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Original Article

Role of Laparoscopic Gastrectomy in Very Elderly Patients with Gastric Cancer Who Have Outlived the Average Lifespan

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No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: This study aimed to investigate the outcomes of laparoscopic gastrectomy in very elderly patients with gastric cancer, who have outlived the average lifespan of the Korean population (men: ≥77 years, women: ≥84 years).
Materials and Methods: Between 2004 and 2015, 836 patients with gastric cancer underwent a laparoscopic gastrectomy. They were divided into the elderly group (EldG) and non-elderly group (nEldG). Propensity score matching for covariates of sex, tumor depth, node status, and extent of resection was performed. Clinicopathologic characteristics, and surgical and survival outcomes were compared between the 2 groups.
Results: The EldG had a higher American Society of Anesthesiologists (ASA) score and a higher number of comorbidities. There was no significant difference in the post-operative complications, except for pulmonary complications, which were more frequent in the EldG (5/56, 8.9%) than in the nEldG (0/56, 0%). The EldG had a shorter overall survival (OS), but cancer-specific survival was similar for both groups. Among deceased patients, 2 (25%) and 8 patients (50%) died within a year of surgery in the nEldG and EldG, respectively. Univariate and multivariate risk factor analyses for OS showed that age, ASA score, tumor, node, metastasis (TNM) stage, and occurrence of complications were significantly related to deterioration in OS.
Conclusions: Laparoscopic gastrectomy can be safely performed in very elderly patients with gastric cancer who have outlived the average lifespan of the Korean population. However, impact of laparoscopic gastrectomy on improving survival is not clear, and careful patient selection is recommended.

Keywords: Stomach neoplasms; Laparoscopy; Elderly

INTRODUCTION

Although the incidence of gastric cancer in Korea is gradually decreasing, it is still the second most prevalent type of cancer and the third most common cause of death. There is an increased risk of developing gastric cancer with increasing age [1,2]. With advances in surgery, gastric surgeons often come across elderly patients who need surgical treatment

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for gastric cancer [3]. The appropriate treatment of elderly patients with gastric cancer has always been a major challenge. The patients' families often weigh the risks and benefits of surgical treatment before making a decision. Initially, this issue, performing surgical treatment or not in far elderly patient, was not dealt with so often. Large-scale Surveillance, Epidemiology and End Results (SEER) data revealed that age alone is not a contraindication for cancer treatment in most elderly patients. However, the data indicated low survival rate during the first year of diagnosis [4]. This reflects the negative impact of cancer treatment on patients' survival, especially in the first year. Hence, a more practical approach towards cancer treatment for the elderly needs to be developed.

There are varying criteria to classify a patient as elderly. Theoretically, elderly can be defined as a person who is older than 65 years of age according to the World Health Organization (WHO) criteria; however, most surgeons do not agree with this definition for clinical studies. Other definitions have been suggested, but no specific number can exactly reflect the biological age criteria. Therefore, we considered a novel criterion for classifying an individual as elderly, on the basis of the average lifespan of the specific country in which the study was performed. The average lifespan can reflect the biologic age criteria to some extent.

Laparoscopic gastrectomy has become a standard treatment for gastric cancer. It has been proven to reduce post-operative complications compared with open gastrectomy, in the KLASS-01 results [5]. In an era where minimal invasion is preferred, laparoscopic gastrectomy for elderly patients with gastric cancer is worth exploring. Before proceeding with the surgery, a plan of post-operative care and quality of life after surgery are also necessary. Thus, we planned to evaluate the safety and efficacy of laparoscopic gastrectomy in very elderly patients.

MATERIALS AND METHODS

Patient selection

We performed a retrospective analysis of a prospectively collected database. In all, 856 patients who underwent laparoscopic gastrectomy for gastric cancer between 2004 and 2015, performed by a single surgeon (W Kim), were enrolled in this study. The laparoscopic approach was employed for all patients with gastric cancer except for those exhibiting tumors with definite serosal invasion. From this database, 14 patients with stage IV cancer, 5 patients who had undergone a partial surgery, and 1 patient with carcinoid tumor were excluded. The remaining 836 patients were divided into the elderly group (EldG) (men: ≥77 years, women: ≥84 years) and non-elderly group (nEldG) (men: <77 years, women: <84 years) considering the average lifespan of the Korean population for the year 2010. This year was selected because 2010 marked the median period of our study. Basic clinicopathologic characteristics and surgical outcomes were compared between the 2 groups.

Surgical procedures were followed according to the Japanese gastric cancer treatment guidelines [6]. Patients with stage II or III cancer underwent adjuvant chemotherapy with S-1 for 1 year. Post-operative complications were considered as events that occurred within 30 days after surgery, and post-operative mortality was defined as death within 30 days after surgery or death directly related to the surgical procedure. This study protocol was reviewed and approved by the Institutional Review Board of Yeouido St. Mary's hospital (IRB number: SC17RESI0085).

