the date of surgery until the last follow up or death. The disease-free survival was calculated from the date of surgery until the date of disease recurrence.

Statistics

For variables following normal distribution, data were presented as mean and standard deviations and were analyzed by Student's t test. For variables following non-normal distribution, data were expressed as median and range and were compared by Mann–Whitney *U* test. Differences of semiquantitative results were analyzed by Mann–Whitney *U* test. Differences of qualitative results were analyzed by chi-square test or Fisher's exact test where appropriate. Survival rates were analyzed using the Kaplan-Meier method and differences between the two groups were analyzed with

Table 1. Preoperative characteristics

Characteristics	*Laparoscopy (N=92) N (%)*	*Open (N=92) N (%)*	*p value*
Age, years, median (range)	63 (42-76)	65 (46-72)	0.268
Sex			
Male	65 (70.7)	59 (64.1)	0.345
Female	27 (29.3)	33 (35.9)	
BMI (kg/m^2), median (range)	19 (16-26)	22 (20 -28)	0.158
Clinical TNM stage (7th AJCC-UICC)			
IB	16 (17.4)	14 (15.2)	0.469
IIA	58 (60.3)	56 (60.9)	
IIB	18 (19.6)	22 (23.9)	
Location of the primary tumor			
Upper	10 (10.9)	12 (13.0)	0.746
Middle	23 (25.0)	26 (28.3)	
Lower	59 (64.1)	54 (58.7)	
ASA score			
I	59 (64.1)	61 (66.3)	0.665
II	23 (25.0)	24 (26.1)	
III	10 (10.9)	7 (7.6)	

Table 2. Surgical outcomes

Outcomes	*Laparoscopy (N=92) N (%)*	*Open (N=92) N (%)*	*p value*
Extent of gastrectomy			
Total gastrectomy	29 (31.5)	32 (34.8)	0.638
Distal gastrectomy	63 (68.5)	60 (65.2)	
Complications	14 (15.2)	20 (21.7)	
Pulmonary embolism	2 (2.2)	1 (1.1)	
Anastomosis leakage	6 (6.5)	8 (8.7)	0.386
Intra-abdominal bleeding	2 (2.2)	3 (3.2)	
Intra-abdominal abscess	2 (2.2)	4 (4.4)	
Ileus	2 (2.2)	2 (2.2)	
Major complications	2 (2.2)	4 (4.4)	0.678
Minor complications	12 (13.0)	16 (17.4)	0.412
Operative time (min), median (range)	230 (180-230)	200 (160-210)	0.020
Estimated blood loss (ml), median (range)	230 (150-280)	290 (240-480)	0.010
Postoperative hospital stay (days), median (range)	7 (5-18)	10 (6-21)	0.008

the log-rank test. Univariate analysis was performed to identify prognostic variables related to overall survival and disease-free survival. Univariate variables with p values <0.05 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted hazard ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. P<0.05 was considered statistically significant. All statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA).

Results

All preoperative baseline variables, including age, sex, BMI, ASA score and clinical TNM stage were well balanced in both groups (Table 1).

Table 2 summarizes short-term outcomes. There were no differences in the extent of gastrectomy between the two groups. Postoperative complications were similar between the two groups. However, when the severity of postoperative complications was compared, more complications were classified as major in patients undergoing open resection, though the difference was not significant (p=0.678). Blood loss and postoperative hospital stay period was significantly shorter in the laparoscopy group than in the open group.

Table 3. Pathological outcomes

Outcomes	*Laparoscopy (N=92) N (%)*	*Open (N=92) N (%)*	*p value*
Retrieved lymph nodes, median (range)	17 (16-21)	18 (17-25)	0.258
Residual tumor (R0/R1/R2)	90/2/0	91/1/0	0.562
Histological differentiation			
Differentiated	27 (29.3)	38 (41.3)	0.090
Undifferentiated	65 (70.7)	54 (58.7)	
Pathological TNM stage (7th UICC)			
IB	12 (13.0)	13 (14.1)	
IIA	23 (25.0)	26 (28.3)	
IIB	26 (28.3)	22 (23.9)	0.580
IIIA	8 (8.7)	6 (6.5)	
IIIB	12 (13.0)	16 (17.4)	
IIIC	11 (12.0)	9 (9.8)	

