JBUON 2016; 21(1): 101-107
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Laparoscopic total gastrectomy compared with open resection for gastric carcinoma: a case-matched study with long-term follow-up

Bo Shu[1], Sanlin Lei[1], Fazhao Li[1], Songwen Hua[1], Yong Chen[1], Zhi Huo[2]

[1]Department of General Surgery, The Second Xiangya Hospital of Central South University, Changsha 410011, People's Republic of China; [2]Department of Immunology, School of Basic Medical Science, Central South University, Changsha 410013, People's Republic of China

Summary

Purpose: *This study was designed to compare the long-term outcomes of patients with gastric carcinoma after open or laparoscopic total gastrectomy.*

Methods: *A case-matched controlled prospective analysis of 136 patients who underwent laparoscopic total gastrectomy for stage I-III gastric carcinoma from 2007 to 2014 was performed. Patients who at the same period underwent open total gastrectomy were matched to the laparoscopy group at the ratio of 1:1 for comparison. The perioperative clinical outcomes, postoperative pathology, and survival were compared between the 2 groups*

Results: *The patient characteristics between the two groups were comparable. Laparoscopic resection resulted in less blood loss, shorter postoperative hospital stay, and longer operating time. The two groups had similar complication rates. Pathological data were similar for both procedures. Cumulative incidence of recurrence, disease-free, or overall survival rates were statistically similar.*

Conclusion: *This study showed that laparoscopic total gastrectomy for gastric carcinoma is acceptable in terms of short-term clinical outcomes and long-term survival results.*

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

Introduction

Laparoscopic gastrectomy is regarded as a technically demanding approach and many surgeons attempt laparoscopic distal gastrectomy with lymphadenectomy for early gastric carcinoma [1-6]. With the improvement in surgical technique and instruments, experienced surgeons have attempted to apply laparoscopic total gastrectomy with lymphadenectomy for gastric carcinoma [7]. However, long-term oncologic outcomes of laparoscopic total gastrectomy for gastric carcinoma remain controversial. Among the published studies comparing the long-term oncologic outcomes of gastric carcinoma between laparoscopic gastrectomy and open resection, there were rare studies involving subgroup comparison of total gastrectomy [8,9]. Laparoscopic gastrectomy for gastric carcinoma has been widely performed by Chinese surgeons. However, few studies evaluated long-term oncologic outcomes of laparoscopic total gastrectomy for gastric carcinoma. The present study was conducted to evaluate the long-term oncologic outcomes of laparoscopic total gastrectomy with curative intent in patients with gastric carcinoma.

Methods

This retrospective study complied with the Declaration of Helsinki rules and was undertaken after

Correspondence to: Zhi Huo, MD. Department of Immunology, School of Basic Medical Science, Central South University, 172 Tongzi Po Road, Changsha 410013, People's Republic of China. Tel and Fax: +86 731 82650001, E-mail: zhihuocn@188.com
Received: 27/06/2015; Accepted: 12/09/2015

Table 1. Baseline data

Baseline data	*Laparoscopy (N=136)*	*Open (N=136)*	*p value*
Age (years, range)	65 (48-78)	64 (42-73)	0.358
Sex			
Male (N)	86	92	0.444
Female (N)	50	44	
BMI (kg/m^2, range)	20 (16-26)	21 (18-29)	0.354
Clinical TNM stage* (N)			
IA	5	4	
IB	33	35	0.543
IIA	58	64	
IIB	40	33	
ASA grade (N)			
I	112	120	0.160
II	16	12	
III	8	4	
Location of the primary tumor (N)			
Upper	87	92	0.523
Middle	49	44	

*7th edition

approval by the local ethics committee. The need for informed consent from all patients was waived because of the retrospective nature of the study.

Between January 2007 and January 2014, 136 consenting patients who underwent laparoscopic total gastrectomy for the treatment of operable gastric carcinoma were prospectively registered. The laparoscopy group was matched against an open resection group with gastric carcinoma that declined to undergo laparoscopic total gastrectomy at a ratio 1:1 by gender, age, body mass index (BMI), clinical TNM stage and tumor location. Patients with clinical T4 stage, those with clinical N2 or N3 disease, those with other organs resection, those with concurrent distant metastases, those with other malignant diseases or those with recurrent gastric carcinoma were excluded.

