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Feasibility and safety comparison of laparoscopy-assisted versus open gastrectomy for advanced gastric carcinoma with D2 lymphadenectomy

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Abstract

Objective: Laparoscopy-assisted gastrectomy for advanced gastric cancer still remains controversial. The aim of this study is to compare oncologic feasibility and technical safety of laparoscopic versus open gastrectomy for advanced gastric cancer with D2 lymphadenectomy by comparing patients' short-term postoperative outcomes.
Methods: One hundred and one patients with laparoscopy-assisted gastrectomy and 101 patients with open gastrectomy were one-to-one matched and then compared in terms of operative outcomes and hospital courses.
Results: The laparoscopic group showed significantly longer operating time (297.4 vs. 198.1 min, $P < 0.001$), earlier first flatus time (2.8 vs. 3.6 days, $P < 0.001$), earlier diet start time (3.8 vs. 4.6 days, $P < 0.001$), shorter hospital stay (10.5 vs. 11.9 days, $P < 0.001$) and less morbidity (21.8 vs. 37.6%, $P = 0.019$). However, retrieval lymph nodes, intraoperative blood loss, transfused patients, postoperative fever and mortality were similar in the two groups. As for complications, incision infection (1.0 vs. 8.9%, $P = 0.021$) was significantly more common in the open group than in the laparoscopic group. In the subgroup comparisons of outcomes of laparoscopy-assisted gastrectomy, the tumor, node, metastasis III group showed significantly increased retrieval lymph nodes (37.2 vs. 31.0, $P < 0.001$), increased intraoperative blood loss (147.2 vs. 120.5 ml, $P = 0.010$), increased length of hospital stay (11.1 vs. 9.9 days, $P < 0.001$) and increased morbidity (32.6 vs. 13.8%, $P = 0.024$) when compared with the tumor, node, metastasis II group.
Conclusions: Laparoscopy-assisted gastrectomy is feasible and safe for the treatment of advanced gastric cancer with D2 lymphadenectomy compared with open gastrectomy. Higher-level tumor stage (tumor, node, metastasis III) may increase the operative risk and should be performed with caution by surgeons with considerable experience of laparoscopic gastrectomy.

Key words: GI surgery, GI medicine, GI-colerectum-surg

Introduction

Compared with conventional open gastrectomy (OG), laparoscopy-assisted gastrectomy (LAG) has widely known clinical advantages of the minimally invasive approach, such as shorter hospital stay, reduced morbidity, decreased pain, better cosmesis, faster postoperative recovery and better postoperative quality of life (1–5). Since LAG for gastric cancer was first introduced by Kitano in 1994 (6), cases of LAG for early-stage gastric cancer have been increasing gradually and the use of this procedure has been increasing rapidly in early-stage gastric cancer in high-prevalence Eastern countries such as Japan, Korea and China. Because of the technical difficulties of LAG and worries about the oncologic efficacy, most of the reports about LAG focus on early-stage gastric cancers, which only need D1 or D1+ lymphadenectomy. Many reports of laparoscopic techniques for early-stage gastric cancer have shown oncologic equivalency to the open technique, with the known benefits of the minimally invasive approach (7–12).

However, contrary to the wide acceptance of laparoscopic surgery for the treatment of early-stage gastric cancer with D1 or D1+ lymphadenectomy, LAG for advanced gastric cancer (AGC) still remains controversial and has not achieved universal acceptance for its uncertain oncologic benefits. The main controversy surrounding LAG for AGC involves whether lymph node clearance is sufficient and concerns about subsequent complications (13,14). Therefore, LAG for AGC with D2 lymphadenectomy has been relatively less frequently performed probably because of associated technical difficulties concerning lymph node dissection and anastomosis. LAG application in AGCs must overcome some problems associated with incomplete D2 lymphadenectomy (15). Because of recent innovative progression in laparoscopic tools and improvement in surgical experience, some surgeons with much laparoscopic procedure experience have attempted to extend their indications of laparoscopic surgery into advanced diseases. The first LAG with D2 lymphadenectomy for gastric cancer was reported in 1999 (16). Some experts have reported the laparoscopic surgical technique of this procedure with operative outcomes in small case series, but only a few studies have evaluated the oncologic feasibility and technical safety of this procedure (17–19). The oncologic feasibility and technical safety of LAG need to be further evaluated in a large patient cohort using a proper study design.