Table 4. Tumor recurrence pattern and site

Recurrences	*Laparoscopy (N=92) N (%)*	*Open (N=92) N (%)*	*p value*
Overall recurrence	28 (30.4)	33 (35.9)	0.434
Locoregional	18 (19.6)	21 (22.8)	
Peritoneal seeding	9 (9.8)	10 (10.9)	
Anastomosis	4 (4.3)	7 (7.6)	-
Lymph nodes	3 (3.3)	2 (2.2)	
Remnant stomach	2 (2.2)	2 (2.2)	
Distant metastases	10 (10.9)	11 (12.0)	
Brain	3 (3.3)	4 (4.4)	-
Liver	5 (5.4)	5 (5.4)	
Lung	1 (1.1)	1 (1.1)	
Bone	1 (1.1)	1 (1.1)	
Time to recurrence (median, months)	16	10	0.199

There was no in-hospital or postoperative 30-day mortality in either group.

Table 3 summarizes the pathological outcomes. All pathological parameters, including harvested lymph nodes, surgical margins and pathological TNM stage were not different between the two groups.

The median follow-up period was 38 months for the laparoscopy group and 40 months for the open group. In the laparoscopy group, 28 patients had tumor recurrence, and 25 of them died of recurrence. In the open group, 33 patients had recurrence, and 29 of them died of recurrence. The pattern of recurrence was similar in both groups (Table 4). The 5-year overall survival rates were 57% in the laparoscopy group and 50% in the open group. The overall survival rates were similar between the two groups (Figure 1). There were no significant difference between the laparoscopy and the open group for overall survival (p=0.606). Significant predictors of worse overall survival were advanced pathologic T stage, pathologic N stage, and tumors with angiolymphatic invasion (Table 5).

The 5-year disease-free survival rates were 48% in the laparoscopy group and 42% in the open group. The disease-free survival rates were similar between the two groups (Figure 2, p=0.515). Significant predictors of worse disease-free survival were pathologic N stage and tumor with

Table 5. Multivariate Cox regression analysis of overall survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Pathological T stage			
T_2	1.00		
T_3	1.45	0.54-1.88	0.089
T_{4a}	3.69	2.54-4.78	0.023
Pathological N stage			
N_0	1.00		
N_1	1.75	0.64 -2.99	0.087
N_2/N_3	4.58	3.01-6.58	0.000
Angiolymphatic invasion			
No	1.00		
Yes	2.30	2.00- 5.54	0.025

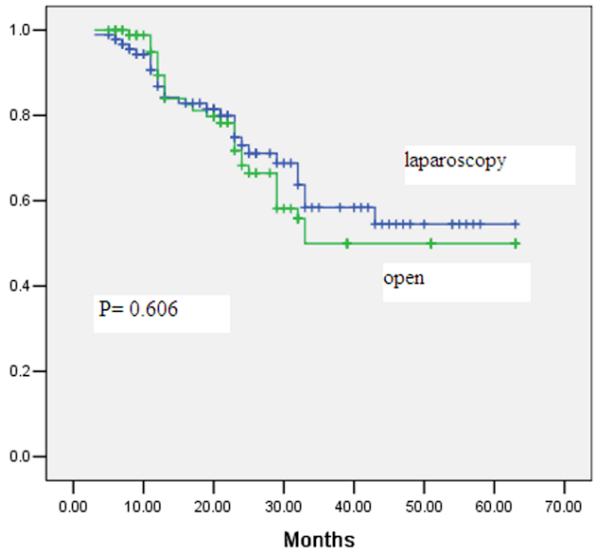

Figure 1. Overall survival for patients with locally advanced gastric carcinoma in the laparoscopy and open group

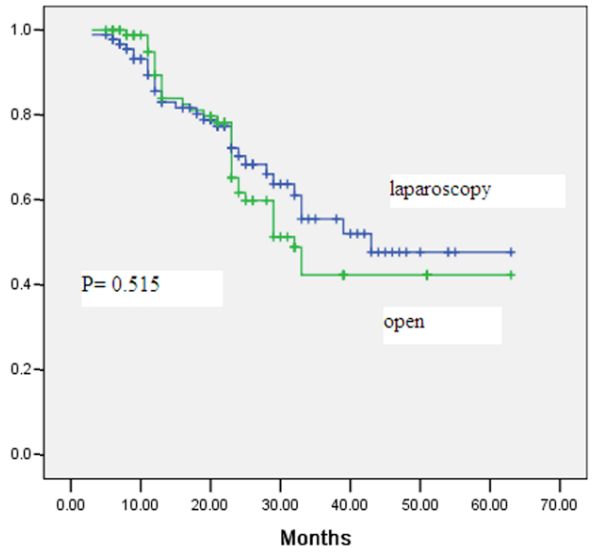

Figure 2. Disease-free survival for patients with locally advanced gastric carcinoma in the laparoscopy and open group.

undifferentiated grade in multivariate Cox regression analysis (Table 6).