All patients underwent physical examination, upper gastrointestinal endoscopy plus biopsy. The anesthetist assessed all patients before the operation and assigned an American Society of Anesthesiologists (ASA) score. Thoracic and abdominal computed tomography (CT) and brain magnetic resonance imaging (MRI) were performed for preoperative clinical staging. If necessary, positron emission tomography-computerized tomography (PET-CT), staging laparoscopy and bone scanning were employed. The stage of gastric carcinoma was based on the 7th edition of the TNM classification of gastric cancer, which was proposed by the Union Internationale Contre Le Cancer (UICC), the Japanese Gastric Cancer Association (JGCA) and the American Joint Committee on Cancer (AJCC) [10]. For patients operated before 2010, their staging was reassessed to match the latest TNM edition.

Patients were under general anesthesia and placed in the supine position with legs apart. 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. The laparoscopic total gastrectomy followed the same oncologic principles as the open procedures as previous reported in the literature [11].

All patients received the same postoperative treatment protocols, including pain control, nutritional support, postoperative rehydration, early ambulation, and early feeding. The discharge criteria included self-feeding, free ambulation, and only mild pain in the wounds.

All surgical specimens were analyzed by experienced pathologists, who assessed the harvested lymph nodes, the surgical margin status, the histological subtype and the pathological TNM stage.

Sex, age, ASA score, tumor location, and preoperative TNM stage of the patients were recorded, as were the operating time, blood loss, postoperative 30-day complications, length of postoperative stay, and pathological information.

The severity of 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 defined as grades 3, 4 and 5 [16-18]. Minor complications were classified as 1 and 2.

Short- and long-term data were recorded using either medical records or by regular follow-up visits.

Patients were followed up as outpatients every 3 months in the first 2 years, every 6 months for the next 3 years, and at 6 months or yearly thereafter. At each visit, they had a physical examination performed and general blood tests. Every 6 months they alternated

thoracic and abdominal CT or abdominal ultrasonography and chest radiography [12-15]. Patient follow-up ended in April 2015.

Survival definitions

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 the date of cancer recurrence or death from any cause. Disease recurrence was defined as locoregional or distant metastasis proven by radiology or pathology.

Statistics

All the statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). For variables following normal distribution, data were presented as mean±standard deviation 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 were analyzed with the log-rank test. Univariate analyses were performed to identify prognostic variables related to overall survival and disease-free survival. Univariate variables with probability 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 as statistically significant.

Results

The patients who underwent open and laparoscopic surgery did not differ significantly according to baseline data (Table 1).

The operative times were longer in the laparoscopy group. There was less blood loss and a lower rate of blood transfusion in the laparoscopy group compared with the open group. No patient required conversion to open procedure (Table 2). There were no significant differences between the two groups in terms of the R0 resection rate, histological type, number of lymph nodes harvested and pathological TNM stage (Table 2). The time of postoperative hospital stay was significantly shorter in the laparoscopy group than in the open group. Postoperative 30-day complications' rate in the laparoscopy group was similar to that in the open group. The severity of complications was similar between the two groups. There was no postoperative 30-day mortality occurred in our series (Table 3).

No statistical differences in recurrence rate, type of tumor recurrence rate and median time to first tumor recurrence were noticed between the laparoscopy group and the open group (Table 4).

The 5-year disease-free survival was comparable between the laparoscopy group and the open group (50 vs 42%, p=0.177) (Figure 1), and there were also no statistical differences in the 5-year disease-free survival rates between the two groups when stratifying by pathological tumor stage (stage I: 82 vs 79%, p=0.562; stage II:68 vs 62%, p= 0.302; stage III: 32 vs 28%, p= 0.120).

The 5-year overall survival rate was similar in

Table 2. Surgical and pathological data

Surgicopathological data	*Laparoscopy (N=136)*	*Open (N=136)*	*p value*
Operative time, min (range)	220 (180-290)	170 (160-260)	0.035
Estimated blood loss, ml (range)	240 (200-420)	300 (250-550)	0.010
Blood transfusion N (%)	10 (7.3)	23 (16.9)	0.016
Histological type			
Differentiated (N)	88	82	0.452
Undifferentiated (N)	48	54	
Dissected lymph nodes, N (range)	18 (16-25)	19 (16-28)	0.258
Pathological TNM stage* (N)			
IB	21	20	
IIA	33	36	
IIB	34	40	0.705
IIIA	33	30	
IIIB	12	10	
IIIC	3	3	
Residual tumor (R0/R1/R2, N)	135/1/0	135/1/0	1.000

