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Original Article

Laparoscopy-assisted total gastrectomyis safe and technique feasible for elderly patients with advanced gastric cancer

Xiaoping Liu[1,2*], Jiliang Qiu[3*], Yi Li[4], Tingyu Mou[1], Jiang Yu[1], Guoxin Li[1]

[1]Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China; [2]Department of Gastrointestinal Surgery, First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, China; [3]Department of Gastrointestinal Surgery, Guangzhou Medical University Cancer Center, Guangzhou, Guangdong, China; [4]Department of Surgery, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: The role of laparoscopy-assisted total gastrectomy (LTG) for elder patients is undetermined. This study was aimed to compare the safety and oncologic outcomes of elderly patients with nonelderly patients who underwent LTG for advanced gastric cancer (AGC). Methods: A total of 148 consecutive AGC patients who underwent total gastrectomy between June 2009 and November 2012 were analyzed retrospectively. Among those patients, 68 patients aged 60 years or more (elderly group) and 80 patients aged 59 years or less (nonelderly group). Postoperative complications and oncologic outcomes were compared between the two groups. Results: The baseline of clinicopathologic characteristics were similar between two groups (all $P>0.05$). Although the elderly group suffered more by pneumonia than the nonelderly group (14.7% *vs.* 5.0%, $P=0.044$), the two groups shared similar total postoperative complications (29.4% *vs.* 26.2%; $P=0.668$). The 3-year recurrence-free survival (RFS) rate was 44.6% in the elderly group and 42.1% in the nonelderly group ($P=0.854$). The 3-year overall survival (OS) rate was 52.3% in the elderly group and 47.4% in the nonelderly group ($P=0.788$). Multivariate analyses revealed that undifferentiated histology and TNM stage III were independent risk factors for RFS and OS. Conclusion: Although the elderly group had a significantly higher postoperative pneumonia complication, the two groups had comparable total postoperative complications. LTG is safe and technically feasible for elderly patients with AGC.

Keywords: Laparoscopy, total gastrectomy, advanced gastric cancer, elderly patients

Introduction

With adeclining incidence of gastric cancer (GC) worldwide, it still remains the second most common causes of cancer-related death. This health problem of GC is especially common in China, where more than half of GC cases are diagnosed at elder age and advanced disease [1-4]. With the improvements in early diagnosis and perioperative management, more and more elderly GC patients are treated with gastric resection.

Radical gastrectomy with D2 lymphadenectomy is one of approaches for treatment of advanced-stage GC (AGC) [5]. However, compared with nonelderly patients, elderly patients are more likely to have poor general conditions and moremedical diseases [6]. Thus, these effects could be more obvious in elderly patients who underwent total gastrectomy for AGC [7, 8].

Minimally invasive laparoscopic surgery has become an exciting area of surgical development. With the improvement of minimally invasive techniques, many studies further demonstrated laparoscopy has the advantage of being less invasive and it causes less pain, less blood loss, and earlier recovery, when compared with open gastrectomy [9]. These advantages from laparoscopy are particularly benefit for elderly patients. Many of previous studies focused on comparing LTG with open total gastrectomy for

