

Impact of Age on Early Surgical Outcomes of Laparoscopy-assisted Gastrectomy with Suprapancreatic Nodal Dissection for Clinical Stage I Gastric Cancer

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Abstract. *Background/Aim:* Although laparoscopy-assisted gastrectomy (LAG) is widely used for the treatment of gastric cancer, its safety and feasibility for elderly patients remains controversial. We herein examined the impact of age on the early surgical outcomes of LAG with suprapancreatic nodal dissection for elderly patients with clinical stage I gastric cancer. *Patients and Methods:* This retrospective study included 292 patients undergoing LAG with suprapancreatic nodal dissection for clinical stage I gastric cancer. We divided patients into an elderly group (age ≥ 75 years; $n=55$) and non-elderly group (age < 75 years; $n=237$). Preoperative conditions, operative findings and postoperative outcomes, including complications, were compared between these two groups. *Results:* The elderly group had a higher incidence of co-morbidities (61.8%) and lower forced expiratory volume in 1 second/forced vital capacity (74.8%). Preoperative levels of hemoglobin (Hb) and serum albumin (Alb), as well as the total lymphocyte count (TLC) were lower in the elderly group ($p<0.001$, <0.001 and $=0.018$, respectively). No significant differences were observed in intraoperative findings between the two groups. The incidence of overall and surgical complications in the elderly group (21.8% and 14.5%, respectively) did not significantly differ from those in the non-elderly group. The frequency of non-surgical complications in the elderly group (9.1%) was significantly higher ($p = 0.018$), whereas no critical complications or

mortality were observed. No significant differences were noted in the severity of complications or hospital courses between the groups. *Conclusion:* LAG with suprapancreatic nodal dissection appears to be safe and feasible for elderly patients with clinical stage I gastric cancer.

Gastric cancer is the most common of all cancers in Japan with the number of elderly patients increasing due to longer life expectancies (1, 2). Complete tumor removal is essential in the treatment of curable gastric cancer, whereas less invasive surgery is recommended, especially for elderly patients who often have many co-morbidities and age-related reduction in physiological functions. Previous studies on the outcomes of surgical treatments for gastric cancer reported that chronological age-alone should not preclude surgical treatment (3-7), while others identified age as an independent factor affecting postoperative morbidity and mortality (8-10). Accordingly, surgeons have hesitated to perform gastrectomy or limited the extent of lymph node dissection in elderly patients, especially in conventional open gastrectomy.

Laparoscopy-assisted gastrectomy (LAG) is widely used for the treatment of gastric cancer because it is associated with less pain, quicker return of gastrointestinal function, better pulmonary function, decreased stress responses, a shorter hospital stay and better postoperative quality of life than conventional open gastrectomy (11-15). A Japanese multi-center phase II trial (JCOG0703) recently confirmed the safety of laparoscopy-assisted distal gastrectomy (LADG) with D1 plus suprapancreatic nodal dissection for clinical stage I gastric cancer (16); however, the patients who entered these clinical trials were relatively young and had no severe co-morbidities. Therefore, the safety and feasibility of LAG with suprapancreatic nodal dissection for elderly patients with clinical stage I gastric cancer remains controversial.

In the present study, in order to evaluate the impact of age on the early surgical outcomes of LAG with suprapancreatic

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Table I. Patients' characteristics.

	Elderly group	Non-elderly group	p-Value
Number of patients	55	237	
Age (years)*	79.5±4.0 (75-89)	60.5±9.7 (35-74)	<0.001
Gender (Male/Female)	35/20	145/92	0.736
BMI (kg/m ²)*	22.2±3.0 (15.4-29.0)	22.8±3.3 (15.7-34.2)	0.184
History of abdominal surgery, n (%)	21 (38.2)	82 (34.6)	0.616
Clinical stage [#]			0.939
T1N0M0 Stage IA	51	217	
T1N1M0 Stage IB	1	4	
T2N0M0 Stage IB	3	16	

*Values are mean±SD (range). [#]Japanese classification of gastric carcinoma. BMI, Body mass index.

Table II. Preoperative conditions.