Due to the relatively more gastric cancer patients, physicians of Eastern Asian countries such as Japan and Korea are more experienced in gastric treatment than physicians of Western countries, especially in LAG. China is also a gastric cancer high-prevalence country, and the laparoscopic technique is developing rapidly in recent years. Shanxi Province Hospital is a tertiary and cancer special hospital in North China, in which LAG has been carried out since 2012. With the accumulation of LAG operation experience and advancement of instruments and surgical techniques for laparoscopic surgery, LAG has also been recently performed to treat AGC with D2 lymphadenectomy by a few experienced surgeons. In this study, we evaluated the oncologic feasibility and technical safety of laparoscopy-assisted versus OG for advanced gastric carcinoma with D2 lymphadenectomy performed by one experienced operator by comparing the short-term postoperative outcomes.

Patients and methods

Between April 2012 and December 2014, 411 consecutive patients with gastric cancer underwent gastrectomy in the Department of General Surgery at Shanxi Province Cancer Hospital. One hundred and sixty-eight patients who underwent LAG for advanced gastric carcinoma and 243 patients who underwent OG for advanced disease were recorded using a prospectively maintained gastric cancer database. We excluded the conditions such as bleeding or perforation, preoperative chemotherapy or radiation therapy, total gastrectomy for remnant gastric cancer, combined major organ resection and noncurative surgery. Sixty-seven patients from the LAG group and 37 patients from the OG group were excluded. Finally, 101 patients with LAG and 206 patients with OG were included in the patients' sample for further propensity score matching.

The selection of laparoscopic or open surgery was determined according to disease stage or patient's choice. One surgeon with much experience with laparoscopic and OG as operator and two assistants performed all operations. Patient data including demographics, operative results, pathologic reports, hospital courses, and morbidity and mortality were prospectively collected. Pathologic stages were based on the seventh edition of American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) classification staging manual (20). The study was approved by the medical ethics committee of Shanxi Province Cancer Hospital and was conducted according to the Declaration of Helsinki Principles.

The patient was placed in a supine position under general anesthesia with legs apart. Five trocars were inserted into the abdominal cavity, with two operator trocars at the right side of the patient, two assistant trocars at the left side of the patient, and an umbilical trocar for laparoscope insertion. The operator stood on the right side of the patient. The liver was retracted upward using an additional 5 mm trocar and placed at the anterior wall of the abdomen. Under pneumoperitoneum pressure of 12–14 mmHg, gastric dissection was started by dividing the greater omentum, then toward the left gastroepiploic area, right gastroepiploic area and the suprapyloric area. All patients underwent D2 lymphadenectomy and the procedure was completed using a harmonic scalpel. The D2 lymphadenectomy was performed according to the lymph node classification by the Japanese Gastric Cancer Association (21). After completing gastric dissection and lymph node dissection, gastrectomy and anastomosis were performed through a 4–6 cm median superior abdominal incision. OG was performed in the same manner as LAG through a 15 cm midline incision at the epigastrium. In both LAG and OG group, anastomotic procedure was performed with the circular stapler in open state.

Patients were managed using a standardized clinical pathway protocol during perioperative period. There are no significant differences in the main elements of perioperative care between laparoscopic and open groups. For example, preoperative mechanical bowel preparation and nasogastric tube insertion were routinely performed. Patients were allowed to eat a semi-liquid diet until the night before the operation. The routine use of prophylactic antibiotics was administered before operation to postoperative Day 3. Postoperative pain was managed using epidural anesthesia for 3 days postoperatively. Patients started feeding diet from the first postoperative day and then started soft diet on postoperative Day 7 in the absence of gastrointestinal symptoms. Catheter was removed and the patients can leave the bed at the first postoperative day. Patients were discharged from the hospital when they could take objective diet without complication.