Table 1. Clinicopathologic, surgical characteristics and postoperative courses

Factors	Elderly (n=68)	Nonelderly (n=80)	*P* value
Male:Female	53:15	53:27	0.116
Age (years)	66.3±5.8	49.6±7.9	0.013
Body mass index (kg/m^2)	22.1±3.0	22.0±3.0	0.738
ECOG[a] status			0.220
0	47 (69.1%)	65 (81.3%)	
1	19 (27.9%)	14 (17.5%)	
2	2 (3.0%)	1 (1.2%)	
Comorbidity			0.001
Present	32 (47.1%)	17 (21.3%)	
Absent	36 (52.9%)	63 (78.7%)	
Prior abdominal surgery			0.543
Yes	4 (5.9%)	3 (3.8%)	
No	64 (94.1%)	77 (96.2%)	
Tumor size (mm)	53.2±22.6	53.4±22.1	0.721
Tumor location			0.138
Upper 1/3	15 (22.1%)	30 (37.5%)	
Middle 1/3	50 (73.5%)	47 (58.8%)	
Whole involvement	3 (4.4%)	3 (3.7%)	
Histology			0.353
Differentiated	45 (66.2%)	47 (58.8%)	
Undifferentiated	23 (33.8%)	33 (41.2%)	
Number of retrieved lymph nodes	30.3±19.5	29.5±16.0	0.064
Tumor invasion[b]			0.314
T2	3 (4.4%)	1 (1.2%)	
T3	3 (4.4%)	7 (8.8%)	
T4a	50 (73.5%)	60 (75%)	
T4b	12 (17.7%)	12 (15%)	
Nodal status[b]			0.143
N0	17 (25.0%)	14 (17.5%)	
N1	18 (26.5%)	18 (22.5%)	
N2	11 (16.2%)	26 (32.5%)	
N3	22 (32.3%)	22 (27.5%)	
TNM stage[b]			0.305
IIA	2 (2.5%)	3 (3.7%)	
IIB	20 (29.4%)	12 (15.0%)	
IIIA	12 (17.6%)	19 (23.8%)	
IIIB	12 (17.6%)	22 (27.5%)	
IIIC	22 (32.4%)	24 (30.0%)	
Extent of lymphadenectomy			0.505
D2	55 (80.9%)	68 (85%)	
D2-No.10[c]	13 (19.1%)	12 (15%)	
Conversion	1 (1.5%)	0 (0%)	
Operating time (min)	229.8±44.4	231.3±46.3	0.947
Estimated blood loss (ml)	150.0±82.8	144.9±107.4	0.402
Intraoperative blood transfusion	3 (4.4%)	1 (1.2%)	0.237
Time to first flatus (days)	3.9±1.1	3.7±1.0	0.259
Time to first liquid intake (days)	4.8±1.4	4.4±1.6	0.558
Postoperative hospital stay (days)	11.7±7.4	10.5±5.2	0.105

LTG, laparoscopiy-assisted total gastrectomy; OTG, open total gastrectomy; BMI, body mass index. Data are expressed mean ± SD. [a]Eastern cooperative oncology group performance status; [b]Tumor staging was classified by Union International Cancer Control (UICC) staging; [c]D2 lymphadenectomy without dissection of splenic hilar LNs.

AGC. However, there is still lack of evidence to support whether laparoscopy total gastrectomy (LTG) or open gastrectomy is more favorable for elderly patients with AGC [10]. Thus, we conducted this study to compare the safety and oncologic outcomes in elder AGC patients who underwent LTG with that of nonelderly patients.

Materials and methods

The clinicopathological data of patients who underwent laparoscopic totally gastrectomy were all prospectively collected in a database since 2009 in the First Affiliated Hospital of Gannan Medical University. Since the first LTG was conducted in June 2009 in our hospital, the data of curative total gastrectomy for AGC between June 2009 and November 2012 was collected. By excluding patients with early-stage, tumor-node-metastases (TNM) stage IV diseases, a total of 148 consecutive AGC patients were retrospectively analyzed. In China, an elderly patient was usually defined as a patient aged over 60 years. Thus, we defined patients with the age of 60 years or more as elderly and with the age of 59 years or less as nonelderly in this study. Sixty-eight patients were classified as elderly (elderly group), and eighty patients were classified as nonelderly (nonelderly group). This study was approved by the Institutional Review Board of the First Affiliated Hospital of Gannan Medical University. Written informed consents were acquired before surgery.

Indications and surgeries

The preoperative staging was based on endoscopy with biopsy, endoscopic ultrasound,

lung and abdominal high-resolution multi-directional computed tomography (CT).

Under general anesthesia, the patient was placed in the supine position with a 20°-30° head up tilt and the lower extremities abducted at the hips. Under general anesthesia, the CO_2 pneumoperitoneum was maintained at a pressure of 12-13 mmHg. The surgeon stood on the left side of the patient, and the laparoscopist was positioned between the patient's legs. Five ports and a 30° rigid electronic laparoscope were used. The laparoscopic procedures have been described in our previously published papers [11, 12]. Most patients underwent D2 lymphadenectomy in the study. However, before 2011, for tumor locating at the lesser curvature, tumor size no more than 50 mm, no obvious bulky lymph node (LN) at the splenic hilum area, splenic hilum LN was not routinely dissected either in LTG (D2-No.10 LN). After 2011, the D2 lymphadenectomy with splenic hilum lymphadenectomy were regular performed for LTG. The impact of D2 or D2-No.10 LN was also analyzed in this study.