*7th edition

Table 3. Data of postoperative course

Postoperative data	*Laparoscopy (N=136) N*	*Open (N=136) N*	*p value*
Postoperative 30-day morbidity	18	21	0.604
Anastomosis leakage	5	4	
Intra-abdominal bleeding	2	3	
Intra-abdominal abscess	2	3	
Pancreatic fistula	2	4	
Ileus	2	2	
Pancreatitis	2	3	
Atelectasis	3	2	
Major complications	3	4	0.702
Minor complications	15	17	
Hospital stay after surgery (days, range)	8 (5-12)	10 (8-35)	0.037

Table 4. Data of cancer recurrence

Disease recurrence	*Laparoscopy (N=136) N*	*Open (N=136) N*	*p value*
Overall recurrence	57	67	0.223
Locoregional	39	45	
Peritoneal seeding	19	21	0.431
Anastomosis	11	15	
Local lymph nodes	9	9	
Metastasis	18	22	
Brain	3	4	
Liver	5	8	0.493
Lung	7	5	
Ovary	3	5	
Time to recurrence, median, months	18	15	0.488

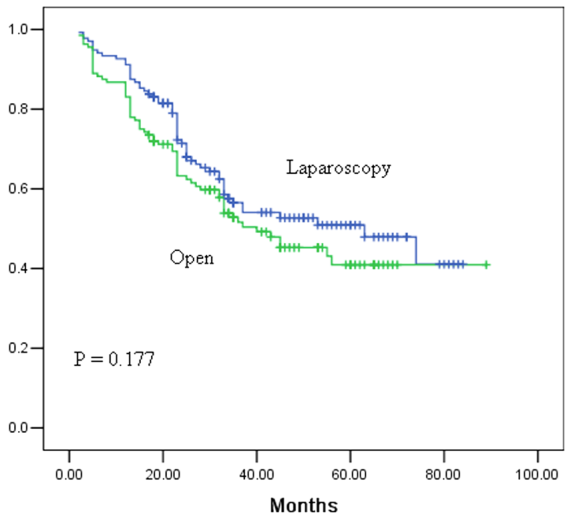

Figure 1. Comparison of disease-free survival rate between laparoscopy and open groups.

the laparoscopy group and in the open group (61 vs 56%, p= 0.197) (Figure 2). By subgroup staging analysis, similar results were found (stage I: 92 vs 85%, p= 0.205; stage II:75 vs 71%, p= 0.208; stage III: 45 vs 36%, p= 0.191).

The multivariate Cox regression analysis showed that the laparoscopic approach was not associated with inferior disease-free survival (HR=0.984, 95%CI: 0.899-1.685, p=0.584), or overall survival (HR=1.125, 95%CI: 0.826-1.601, p=0.917). Multivariate analysis revealed that advanced pathologic T stage and pathologic N2/3 disease did influence disease-free survival (Table 5). Significant predictors of worse overall survival were advanced pathologic T stage, pathologic N2/3 disease, and patients older than 70 years (Table 6).

Discussion

Laparoscopic gastrectomy is a technically demanding procedure for the difficulties in adequate lymphadenectomy. The application of laparoscop-

Table 5. Multivariate analysis of disease-free survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Pathological T stage			
T_1-T_2	1.00		
T_3-T_4	1.89	1.26-2.80	0.021
Pathological N stage			
N_0-N_1	1.00		
N_2-N_3	3.02	1.55-3.65	0.012

ic distal gastrectomy in early gastric carcinoma

Table 6. Multivariate analysis of overall survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Pathological T stage			
T_1-T_2	1.00		
T_3-T_4	2.36	1.87-3.20	0.002
Pathological N stage			
N_0-N_1	1.00		
N_2-N_3	2.54	1.41-3.02	0.028
Older than 70 years			
No	1.00		
Yes	1.53	1.20-2.98	0.038