	Elderly group (n=55)	Non-elderly group (n=237)	p-Value
Co-morbidities, n (%)	34 (61.8)	102 (43.0)	0.012
Hypertension	27 (49.1)	70 (29.5)	0.006
Diabetes mellitus	10 (18.2)	32 (13.5)	0.373
Cardiovascular disease	9 (16.4)	12 (5.1)	0.004
Cerebral disease	4 (7.3)	11 (4.6)	0.426
Respiratory disease	3 (5.6)	11 (4.6)	0.799
Spirometry			
FEV1.0% (%)*	74.8±9.4	77.7±7.5	0.016
%VC (%)*	106.3±19.3	110.7±15.4	0.073
Laboratory findings			
Hemoglobin (g/dl)*	12.8±1.4	13.8±1.5	<0.001
Alb (g/dl)*	4.249±0.297	4.396±0.287	<0.001
TLC (cells/μl)*	1623±594	1862±686	0.018

*Values are the mean±SD. FEV1.0%, Forced expiratory volume in 1 sec/forced vital capacity; %VC, percent vital capacity; Hb, hemoglobin; Alb, albumin; TLC, total lymphocyte count.

nodal dissection, we compared operative findings, postoperative outcomes and hospital courses between elderly patients (75 years old or older) and non-elderly patients (younger than 75 years old). The aim of the study was to determine whether LAG with suprapancreatic nodal dissection was safe and feasible for elderly patients aged 75 years old or older with clinical stage I gastric cancer.

Patients and Methods

Patients. We retrospectively reviewed 292 patients who underwent LAG with suprapancreatic nodal dissection for clinical stage I gastric cancer between February 2002 and May 2013 at Kyoto Prefectural University of Medicine. Each tumor was histologically diagnosed as gastric adenocarcinoma and the staging was classified according to the Japanese classification of gastric carcinoma(17). During this period, LAG was the first choice of surgical treatment for clinical stage I gastric cancer. Patients undergoing simultaneous surgery for synchronous malignancy were excluded from this study to exclude the effects of such additional procedures on surgical outcomes.

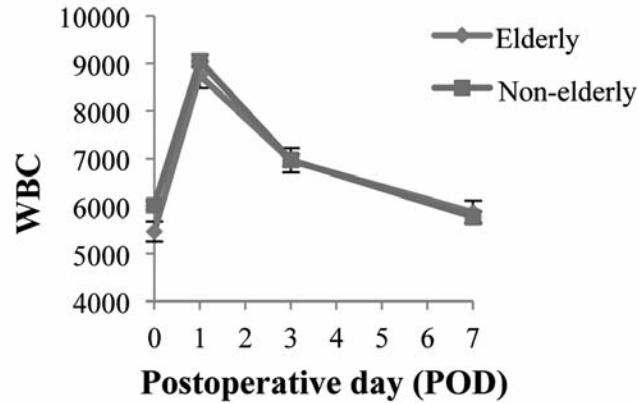
Furthermore, patients who needed conversion to the open procedure based on the intraoperative findings of tumor invasion into the subserosa or deeper or metastases to suprapancreatic nodes by frozen pathology were also excluded from the present study.

To evaluate the impact of age on early surgical outcomes, we divided patients into an elderly group (75 years old or older) and non-elderly group (younger than 75 years old).

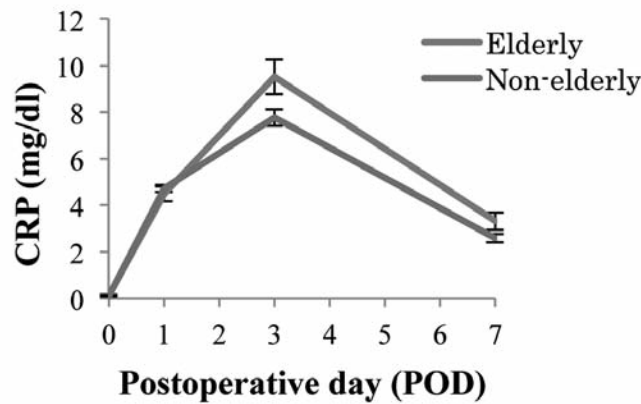
Patients' characteristics. The following clinical data were obtained from the medical records: age, gender, body mass index (BMI), history of abdominal surgery and clinical stage of patients. Blood analyses, chest X-rays, electrocardiograms and spirometry were routinely examined in all patients to assess cardiopulmonary function and other co-morbidities. Spirometry tests examined forced expiratory volume in 1 second/forced vital capacity (FEV1.0%) and percent vital capacity (%VC). The following laboratory findings were recorded to evaluate preoperative nutritional status: hemoglobin (Hb) and serum albumin (Alb) levels, as well as the total lymphocyte count (TLC).