Follow up

The duration of follow-up was defined as the interval between the date of the operation and the date of death or the last follow-up. Postoperative complications were classified accordion to severity grading system of surgical complications. Recurrence-free survival (RFS) was defined as the interval from resection to gastric cancer metastasis around hematogenous, peritoneal, locoreginal distant lymph node, and mixed recurrence during follow-up period. Overall survival (OS) was defined as the interval from resection to death or last follow-up. After surgery, patients were recommended to receive 5-FU based adjuvant chemotherapy and followed-up every three months during the first two years from surgery and every six months afterwards. The last follow-up was conducted in December, 2015 in this study.

Statistical analysis

SPSS 17.0 (SPSS, Chicago, IL, USA) was used for statistical analyses. Data were expressed as the mean ± SD. The Mann-Whitney test or independent sample t test was applied for continuous variable after normality tests, and the Chi-square test was used for categorical variables to determine the significance of intergroup differences. Survival analyses were conducted by Kaplan-Meier method. The results of Univariate factor analysis with $P<0.1$ for screening criteria, which were taken into the binary Logistic regression model, using the method of stepwise regression analysis of Multivariate factors. $P<0.05$ based on two-sided statistical tests was considered statistically significant.

Results

Clinicopathologic characteristics

The clinicopathologic characteristics of patients were described in **Table 1** and Supplementary Table. Eighty were equal or less than 59 years (nonelderly group) and sixty-eight were no less than 60 (elderly group), with a medianage of 49.6±7.9 and 66.3±5.8, respectively, in the two groups. No significant differences was observed in baseline materials including gender, body mass index (BMI), ECOG status, prior abdominal surgery, tumor size, location, invasion depth, and TNM stage. However, the elderly group had higher rates of comorbidities than the nonelderly group ($P=0.001$).

Surgical outcomes, postoperative course

To complete remove the splenic hilar lymph nodes in LTG for AGC, we took retropancreatic approach, which was along the infra pancreatic tail to enter the retropancreatic space (**Figure 1A**). According to the sequence of down-to-up and proximal-to-distal, splenic vessels was dissociated with ultrasound scalpel (**Figure 1B**). Then the fatty and lymph tissues was dissected towards the splenic hilum. Finally, the short gastric vessels of superior spleen was divided (**Figure 1C**).

Surgical outcomes and postoperative course were also shown in **Table 1**. During postoperative course, the differences of lymph nodes retrieved, blood loss, intraoperative blood transfusion, first flatus, and liquid intake were not significant between the two groups. The operation time and postoperative hospital stay were also not prolonged in the elderly group. One patientshad conversion due to bulky tumor in elderly group.

Postoperative complications

Postoperative morbidity and mortality outcomes in the two groups are listed in **Table 2**.

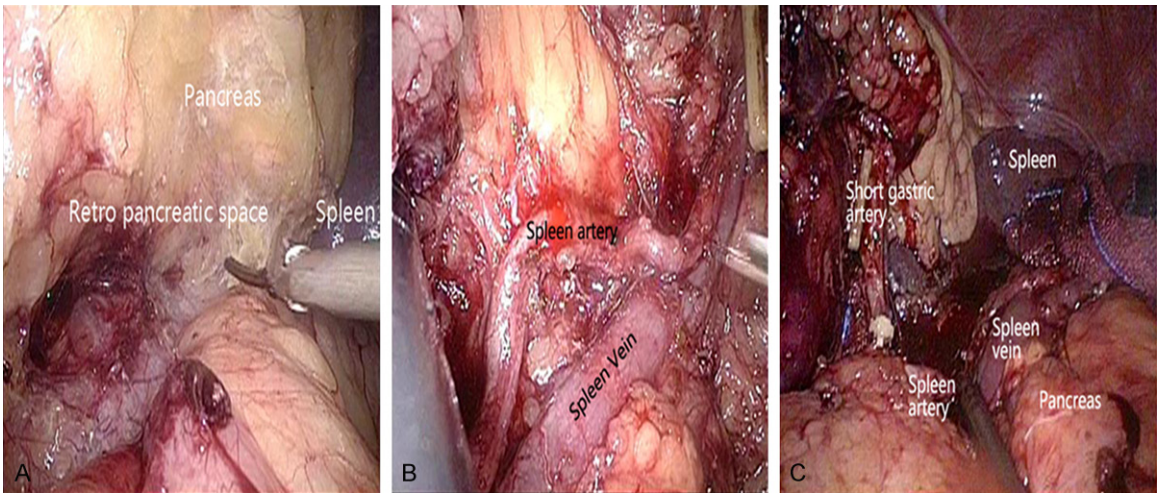

Figure 1. Represent laparoscopy figure of remove the splenic hilar lymph nodes: enter retropancreatic space (A); dissociate splenicvessels (B); divide short gastric vessels (C).