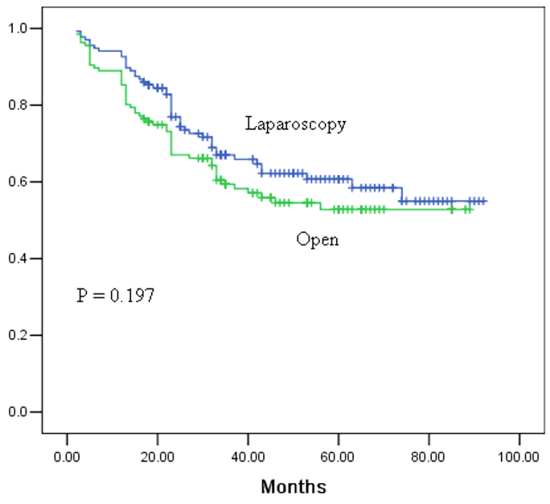

Figure 2. Comparison of overall survival rate between laparoscopy and open groups.

is usually accepted by laparoscopic surgeons [19-21]. Although more and more laparoscopic total gastrectomies with D2 lymphadenectomy have been performed by experienced hands, skepticism exists on the application of laparoscopic total gastrectomy with D2 lymphadenectomy for gastric carcinoma owing to the limited data on the long-term oncologic outcomes. To the best of our knowledge, there are no randomized controlled trials (RCTs) comparing laparoscopic and open total gastrectomy for gastric carcinoma [22]. This study showed that, compared to open total gastrectomy, laparoscopic total gastrectomy for gastric carcinoma had less blood loss, faster recovery, and, most importantly, similar 5-year tumor recurrence, disease-free survival, and overall survival rates. Cox regression analysis indicated that the surgical method was not the factor that significantly impacted 5-year disease-free survival and overall survival rates.

Studies demonstrated that the resection margin status was highly associated with long-term outcomes. Pathological involvement of the resection margin after radical gastrectomy with lymphadenectomy is a well established prognostic indicator [23]. R0 resection is of great importance because the risk of local recurrence increases when resection margins are invaded by cancer cells. Our results showed that laparoscopic approach did not have an adverse effect on tumor recurrence or disease-free survival.

Previous studies and meta-analyses have shown that laparoscopic distal gastrectomy for early gastric carcinoma was an oncologically correct technique [5,8,11,16-18]. The rate of surgical margin involvement and the number of isolated lymph nodes were similar for both laparoscopic and open techniques [5,11]. Nevertheless, data on the number of harvested lymph nodes, positive margin rate, and recurrence rate were seldom reported in laparoscopic total gastrectomy. The pathological data in our study suggested that laparoscopic total gastrectomy was oncologically acceptable for gastric carcinoma.

By far the most ominous concern raised so far has been the issue of port-site recurrences. The possibility was raised that the pneumoperitoneum during laparoscopic resection alters somehow the pattern of spread and local wound biology, possibly contributing to more frequent occurrence of port-site recurrence. Previous studies reported that the implantation rate at trocar sites is low, between 0 and 1.4% [8,24-26]. This rate is comparable to that reported with open resections. Our total wound recurrence rate was zero.

Despite the short-term benefits, the long-term survival outcome of laparoscopic total gastrectomy for gastric carcinoma was rarely reported, which, however, is mandatory for establishing the value of laparoscopic total gastrectomy in the surgical treatment [24-27]. The short-term benefits of laparoscopic total gastrectomy should not be compromised by the incidence of cancer recurrence and long-term survival. In our series, the 5-year disease-free survival and overall survival rates were similar between the two groups, and were in line with other reports [24-30].

The retrospective design was the main limitation of the present study and selective biases were unavoidable, though they had not significantly different impact on the long-term survival outcome by Cox regression multivariate analysis. Furthermore, the median follow-up period was not very long, so some cancer recurrences occurring later could not be detected in our series. Despite these limitations mentioned above, this cohort study was created to compare tumor recurrence, disease-free survival and overall survival rates between laparoscopic and open total gastrectomy for gastric carcinoma in a Chinese population.

In conclusion, laparoscopic total gastrectomy for gastric carcinoma can yield comparable long-term survival while achieving short-term benefits compared to open total gastrectomy.

Acknowledgements

We sincerely thank the patients, their families and our hospital colleagues who participated in this research.