Surgical procedures. The detailed surgical procedure of LAG was described in our previous study (18-21). Briefly, a total of 6 trocars

A



B



	Baseline	1POD	3POD	7POD
Elderly group	5471 ± 209	8760 ± 277	6960 ± 257	5873 ± 239
Non-elderly group	6015 ± 101	9062 ± 133	6964 ± 125	5774 ± 117
<i>p</i> -value	0.020	0.326	0.988	0.711

	Baseline	1POD	3POD	7POD
Elderly group	0.121 ± 0.028	4.486 ± 0.318	9.512 ± 0.746	3.312 ± 0.378
Non-elderly group	0.096 ± 0.014	4.713 ± 0.156	7.773 ± 0.362	2.588 ± 0.185
<i>p</i> -value	0.429	0.709	0.037	0.087

WBC, white blood cell. CRP, c-reactive protein. LAG, laparoscopy-assisted gastrectomy. SE, standard error.

Figure 1. (A) Mean WBC levels at baseline and 1, 3 and 7 days after LAG. (B) Mean CRP levels in patients at baseline and 1, 3 and 7 days after LAG. Data are expressed as the mean ±SE.

Table III. Operative findings.

	Elderly group (n=55)	Non-elderly group (n=237)	p-Value
Type of gastrectomy, n (%)			0.333
TG	11 (20.0)	32 (13.5)	
PG	4 (7.3)	18 (7.6)	
DG	40 (72.7)	178 (75.1)	
PPG	0 (0)	9 (3.8)	
Lymph node dissection [#] , n (%)			0.101
D1+	54 (98.2)	218 (92.0)	
D2	1 (1.8)	19 (8.0)	
Combined resection, n (%)			0.100
Gall bladder	2 (3.6)	13 (5.5)	
Spleen	1 (1.8)	0 (0)	
Conversion to open surgery, n (%)	2 (3.6)	5 (2.1)	0.505
Difficulty in keeping pneumoperitoneum	0 (0)	0 (0)	-
Operation time (min) [*]	328.7±94.0	337.1±90.4	0.535
Estimated blood loss (ml) [*]	117.1±146.3	87.7±124.5	0.129
Number of retrieved lymph nodes [*]	27.1±12.0	30.7±14.4	0.090
R0 resection, n (%)	55 (100)	137 (100)	-

*Values are the mean±SD. [#]Japanese gastric cancer treatment guidelines. TG, total gastrectomy; PG, proximal gastrectomy; DG, distal gastrectomy; PPG, pylorus preserving gastrectomy.

were used and a pneumoperitoneum was created by the injection of carbon dioxide (10-12 mmHg). According to the location of the tumor, LADG, laparoscopy-assisted pylorus preserving gastrectomy (LAPPG), laparoscopy-assisted total gastrectomy (LATG) or laparoscopy-assisted proximal gastrectomy (LAPG) was performed. The extent of lymph node dissection was D1+ or D2 based on the Japanese gastric cancer treatment guidelines (JGCTG) (22). After LADG, extracorporeal Billroth-I reconstruction or Roux-en Y reconstruction (R-Y) was performed using a 4-cm upper midline incision. In the case of LAPPG, extracorporeal hand-sewn gastro-gastrostomy was performed using a 4 cm upper midline incision. With respect to LATG, intracorporeal circular-stapled esophago-jejunoscopy and extracorporeal jejunojejunoscopy was performed through a 4 cm left upper transverse incision and ante-colic R-Y reconstruction was then completed. In the case of LAPG, intracorporeal esophagogastrostomy was performed via a 4-cm left upper transverse incision.