Table 2. Postoperative complications according to the accordion severity grading system

Complications	Elderly (n=68)	Nonelderly (n=80)	Chi-square value	*P* value
Total number o	20 (29.4%)	21 (26.3%)	0.183	0.668
Mild complications	1 (1.5%)	2 (2.5%)	0.000	1.000
Wound problem	1 (1.5%)	2 (2.5%)		
Moderate complications	15 (22.1%)	18 (22.5%)	0.004	0.949
Pneumonia	10 (14.7%)	4 (5.0%)		
Ileus	1 (1.5%)	2 (2.5%)		
Lymphatic fistula	1 (1.5%)	3 (3.7%)		
Hepatic malfunction	0 (0%)	2 (2.5%)		
Pancreatic fistula	2 (2.9%)	3 (3.7%)		
Intra-abdominal abscess	1 (1.5%)	2 (2.5%)		
Reflux	0 (0%)	1 (1.3%)		
Anastomosis obstruction	0 (0%)	1 (1.3%)		
Severe complications	3 (4.4%)	1 (1.3%)	0.454	0.501
Anastomosis leakage	1 (1.3%)	1 (1.3%)		
Death	1 (1.5%)	0 (0%)		
Vascular bleeding	1 (1.5%)	0 (0%)		

Postoperative complications occurred in 20 of 68 (29.4%) of elderly patients, and in 21 of 80 (26.2%) of nonelderly patients (*P*=0.668). According to the Severity Grading System, the difference of mild, moderate, and severe complications were not significant. Among the major difference, elderly patients suffered more by pneumonia (*P*=0.044) than the nonelderly patients. One elderly patient died of severe left gastric artery bleeding 10 days after LTG in the intensive care unit. And no patients died within 30 day after laparoscopy in the nonelderly group.

Oncologic outcomes

During the follow-up period, the number of lost to follow-up were 3 and 4, respectively, in the elderly and nonelderly groups. Tumor recurred in 36 patients (55.4%) in the elderly group and 44 (57.9%) in the non elderly group (*P*=0.764).

The median follow-up time was 33 months (range, 2-55) months. For the whole study, the cumulative 3-year rate was 43.3% for the RFS, and 49.6% for the OS. The 3-year RFS rate was 44.6% in the elderly group, which was similar to that of the nonelderly group (42.1%, *P*=0.854, **Figure 2A**). Moreover, the 3-year OS rate was 52.3% in the elderly group, which was similar to that of the nonelderly group (47.4%, *P*=0.788, **Figure 2B**).

Risk factors for recurrence and survival

Table 3 shows the univariate and multivariate analyses of risks for RFS and OS. Regarding RFS, undifferentiated histology and TNM stage III were significant risk factors in the univariate