Patients in the LAG and OG groups were matched using the propensity score method as described by Rosenbaum and Rubin (22). The propensity score for an individual was generated based on the covariates including age, sex, body mass index (BMI), comorbidity, American Society of Anesthesiologists (ASA) score, TNM stage and distal or total gastrectomy using a multivariable logistic regression model. Using these propensity scores, 101 LAG patients were individually matched to 101 OG patients.

The statistical analysis was performed using commercially available statistical software (SPSS 21.0, IBM-SPSS, Chicago, USA). Clinicopathologic characteristics and surgical outcomes of the matched data were compared using paired t-test or Wilcoxon signed ranks test for continuous variables and McNemar's test for binary proportions. In the subgroup analysis according to the TNM stage, Student's

Table 1. Clinicopathologic characteristics

Characteristic	LAG (n = 101)	OG (n = 101)	P value
Age, mean, year ± SD	57.7 ± 10.5	59.9 ± 10.1	0.163
Gender			1.000
Male	54 (53.5%)	53 (52.5%)	
Female	47 (46.5%)	48 (47.5%)	
BMI, mean, kg/m^2 ± SD	23.7 ± 1.1	23.7 ± 1.0	0.459
Comorbidity	27 (26.7)	31 (30.7)	0.571
ASA score			0.923
1	29 (28.7%)	28 (27.7%)	
2	54 (53.5%)	52 (51.5%)	
3	18 (17.8%)	21 (20.8%)	
TNM stage			0.528
II	58 (57.4%)	60 (59.4%)	
III a	24 (23.8%)	23 (22.8%)	
III b	19 (18.8%)	18 (17.8%)	
Tumor location			1.000
Upper	62 (61.4%)	62 (61.4%)	
Middle	10 (9.9%)	10 (9.9%)	
Distal	29 (28.7%)	29 (28.7%)	
Operation mode			1.000
Total	63 (62.4%)	63 (62.4%)	
Distal	38 (37.6%)	38 (37.6%)	
Pathology			0.845
Undifferentiated	58 (57.4%)	60 (59.4%)	
Differentiated	43 (42.6%)	41 (40.6%)	

Data are presented as mean ± standard deviation or n (%).

ASA, American Society of Anesthesiologists; TNM, tumor, node, metastasis classification staging system, LAG, laparoscopy-assisted gastrectomy; OG, open gastrectomy.

Table 2. Surgical outcomes of laparoscopy-assisted gastrectomy and open gastrectomy

Outcomes	LAG (n = 101)	OG (n = 101)	P value
Operative outcomes			
Operating time, mean, min ± SD	297.4 ± 57.9	198.1 ± 24.7	<0.001*
EBL, mean, ml ± SD	131.9 ± 52.1	129.5 ± 50.3	0.680
Retrieval lymph nodes, mean, n ± SD	33.7 ± 7.1	33.1 ± 7.6	0.358
Hospital courses			
Hospital stay, mean, days ± SD	10.5 ± 2.0	11.9 ± 1.8	<0.001*
First flatus time, mean, days ± SD	2.8 ± 0.7	3.6 ± 0.5	<0.001*
Diet start time, mean, days ± SD	3.8 ± 0.7	4.6 ± 0.5	<0.001*
Transfused patients, n (%)	20 (19.8%)	18 (17.8%)	0.832
Postoperative fever, n (%)	14 (13.9%)	15 (14.9%)	1.000
Morbidity, n (%)			0.019*
None	79 (78.2%)	63 (62.4%)	
Mild	1 (1.0%)	14 (13.9%)	
Moderate	4 (4.0%)	4 (4.0%)	
Severe	17 (16.8%)	20 (19.8%)	
Mortality, n (%)	1 (1.0%)	2 (2.0%)	1.000

Data are presented as mean ± standard deviation or n (%).

EBL, estimated blood loss.

*Statistically significant.

t-test, χ^2-test, or Fisher's exact test was used for comparison as appropriate. P values were based on two-sided tests and, if <0.05 were regarded as statistically significant.