Operative data and postoperative outcomes. Operative data, such as the type of gastrectomy performed, extent of lymph node dissection, combined organ resection, conversion to open surgery, operation time, estimated blood loss, number of retrieved lymph nodes and residual tumor (R), were recorded. The following data were recorded to evaluate early postoperative outcomes: morbidity (surgical and non-surgical complications), mortality, time to first flatus, time to first diet and postoperative hospital stay. Surgical complications consisted of anastomotic leakage, anastomotic stricture, anastomotic bleeding, pancreatic fistula, intra-abdominal abscess, duodenal stump leakage, bile leakage, ileus, stasis, wound infection and acute cholecystitis, while non-surgical complications included pneumonia, pleural effusion, pneumothorax, arrhythmia and enterocolitis. The incidence and severity of postoperative complications were determined by the Clavien-Dindo classification of surgical complications (23, 24) and complications ≥grades II were reviewed. Meanwhile, the white blood cell (WBC) count and

C-reactive protein (CRP) levels 1, 3 and 7 days after surgery were collected to evaluate acute inflammatory responses caused by LAG.

Statistical analysis. To compare background characteristics, surgical outcomes and laboratory findings between the elderly and non-elderly groups, the χ^2 -test and Student's t-test were used for categorical variables and continuous variables, respectively. Statistical analyses were performed with JMP 10 (SAS Institute, Cary, NC, USA). All p-values cited are two-sided and significant levels were set at 5%.

Results

Patients' characteristics. Among 292 patients, 55 were 75 years old or older (elderly group) and the remaining 237 patients were younger than 75 years old (non-elderly group). Table I details the characteristics of patients in the elderly and non-elderly groups. The mean age in the elderly group was 79.5 years (range=75-89), while that in the non-elderly group was 60.5 years (range=35-74). No significant differences were observed in gender, BMI, history of abdominal surgery or clinical stage between the two groups.

Preoperative conditions. Co-morbidities, respiratory functions and laboratory findings, such as Hb, Alb and TLC in the elderly and non-elderly groups are summarized in Table II. The incidence of having any co-morbidities in the elderly group was 61.8%, which was significantly higher than that in the non-elderly group (43.0%, $p=0.006$). The elderly group had a higher incidence of hypertension (49.1%, $p=0.006$) and cardiovascular disease (16.4%, $p=0.006$), while the incidences of diabetes mellitus, cerebral disease and

Table IV. *Postoperative outcomes.*

	Elderly (n=55)	Non-elderly (n=237)	p-Value
Morbidity [#] (any), n (%)	12 (21.8)	39 (16.5)	0.345
Surgical complication, n (%)	8 (14.5)	36 (15.2)	0.904
Anastomotic leakage	0 (0)	0 (0)	-
Anastomotic stricture	0 (0)	5 (2.1)	0.277
Anastomotic bleeding	1 (1.8)	2 (0.8)	0.519
Pancreatic fistula	1 (1.8)	3 (1.3)	0.751
Intra-abdominal abscess	1 (1.8)	5 (2.1)	0.897
Duodenal stump leakage	0 (0)	0 (0)	-
Bile leakage	1 (1.8)	0 (0)	0.038
Ileus	0 (0)	2 (0.8)	0.494
Stasis	2 (3.6)	9 (3.8)	0.955
Wound infection	3 (5.5)	11 (4.6)	0.799
Acute cholecystitis	0 (0)	2 (0.8)	0.494
Non-surgical complication, n (%)	5 (9.1)	4 (1.7)	0.004
Pneumonia	1 (1.8)	2 (0.8)	0.519
Pleural effusion	2 (3.6)	0 (0)	0.003
Pneumothorax	1 (1.8)	0 (0)	0.038
Arrhythmia	0 (0)	1 (0.4)	0.629
Enterocolitis	0 (0)	1 (0.4)	0.629
Others	1 (1.8)	0 (0)	0.038
Severity of complications, n (%)			0.627
Grade II	10 (18.2)	32 (13.5)	
Grade IIIA	4 (7.3)	9 (3.8)	
Grade IIIB	0 (0)	2 (0.8)	
Mortality, n (%)	0 (0)	0 (0)	-
Time to first flatus (days)*	2.8 ±1.2	2.5±0.9	0.018
Time to first diet (days)*	3.5±0.9	3.6±1.0	0.499
Postoperative hospital stay (days)*	15.3±6.3	14.9±11.9	0.808