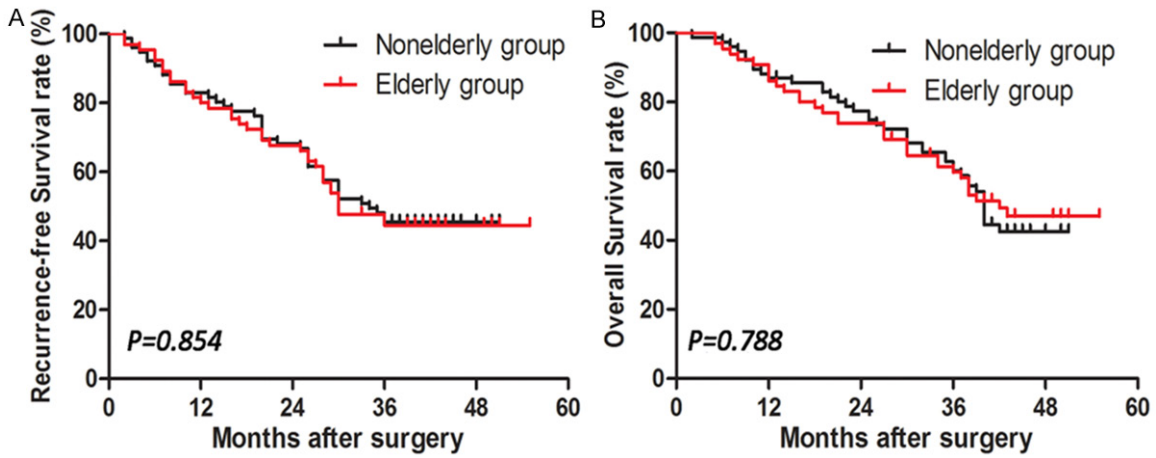

Figure 2. Kaplan-Meier analysis of recurrence-free survival (A) and overall survival (B) of elderly patients and non-elderly patients.

analysis. Multivariate analyses showed that undifferentiated histology (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.37-0.90; *P*=0.015) and TNM stage III (HR 2.24; 95% CI 1.23-4.09; *P*=0.008) were independent risk factors. Regarding OS, undifferentiated histology and TNM stage III were also significantly influenced the survival rate in the univariate analysis. Multivariate analyses indicated that undifferentiated histology (HR 0.59; 95% CI 0.37-0.93; *P*=0.023) and TNM stage III (HR 2.45; 95% CI 1.29-4.67; *P*=0.006) were independent risk factors.

Discussion

With the improvement of the diagnostic medicine, more and more elderly gastric cancer will be recommended for gastric resection. Of them, more than 90% are diagnosed at an advanced stage when they first present [13, 14]. Several studies have shown favorable outcomes for laparoscopic chole-cystectomy [15-17] and laparoscopic colorectal surgery [18, 19] in elderly patients. However, there is still a paucity of data regarding laparoscopic gastrectomy for those patients with advanced stage disease. A multicenter study [20] showed that no significant difference in postoperative morbidity and mortality between the elderly and non-elderly groups. Although elderly patients had greater co-morbidity, laparoscopicgastrectomy was a safe treatment for gastric cancer, when compared nonelderly patients in this age group. Another study from Kim's group [21] demonstrated that there were no differences in the short term outcome or minor complication rate between the elderly and nonelderly groups. Therefore, this study confirmed that it was feasible to perform laparoscopy gastrectomy for gastric cancer in elderly patients.

Although with the improvement of laparoscopy technique, some surgeons are still hesitant to perform laparoscopic surgery in elderly patients because of the relative high rates of postoperative morbidity and mortality. A study from Japan [22] demonstrated significantly more major complications occurred, including leakage and anastomotic bleeding, in the elderly group after laparoscopic distal gastrectomy. In the present study, the total complication rate was 29.4% in the elderly group, which was similar with that in the nonelderly group (26.3%, *P*=0.668). Meanwhile, 14.7% elderly patients had pneumonia, which was higher than that of nonelderly patients. We hypothesize that old age itself increase pre-operatively comorbidities. However, these comorbidities didn't increase the risk of severe complications and deaths [23, 24]. Severe complications were similar between the two groups. Studies have showed that the incidence of postoperative complications was ranged from 9.4% to 35.6% [25-27] in laparoscopy gastrectomy for gastric cancer, which was also supported by our study. Thus, it was suggested that laparoscopy was a safe and technique feasible for elder patients.

Currently, laparoscopy-assisted gastrectomy for AGC has been demonstrated by several

Table 3. Uni- and multivariate Cox regression analyses of risk factors for recurrence and survival