Results

Table 1 summarized the clinicopathologic characteristics of the two study groups. Both groups were well balanced for the variables (age, sex, BMI, comorbidity, ASA score, TNM stage, and distal or total gastrectomy) that were considered in the propensity score derivation model. In the LAG group, there were 54 men and 47 women, with a mean age of 57.7 years. In the OG group, there were 53 men and 48 women, with a mean age of 59.9 years. The mean BMI was 23.7 kg/m^2, and 27 (26.7%) patients had underlying comorbidities. Pathologic examination revealed 58 (57.4%) patients with Stage II, 24(23.8%) with Stage IIIa and 19 (18.8%) patients with Stage IIIb tumors. D2 lymphadenectomy was performed in all cases.

Table 2 summarized the operative outcomes and hospital courses of the LAG and OG groups. The LAG group had a significantly longer operating time (297.4 vs. 198.1 min, P < 0.001) and shorter duration of hospital stay (10.5 vs. 11.9 days, P < 0.001) than the OG group. Meanwhile, the first flatus time (2.8 vs. 3.6 days, P < 0.001) and diet start time (3.8 vs. 4.6 days, P < 0.001) were significantly shorter in the LAG group than the OG group. Morbidity rate (21.8 vs. 37.6%, P = 0.019) was also significantly lower in the LAG group than the OG group. However, intraoperative blood loss (139.1 vs. 129.5 ml, P = 0.680), retrieval lymph nodes (33.7 vs. 33.1, P = 0.358), transfused patients (19.8 vs. 17.8%, P = 0.832), postoperative fever (13.9 vs. 14.9%, P = 1.000) and mortality (1.0 vs. 2.0%, P = 1.000) were similar in the two groups.

Table 3 showed the postoperative complications in the two groups. Concerning local complications, incision infection (1.0 vs. 8.9%, P = 0.021) was significantly more common in the OG group than in the LAG group. Meanwhile, anastomosis leakage (6.9 vs. 4.0%, P = 0.508) tended to be more common in the LAG group, and abdominal infection (5.9 vs. 4.0%, P = 0.754) and luminal bleeding (5.9 vs. 3.0%, P = 0.453) tended to be more common in the OG group. There were no significant differences in systemic complications between the two groups.

Table 4 showed the surgical outcomes of LAG group according to the TNM stage. Patients with TNM III tumors showed significantly more retrieval lymph nodes (37.2 vs. 31.0, P < 0.001), longer duration of hospital stay (11.1 vs. 9.9 days, P < 0.001), more intraoperative blood loss (147.2 vs. 120.5 ml, P = 0.010) and more morbidity (32.6 vs. 13.8%, P = 0.024) than those with TNM II tumors. There were no significant differences in operating time, first flatus time, diet start time and mortality between the two groups.

Discussion

Although the feasibility and safety of LAG for early-stage gastric carcinoma have been verified and widely accepted, LAG for AGC especially with D2 lymphadenectomy is still a controversial item mainly because of its technical difficulties and limited lymphadenectomy. For gastric cancer located in the lower-third, lymph nodes around the hepatoduodenal ligament (no.12a) and the superior mesenteric vein (no.14v) should be included in Group 2 by the 13th edition of the Japanese classification of gastric carcinoma (21). In addition, the Japanese Gastric Cancer Association has presented complete D2

Table 3. Postoperative complications of laparoscopy-assisted gastrectomy and open gastrectomy

Complication	LAG (n = 101) N (%)	OG (n = 101) N (%)	P value
Local complications			
Abdominal infection	4 (4.0%)	6 (5.9%)	0.754
Anastomosis leakage	7 (6.9%)	4 (4.0%)	0.508
Luminal bleeding	3 (3.0%)	6 (5.9%)	0.453
Anastomosis stricture	2 (2.0%)	1 (1.0%)	1.000
Incision infection	1 (1.0%)	9 (8.9%)	0.021*
Duodenal stump leakage	2 (2.0%)	3 (3.0%)	1.000
Ileus	1 (1.0%)	1 (1.0%)	1.000
Ascites	0 (0.0%)	4 (4.0%)	0.125
Systemic complications			
Pneumonia	2 (2.0%)	3 (3.0%)	1.000
Pleural effusion	0 (0.0%)	1 (1.0%)	1.000
Delirium	0 (0.0%)	1 (1.0%)	1.000

Data are presented as n (%).
*Statistically significant.