*Values are the mean±SD. #Complications >grade II according to the Clavien-Dindo classification.

respiratory disease were not significantly different between the two groups. FEV1.0% was significantly lower, while %VC was slightly lower in the elderly group than in the non-elderly group ($p=0.016$ and 0.073 , respectively). With respect to preoperative laboratory findings, Hb levels were significantly lower in the elderly group ($p<0.001$). The values of Alb and TLC were significantly lower in the elderly group ($p<0.001$ and 0.018 , respectively).

Operative findings. Operative findings in the elderly and non-elderly groups are summarized in Table III. No significant difference was observed in the type of gastrectomy performed between the two groups; however, LAPPG was not performed in the elderly group. Regarding the extent of lymph node dissection, D2 was more frequently performed in the non-elderly group, whereas this difference was not significant between the groups. In the elderly group, 2 patients underwent simultaneous cholecystectomy for

gallbladder stones and 1 patient undergoing LADG needed conversion to the open procedure because of bleeding of the spleen followed by simultaneous splenectomy with total gastrectomy. Although 2 patients in the elderly group and 5 patients in the non-elderly group required the open procedure due to severe adhesion or bleeding, difficulties in maintaining general anesthesia during pneumoperitoneum did not occur in either group. No significant differences were observed regarding operating time, estimated blood loss or number of retrieved lymph nodes between the groups. All patients in the elderly group underwent R0 resection, as did those in the non-elderly group.

Postoperative outcomes. Postoperative outcomes in the elderly and non-elderly groups are summarized in Table IV. Fourteen postoperative morbidities were observed in 12 patients (21.8%) in the elderly group, while 43 complications occurred in 39 patients (16.5%) in the non-elderly group, thus, there was no significant difference in the morbidity rate between the two groups. Regarding surgical complications, there were 9 postoperative complications in 8 patients (14.5%) in the elderly group and 39 complications in 36 patients (15.2%) in the non-elderly group; therefore, no significant difference was noted between the two groups. The incidence of re-operation, which was equal to complication grade IIIB, was 0 (0%) in the elderly group and 2 (0.8%) for pancreatic fistula and ileus in the non-elderly group. There were 5 non-surgical complications in the elderly group and 4 complications in the non-elderly group; thus, the frequency of non-surgical complications was significantly higher in the elderly group (9.1%) than that in the non-elderly group (1.7%) ($p=0.004$). However, only 2 out of the 5 patients in the elderly group required thoracic drainage for pleural effusion or pneumothorax, while the other 3 patients only required medical therapies. No significant difference was observed in complication grades between the two groups. No mortality was recorded in either the elderly group or non-elderly group. Time to first flatus was significantly longer in the elderly group ($p=0.018$), whereas time to first diet did not differ significantly between the two groups. The mean postoperative hospital stay in the elderly group was 15 days, which was similar to that in the non-elderly group.

Perioperative levels of WBC and CRP. Figure 1 shows the pre- and postoperative mean levels of WBC and CRP in the elderly and non-elderly groups. Although the mean baseline WBC level was significantly lower in the elderly group, mean WBC levels 1, 3 and 7 days after surgery were not significantly different between the two groups. Furthermore, although mean baseline CRP levels were not significantly different between the two groups, they were significantly higher in the elderly group than in the non-elderly group 3

days after surgery. Furthermore, CRP levels 7 days after surgery were slightly higher in the elderly group.

Discussion

In the present study, although the elderly group had a higher incidence of co-morbidities, lower pulmonary function and lower levels of Hb, Alb and TLC than the non-elderly group, no significant difference was observed in the incidence of overall and surgical complications between the two groups. Although the frequency of non-surgical complications was higher in the elderly group, no critical complications or mortality were observed.