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Propensity score matching analysis

To eliminate a bias in the basic characteristics, a propensity score matching was done for covariates, including sex, tumor depth, node status, and extent of resection. Score-matched patients were also compared in terms of their clinicopathologic characteristics and surgical outcomes. In addition, overall and cancer-specific survival rates were compared between the 2 groups. Risk factor analysis for post-operative complications and overall survival (OS) were performed considering various variables, including age, American Society of Anesthesiologists (ASA) score, tumor, node, metastasis (TNM) stage, and complication occurrence.

Statistical methods

Categorical variables were compared using Pearson's χ^2 test, and continuous variables were compared using the Student's t-test. All continuous variables are expressed as means±standard deviation. Survival analysis was performed using the Kaplan-Meier method and log-rank test. Multivariate risk factor analysis for OS was performed using the logistic regression model. All statistical results were considered significant when the P-value was less than 0.05. Statistical analyses were performed using the SPSS statistical software version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinicopathologic characteristics and surgical results

Of the 780 patients in the nEldG, 56 were considered for further analyses after propensity score matching with the patients in the EldG. On comparing the clinicopathologic characteristics, the EldG showed a higher ASA score and a higher rate of comorbidities. The incidence of hypertension was nearly 2 times higher in the EldG (28/56, 50%) than in the nEldG (18/56, 32.1%), with a marginal significance (P=0.055). Nearly the same distribution of tumor depth, lymph node metastasis, and cancer stage was observed following matching between the 2 groups (**Table 1**).

After propensity matching, 3 types of resection based on the extent of surgery were considered. A pylorus-preserving gastrectomy was performed only in the nEldG. Distal gastrectomy was performed on 42 (75.0%) and 43 (76.8%) patients of the EldG and nEldG, respectively. D2 lymph node dissection was performed more often in the nEldG (69.6%) than in the EldG (44.6%), and the number of retrieved lymph nodes and surgical time were less in the EldG (**Table 2**).

There were no statistical differences in the rate of post-operative complications, both, in terms of overall complications and complications with Clavien-Dindo IIIa or more (**Table 3**). Additionally, there was no difference in the in-hospital mortality between the groups. Although the rate of other specific types of complications was similar between the groups, pulmonary complications developed more frequently in the EldG than in the nEldG (EldG vs. nEldG, 8.9% vs. 0%, respectively; P=0.022).

Survival and risk factor analysis

Fig. 1 shows survival analysis between the EldG and nEldG. The 5-year OS rate was significantly lower in the EldG than in the nEldG in the matched population (EldG vs. nEldG, 51.5% vs. 80.9%, respectively; P=0.006) However, there was no difference in cancer-specific survival between the 2 groups (EldG vs. nEldG, 88.4% vs. 88.0%, respectively; P=0.385). In addition, there was no difference in the disease-free survival between the groups. In all, 8 and

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Table 1. Clinicopathologic characteristics between elderly and non-elderly patients in the entire study population and in the matched population