Table 4. Surgical outcomes of laparoscopy-assisted gastrectomy according to TNM tumor stage

Outcomes	TNM II (n = 58)	TNM III (n = 43)	P value
Operating time, mean, min ± SD	296.7 ± 59.8	298.4 ± 55.8	0.888
EBL, mean, ml ± SD	120.5 ± 55.1	147.2 ± 43.9	0.010*
Retrieval lymph nodes, mean, n ± SD	31.0 ± 7.0	37.2 ± 5.4	<0.001*
Hospital stay, mean, days ± SD	9.9 ± 1.5	11.1 ± 2.3	<0.001*
First flatus time, mean, days ± SD	2.8 ± 0.7	2.8 ± 0.6	0.774
Diet start time, mean, days ± SD	3.8 ± 0.7	3.8 ± 0.6	0.774
Morbidity, n (%)	8 (13.8%)	14 (32.6%)	0.024*
Mortality, n (%)	1 (1.0%)	2 (2.0%)	0.426

Data are presented as mean ± standard deviation or n (%).
*Statistically significant.

lymph node dissection as the standard therapy for local AGC (23). Recently, a small series of studies have reported the possibility of applying LAG with D2 lymphadenectomy for AGC (24,25). This study introduced the operative experience of one experienced operator from Shanxi Province Cancer Hospital. The propensity score matching method was used for the case–control comparison to overcome the biased estimates in observation studies. The results showed that similar numbers of lymph node dissection could be completed by LAG compared with OG in the operation of AGC, which suggested that our procedure for lymphadenectomy was sufficient for AGC and also addressed the long-held doubts about inadequate lymphadenectomy for LAG. Hur et al. (15) also presented that LAG with D2 lymphadenectomy was a sufficient procedure for AGC, and showed that the follow-up results for patients with AGC were acceptable compared with OG. However, to complete the tumor resection and lymph node dissection, the operative time was significantly prolonged (297.4 vs. 198.1 min, $P < 0.001$), and the estimated intraoperative blood loss increased (131.9 vs. 129.5 ml, $P = 0.680$) slightly without significance in LAG group than in the OG group. Previous studies generally showed that LAG had longer operative time and less bleeding compared with OG, but in the present study, the results are just the opposite, we think the following two points may be the possible reasons. First, it is possible to be related to the method of measuring the amount of bleeding. The bleeding volume in the open operation is usually determined by the amount of negative sucking and yarn cushion absorption. The quantity of yarn cushion absorption is usually obtained by weighing, which is easy to cause deviation in practice. However, the bleeding volume in laparoscopic surgery is only determined by the amount of negative sucking, which is relatively more accurate. Second, there are still some distances between the operative skill of laparoscopic surgery and open surgery, so for laparoscopic surgery it is more likely to encounter intraoperative bleeding and the treating of bleeding is also very complicated.

Moreover, this study revealed more rapid postoperative recovery in LAG group patients than patients in OG group in terms of significantly earlier first flatus time (2.8 vs. 3.6 days, $P < 0.001$) and diet start time (3.8 vs. 4.6 days, $P < 0.001$) and significantly shorter stay in hospital (10.5 vs. 11.9 days, $P < 0.001$). The mean postoperative hospital stay in this study was comparable with studies from Japan and Korea (12,15). Above results indicated that the LAG group has obvious advantages in the postoperative recovery in spite of the obviously longer operative time and slightly more intraoperative blood loss. These results were consistent with results from previous studies (7,26).