References

1. Karagulle M, Fidan E, Kavgaci H, Ozdemir F. The effects of environmental and dietary factors on the development of gastric cancer. J BUON 2014;19:1076-1082.
2. Li B, Liu HY, Guo SH et al. The postoperative clinical outcomes and safety of early enteral nutrition in operated gastric cancer patients. J BUON 2015;20:468-472.
3. Varol U, Alacacioglu A, Yildiz I, Kucukzeybek Y, Uslu R. Gastric cancer with diffuse hepatic metastases and complete radiological response to triplet chemotherapy. J BUON 2014;19:1128-1129.
4. Liu ML, Zhang SJ. Effects of resveratrol on the protein expression of survivin and cell apoptosis in human gastric cancer cells. J BUON 2014;19:713-717.
5. Huang YL, Lin HG, Yang JW et al. Laparoscopy-assisted versus open gastrectomy with D2 lymph node dissection for advanced gastric cancer: a meta-analysis. Int J Clin Exp Med 2014;7:1490-1499.
6. Emir S, Sözen S, Bali I et al. Outcome analysis of laporoscopic D1 and D2 dissection in patients 70 years and older with gastric cancer. Int J Clin Exp Med 2014;7:3501-3511.
7. Lan H, Zhu N, Lan Y, Jin K, Teng L. Laparoscopic gastrectomy for gastric cancer in China: an overview. Hepatogastroenterology 2015;62:234-239.
8. Phillips JD, Nagle AP, Soper NJ. Laparoscopic gastrectomy for cancer. Surg Oncol Clin N Am 2013;22:39-57.
9. Kim CH, Song KY, Park CH et al. A comparison of outcomes of three reconstruction methods after laparoscopic distal gastrectomy. J Gastric Cancer 2015;15:46-52.
10. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113-123.
11. Fang C, Hua J, Li J et al. Comparison of long-term results between laparoscopy-assisted gastrectomy and open gastrectomy with D2 lymphadenectomy for advanced gastric cancer. Am J Surg 2014;208:391-396.
12. Yegin EG, Duman DG. Staging of esophageal and gastric cancer in 2014. Minerva Med 2014;105:391-411.
13. Ramagem CA, Linhares M, Lacerda CF et al. Comparison of laparoscopic total gastrectomy and laparotomic total gastrectomy for gastric cancer. Arq Bras Cir Dig 2015;28:65-69.
14. Deng Y, Zhang Y, Guo TK. Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer: A meta-analysis based on seven randomized controlled trials. Surg Oncol 2015; 24:71-77.
15. Parisi A, Nguyen NT, Reim D et al. Current status of minimally invasive surgery for gastric cancer: A literature review to highlight studies limits. Int J Surg 2015; 17:34-40.
16. Clavien PA, Barkun J, de Oliveira ML et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-196.
17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.
18. Tokunaga M, Kondo J, Tanizawa Y et al. Postoperative intra-abdominal complications assessed by the Clavien-Dindo classification following open and laparoscopy-assisted distal gastrectomy for early gastric cancer. J Gastrointest Surg 2012;16:1854-1859.
19. Ye LY, Liu DR, Li C et al. Systematic review of laparos-

copy-assisted versus open gastrectomy for advanced gastric cancer. J Zhejiang Univ Sci B 2013;14:468-478.

20. Ilson DH. Adjuvant treatment for gastric cancer: too much is not enough. Lancet Oncol 2014;15:788-789.
21. Davidov M, Pajic B, Palanacki V, Popov D, Ognjenovic A. Early results of laparoscopic resection of the stomach. Hepatogastroenterology 2012;59:1135-1137.
22. Chen XZ, Wen L, Rui YY et al. Long-term survival outcomes of laparoscopic versus open gastrectomy for gastric cancer: a systematic review and meta-analysis. Medicine (Baltimore) 2015;94:e454.
23. Jin Z, Jiang W, Wang L. Biomarkers for gastric cancer: Progression in early diagnosis and prognosis (Review). Oncol Lett 2015;9:1502-1508.
24. Bo T, Peiwu Y, Feng Q et al. Laparoscopy-assisted vs. open total gastrectomy for advanced gastric cancer: long-term outcomes and technical aspects of a case-control study. J Gastrointest Surg 2013;17:1202-1208.
25. Lin J, Huang C, Zheng C et al. A matched cohort study of laparoscopy-assisted and open total gastrectomy for advanced proximal gastric cancer without serosa invasion. Chin Med J (Engl) 2014;127:403-407.
26. Cai J, Zhang C, Zhang H et al. Open versus laparoscopy-assisted D2 radical gastrectomy in advanced upper gastric cancer: a retrospective cohort study. Hepatogastroenterology 2013;60:1805-1808.
27. Lee J, Kim W. Clinical experience of 528 laparoscopic gastrectomies on gastric cancer in a single institution. Surgery 2013;153:611-618.