Discussion

Up to now, there have been no multicenter randomized controlled clinical trials directly comparing laparoscopic and open gastrectomy for patients with locally advanced gastric carcinoma due to technically demanding [7]. We used the propensity score matching method, which was designed to balance the baseline covariates between groups. In the absence of a randomized controlled study of laparoscopic vs open gastrectomy for locally advanced gastric carcinoma, this method would be desirable for a comparative study showing the oncologic safety and efficacy of laparoscopic gastrectomy. Our results demonstrate that although the blood loss and duration of hospital stay were significantly shorter in patients who underwent laparoscopic gastrectomy compared with those with open gastrectomy, other surgical and oncological outcomes were comparable between the two groups.

The present study focused on the oncologic safety and efficacy of laparoscopic gastrectomy for locally advanced gastric carcinoma. Therefore, unlike previous studies, tumor factors that could affect long-term outcomes regardless of procedure types were excluded. Previous treatment such as neoadjuvant therapy also could become a

Table 6. Multivariate Cox regression analysis of disease-free survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Pathological N stage			
N_0	1.00		
N_1	1.86	0.55-2.69	0.156
N_2/N_3	3.58	2.01-4.88	0.013
Differentiation grade			
Differentiated	1.00		
Undifferentiated	3.88	2.50-5.80	0.010

confounding factor [17,18]. Open conversion cases were also excluded because these cases were too vague to classify as either laparoscopy or open group.

Short-term surgical and postoperative advantages of laparoscopic gastrectomy have been demonstrated in several studies so far [7,19]. Compared with open gastrectomy, laparoscopic gastrectomy has been shown to result in lower intraoperative blood loss, shorter duration of intravenous anesthesia use and hospital stay. Moreover, postoperative complications and adverse events rates were reported to be comparable or even more favorable in laparoscopic gastrectomy patients compared with open gastrectomy patients [7,19]. Likewise, in our study, we demonstrated that laparoscopic gastrectomy is associated with less blood loss and significantly shorter hospital stay compared with open resection, although the severity of postoperative complications was not significantly different due to the small sample size.

Oncological safety of laparoscopic gastrectomy for locally advanced gastric carcinoma has been always a matter of debate in the surgical community [20]. Although initially there were concerns about the ability to achieve negative resection margin, adequate lymph node dissection or good long-term outcomes of patients undergoing laparoscopic gastrectomy for locally advanced gastric carcinoma, recent studies have reported similar, if not better, oncological outcomes like the rate of negative resection margin, lymph node dissection, tumor recurrence rate, or all-cause mortality with laparoscopic gastrectomy compared with open resection [21-28]. Similarly, our findings demonstrated that the rates of negative resection margin, lymph node dissection, tumor recurrence rate, and all-cause mortality in the laparoscopy and open groups were comparable.

Of great interest concerning the long-term outcome, no differences in the patient overall survival and disease-free survival rate were found between the two groups. It is also important that no tumor recurrence was detected in the port site after laparoscopic resection [28-31].

The strengths of our study are the good matching of the patients with respect to preoperative baseline variables. Although at baseline the patient groups were well balanced, this was a retrospective and nonrandomized study. In addition, the propensity score matching itself has limitations. Therefore, the best study design to compare laparoscopic gastrectomy vs open gastrectomy is a randomized controlled trial where randomization would omit the selection bias we face in retrospective studies. The small sample size is another limitation of this study.

In conclusion, laparoscopic gastrectomy for locally advanced gastric carcinoma is safe, and long-term outcomes were comparable to those of open gastrectomy for locally advanced gastric carcinoma in selected patients. Based on the present results, a well-designed prospective study will be needed to affirm the validity of laparoscopic gastrectomy for locally advanced gastric carcinoma.

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