The postoperative complications were more common in the OG group than in the LAG group (21.8 vs. 37.6%, $P = 0.019$), and the complication spectrums were also different between the two groups. The profiles mainly included abdominal infection, luminal bleeding, incision infection, anastomosis leakage and duodenal stump leakage. The incision infection was a major cause of the difference, which was significantly higher in the OG group than that in the LAG group (1.0 vs. 8.9%, $P = 0.021$). Similarly, Zhao et al. (27) reported that in their operation of AGC, incision infection was significantly less common in the LAG group. However, anastomosis complications, such as anastomotic leakage, which was one of the most important complications in the laparoscopic group, was slightly higher without significance in the LAG group than that in the open group (6.9 vs. 4%, $P = 0.508$). Similar to our results, Lee et al. (26) investigated 67 patients with LAG and reported anastomosis-related problems as a major complication arising after LAG. In this study, the operation anastomosis was completed through the small incision in the open condition with the same anastomosis instruments and methods in all cases, but the anastomosis leakage incidence was higher in the LAG group than in the OG group, which may be related with the small incision and inadequate exposure. In contrast, totally laparoscopic anastomosis is operated under laparoscopic amplification and the 30° mirror can rotate to observe some hidden parts, so it is possible to increase the security of anastomosis. Overall, anastomosis-related complications accounted for most of the postoperative morbidity in patients undergoing LAG, if this problem could be reduced with development of proper surgical technique, the true minimal invasiveness of LAG might be really appreciated.

According to the postoperative pathological staging, the surgery condition was compared between patients of TNM II and patients of TNM III. We found that the retrieval lymph node increased with TNM stage accordingly (37.2 vs. 31.0, $P < 0.001$). Although the operation time (298.4 vs. 296.7 min, $P = 0.888$) did not prolong obviously, estimated intraoperative blood loss (147.2 vs. 120.5 ml, $P = 0.010$) increased significantly. At the same time, we also observed that postoperative complication incidence increased (32.6 vs. 13.8%,

$P = 0.024$) significantly and hospitalization time was prolonged significantly (11.1 vs. 9.9 days, $P < 0.001$). All the above results indicated that the difficulty of laparoscopic operation increased with the disease progressing into higher-level TNM tumor stage. Similar conditions were demonstrated in previous studies (7,28).

Although this study indicated oncologic feasibility and technical safety of LAG for AGC, it failed to show the definite clinical advantages of LAG over OG. In terms of postoperative recovery, such as postoperative bowel recovery, diet start, blood transfusion, postoperative fever and hospital stay, the laparoscopic group was better than the open group. However, for some other indicators such as operation time and incision infection, the laparoscopic group was inferior to the open group. Laparoscopic operation could reduce the incidence of postoperative complications, but only in the terms of incision infection, of which the effect was significant. On the whole, complications other than incision infection and mortality were similar in the two groups. We believe in order to evaluate the clinical benefits of LAG carefully, more aspects should be involved, such as better pain relief and cosmoses, reduced postoperative stress and patient survival quality, and a large randomized controlled trials should be needed.

Potential limitations of this study should be mentioned. First, it was a hospital-based study with the inherent risk of referral bias. Second, although propensity matching was used to reduce the inherent biases in observational studies, hidden bias was unavoidable because the propensity score matching controlled only for observational variables. Third, due to the short duration of patient follow-up, this study did not address the long-term oncologic outcomes of LAG for AGC. We have been accumulating long-term data on tumor recurrence and patient survival in order to evaluate the long-term oncologic efficacy of LAG for AGC in the near future. Strength of this study was that it was the first study of LAG for AGC from a tertiary and cancer special hospital in North China. We believed that this study could serve as an important background research of future randomized clinical trials on LAG for advanced gastric carcinoma.

In conclusion, this study suggests the oncologic feasibility and technical safety of LAG for AGC, as reflected by its comparable postoperative outcomes to OG. In addition, higher-level TNM stage disease will increase the difficulty of laparoscopic operation and affect the safety and feasibility of LAG. Therefore, the operation should be performed by experienced surgeons carefully. Finally, a study on the long-term oncologic outcomes of LAG for AGC will be warranted.

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Conflict of interest statement

None declared.

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