Several retrospective studies have previously reported that LAG could be considered safe and feasible for elderly patients with gastric cancer (25-32). However, the definition of "elderly" differs among studies, with most defining the elderly as patients aged 70 years old or more. Furthermore, only few studies strictly defined the incidence and severity of each postoperative complication. Due to the aging society in Japan, the number of elderly patients with gastric cancer is increasing (1, 2). In the present study, the mean age of patients was 64 years and patients aged 70 years old or more accounted for 33.9% of all patients. Therefore, we defined patients aged 75 years old or older as being elderly in the present study, which accounted for 18.8% of all patients in this series. Meanwhile, the severity of each complication was determined by the Clavien-Dindo classification (23, 24).

The elderly group had lower levels of Alb and TLC than the non-elderly group in the present study. Alb has been proposed as an indicator of nutritional status and TLC is considered a useful indicator of nutritional status, as well as host immunity (33, 34). These parameters have often been reported to be lower in elderly patients and correlated with postoperative morbidity and mortality (34-38). Katai *et al.* (39) retrospectively investigated the surgical outcomes of patients undergoing open gastrectomy and reported that extended gastrectomy was associated with a higher operative mortality in elderly patients, especially in those with comorbidities. Hayashi *et al.* (40) assessed the severity of postoperative complications after extended gastrectomy in elderly patients and suggested that this surgery was risky for the elderly due to the high incidence of severe complications. Accordingly, a less invasive surgical approach is theoretically needed for elderly patients who are vulnerable to surgical stress because elderly patients, who often have co-morbidities and worse nutritional status and host immunity, may be at risk of mortality once postoperative complications develop.

Laparoscopic surgery is one of the promising surgical approaches that reduce surgical stress and is widely used for various abdominal surgeries. Laparoscopic colectomy

and cholecystectomy in elderly patients have been associated with reduced morbidity and a shorter hospital stay than their open counterparts (41-45). With respect to LAG, Hayashi *et al.* (12) compared early surgical outcomes between LADG and open distal gastrectomy in a prospective randomized fashion and reported that the LADG group showed significantly lower levels of postoperative serum interleukin-6 (IL-6) and CRP and had no major postoperative complications. Therefore, they concluded that LADG with extraperigastric lymph node dissection was a safe and less invasive alternative to the open procedure, even though the exclusion criteria of the study specified an age exceeding 80 years.

On the other hand, the present study was only aimed at patients undergoing LAG with suprapancreatic nodal dissection for clinical Stage I gastric cancer and evaluated the impact of age on an acute inflammatory response and its association with the incidence and severity of postoperative complications. As a consequence, postoperative CRP levels were higher in the elderly group suggesting that the acute inflammatory response induced by LAG was stronger in the elderly group. However, the overall morbidity rate, severity of postoperative complications and postoperative hospital courses were not significantly different between the elderly and the non-elderly groups. The absolutely low surgical stress of LAG might explain the low impact of relatively higher acute inflammatory response in the elderly patients on the early surgical outcomes.

There exist certain limitations to this study. This was a retrospectively study that only included elderly patients undergoing LAG. Therefore, patients with severe comorbidities who underwent open gastrectomy or avoided any surgical treatments were not included. The final indication for LAG depended on the decision of the attending physicians and this selection bias was a limitation. Our first choice of surgical treatment for clinical stage I gastric cancer (LAG or open gastrectomy) markedly changed at different times; therefore, it may be difficult to conduct a comparative examination of LAG and open gastrectomy. In addition, it may be too simple to evaluate the level of surgical stress of LAG by measuring of only WBC and CRP. Certain cytokines and hormones, such as IL-1, IL-6 and tumor necrosis factor alpha, as well as catecholamines and corticosteroids should be examined to accurately evaluate the level of surgical stress induced by LAG on elderly patients; however, we did not measure them in the present study.

Conclusion

LAG with suprapancreatic nodal dissection based on the JGCTG is considered safe and feasible for elderly patients aged 75 years old or older with clinical stage I gastric cancer.

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