Factors	Recurrence-free survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR[a] (95% CI[b])	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender (female: male)	0.78 (0.45-1.33)	0.35			0.80 (0.46-1.40)	0.44		
Age (≥60:<60 years)	1.24 (0.78-2.00)	0.85			1.24 (0.75-2.05)	0.78		
Body mass index (>25.0:≤25.0 kg/m^2)	0.71 (0.35-1.42)	0.33			0.57 (0.26-1.24)	0.16		
Prior abdominal surgery (yes: no)	1.62 (0.57-4.62)	0.37			2.26 (0.78-6.57)	0.13		
Comorbidity (no:yes)	0.69 (0.42-1.15)	0.15			0.67 (0.40-1.14)	0.14		
Histology (differentiated: undifferentiated)	0.54 (0.34-0.87)	0.012	0.58 (0.37-0.90)	0.015	0.54 (0.33-0.89)	0.015	0.59 (0.37-0.93)	0.023
Tumor size (>50:≤50 mm)	1.27 (0.80-2.01)	0.31			1.24 (0.65-2.83)	0.38		
Adjuvant chemotherapy (no:yes)	1.48 (0.83-2.65)	0.19			1.37 (0.77-2.02)	0.46		
Lymphadenectomy (D2-No.10:D2)	1.86 (0.87-3.98)	0.11			1.63 (0.76-3.50)	0.21		
Surgery time (>220:≤220 min)	0.81 (0.50-1.34)	0.41			0.77 (0.46-1.29)	0.32		
Blood loss (>200:≤200 mL)	1.09 (0.54-2.18)	0.82			0.93 (0.43-2.00)	0.85		
Blood transfusion (no:yes)	0.91 (0.26-3.17)	0.88			1.11 (0.31-3.95)	0.88		
Tumor stage (III:I/II)	2.12 (1.13-3.97)	0.019	2.24 (1.23-4.09)	0.008	2.39 (1.22-4.70)	0.011	2.45 (1.29-4.67)	0.006

[a]Hazard ratio (HR) was calculated from Cox regression model. [b]Confidence interval (CI).

studies [28, 29]. With the improvement of laparoscopy technique, we have successfully performed LTG for AGC with D2 lymphadenectomy. Standard D2 LN dissection during total gastrectomy for proximal gastric cancer requires the removal of the No.10 LNs. Spleen-preserving No.10 lymphadenectomy is technically feasible and safe for patients undergoing OTG, but not for LTG, which is technically difficult because of the complex vessels and a narrow and deep space at the splenic hilum. After 2011, we regular performed D2 lymphadenectomy including No.10 LN when the tumor was just locating at the middle-third of the stomach according to the Japanese classification of gastric carcinoma Japanese Gastric Cancer Association suggestion [30]. Previous studies have showed that for patients with proximal AGCs, splenic hilar LN involvement was positively correlated with a Bormann type of III/IV [31, 32] and tumor size of >5 cm [33]. In another study, we found that D2-No.10 LN dissection was not a risk factor for either RFS or OS [34]. Thus, we believe laparoscopy will not influence our findings.

In the present study, according to the definition of "elderly" in China and the latest Cancer statistics in China, 2015, patients over 60 years old was an important age population [35]. Therefore, patients more than 60 years old were categorized as elderly patients. Moreover, there were no differences in RFS and OS rates between the two groups, which indicated that laparoscopic surgery is a promising method for elderly AGC. Furthermore, multivariable COX analyses showed undifferentiated histology and tumor stage were independent risks for RES and OS rates, but not age, which further indicated that laparoscopic surgery is a promising method for elderly AGC.

The ability to ensure sufficiently extended lymph node dissection satisfying D2 lymphadenectomy which has been considered a standard procedure for AGC is recognized as the key factor affecting oncologic outcome, especially for the spleen-preserving splenic hilar lymph node dissection. Previous study showed that the possibility of precisely evaluate tumor stage was 86% for patients who underwent laparoscopic gastrectomy with no less than 15 lymph nodes retrieved, the minimum requirement for TNM staging [36]. In this study, the mean number of retrieved lymph nodes by LTG, was 30 both in the elderly and nonelderly groups. Moreover, the two groups had similar number of retrieved lymph nodes. Our study showed that it is technique feasible to perform LTG with radical region lymph node dissection for elderly patients.

This study also had several limitations as following: results based on a retrospectively study and lack of validation in independent centers. Thus, a multicenter study with a larger patient database will be required to further determine the impact of age on the surgical and oncological outcomes of LTG.

In summary, our preliminary data demonstrated that LTG is safety and technique feasible for elderly patients, which was similar to that of nonelderly patients. However, a large-scaled, prospective, controlled study is necessary to further evaluate the clinical value of laparoscopy in elderly AGC patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Guoxin Li, Department of General Surgery, Nanfang Hospital, Southern Medical University, No. 1838, The North Guangzhou Avenue, Guangzhou 510515, Guangdong, China. Tel: +86-20-6164-1681; Fax: +86-20-6164-1683; E-mail: gzliguoxin@163.com

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