Variables	All patients (n=836)			Matched patients (n=112)		
	nEldG (n=780)	EldG (n=56)	P	nEldG (n=56)	EldG (n=56)	P
Sex			<0.001			0.792
Male	486 (62.3)	48 (85.7)		47 (83.9)	48 (85.7)	
Female	294 (37.7)	8 (14.3)		9 (16.1)	8 (14.3)	
Age (yr)	61.1±11.1	81.4±3.8	<0.001	61.9±11.1	81.4±3.8	<0.001
BMI (kg/m^2)	23.6±3.3	22.6±3.5	0.035	23.2±3.5	22.6±3.5	0.396
ASA score			<0.001			<0.001
1	417 (53.5)	14 (25.0)		33 (58.9)	14 (25.0)	
2	319 (40.9)	32 (57.1)		21 (37.5)	32 (57.1)	
3	43 (5.5)	10 (17.9)		2 (3.6)	10 (17.9)	
4	1 (0.1)	0 (0)				
No. of comorbidities			0.017			0.027
0	386 (49.5)	19 (33.9)		29 (51.8)	19 (33.9)	
1	252 (32.3)	24 (42.9)		18 (32.1)	24 (42.9)	
2	112 (14.4)	7 (12.5)		9 (16.1)	7 (12.5)	
≥3	30 (3.8)	6 (10.7)		0 (0)	6 (10.7)	
Type of comorbidity						
Hypertension	247 (31.7)	28 (50.0)	0.005	18 (32.1)	28 (50.0)	0.055
Diabetes	121 (15.5)	9 (16.1)	0.911	10 (17.9)	9 (16.1)	0.801
Pulmonary	39 (5.0)	3 (5.4)	0.906	2 (3.6)	3 (5.4)	0.647
Cardiovascular	30 (3.8)	5 (8.9)	0.067	1 (1.8)	5 (8.9)	0.093
Renal	15 (1.9)	3 (5.4)	0.087	0 (0)	3 (5.4)	0.079
Hepatic	28 (3.6)	1 (1.8)	0.476	1 (1.8)	1 (1.8)	1.000
Cancer	17 (2.2)	2 (3.6)	0.500	2 (3.6)	2 (3.6)	1.000
Other	69 (8.8)	6 (10.7)	0.637	2 (3.6)	6 (10.7)	0.142
pT stage			0.212			0.995
T1a	299 (38.3)	15 (26.8)		15 (26.8)	15 (26.8)	
T1b	220 (28.2)	15 (26.8)		14 (25.0)	15 (26.8)	
T2	85 (10.9)	6 (10.7)		7 (12.5)	6 (10.7)	
T3	108 (13.8)	11 (19.6)		10 (17.9)	11 (19.6)	
T4a	64 (8.2)	9 (16.1)		10 (17.9)	9 (16.1)	
T4b	4 (0.5)	0 (0)		0 (0)	0 (0)	
pN stage			0.384			0.967
N0	573 (73.5)	42 (75.0)		43 (76.8)	42 (75.0)	
N1 (1–2)	67 (8.6)	4 (7.1)		3 (5.4)	4 (7.1)	
N2 (3–6)	62 (7.9)	2 (3.6)		2 (3.6)	2 (3.6)	
N3a (7–15)	42 (5.4)	6 (10.7)		7 (12.5)	6 (10.7)	
N3b (≥16)	36 (4.6)	2 (3.6)		1 (1.8)	2 (3.6)	
pTNM stage			0.144			0.998
Ia	475 (60.9)	29 (51.8)		29 (51.8)	29 (51.8)	
Ib	73 (9.4)	5 (8.9)		6 (10.7)	5 (8.9)	
IIa	64 (8.2)	6 (10.7)		6 (10.7)	6 (10.7)	
IIb	43 (5.5)	7 (12.5)		5 (5.8)	7 (12.5)	
IIIa	50 (6.4)	1 (1.8)		1 (1.8)	1 (1.8)	
IIIb	41 (5.3)	3 (5.4)		3 (5.4)	3 (5.4)	
IIIc	34 (4.4)	5 (8.9)		6 (10.7)	5 (8.9)	

Continuous variables were presented with mean±standard deviation and compared with Student's t-test. Nominal variables were presented with a number (%) and compared with χ^2 analysis.
EldG = elderly group; nEldG = non-elderly group; BMI = body mass index; ASA = American Society of Anesthesiologists; pT = pathologic tumor; pN = pathologic node; pTNM = pathologic tumor, node, metastasis.

16 patients died in the nEldG and EldG, respectively. Two (25%) and 8 patients (50%) died within a year of the surgery in the nEldG and EldG, respectively. Two patients in the nEldG and 6 patients in the EldG died of non-cancer-related problems.

On univariate and multivariate risk factor analyses for overall mortality, age, ASA score, TNM stage, and development of complications were found to be related to a significant reduction in OS (**Table 4**).

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Table 2. Surgical results between the elderly and non-elderly patients in the entire study population and in the matched population

Variables	All patients (n=836)			Matched patients (n=112)		
	nEldG (n=780)	EldG (n=56)	P	nEldG (n=56)	EldG (n=56)	P
Open conversion	22 (2.8)	4 (7.1)	0.072	1 (1.8)	4 (7.1)	0.170
Extent of resection			0.628			0.968
Total gastrectomy	106 (13.6)	9 (16.1)		10 (17.9)	9 (16.1)	
Distal gastrectomy	636 (81.5)	43 (76.8)		42 (75.0)	43 (76.8)	
Proximal gastrectomy	33 (4.2)	4 (7.1)		4 (7.1)	4 (7.1)	
PPG	5 (0.6)	0 (0)		0 (0)	0 (0)	
Lymph node dissection			0.034			0.028
D1	6 (0.8)	2 (3.6)		1 (1.8)	2 (3.6)	
D1+	330 (42.3)	29 (51.8)		16 (28.6)	29 (51.8)	
D2	444 (56.9)	25 (44.6)		39 (69.6)	25 (44.6)	
Combined resection	42 (5.4)	7 (12.5)	0.029	2 (3.6)	7 (12.5)	0.082
Operation time (min)	257.7±90.0	241.6±72.0	0.192	274.5±85.7	241.6±72.0	0.030
Retrieved lymph nodes	34.1±14.9	30.5±13.5	0.077	36.0±13.9	30.5±13.5	0.036
Hospital stay (day)	10.5±6.3	14.5±16.6	0.079	11.3±5.3	14.5±16.6	0.175
Complication (All)	146 (18.7)	16 (28.6)	0.072	9 (16.1)	16 (28.6)	0.112
Complications (≥Dindo IIIa)	85 (10.9)	9 (16.1)	0.236	5 (8.9)	9 (16.1)	0.253
In-hospital mortality	5 (0.64)	0 (0)	0.548	1 (1.7)	0 (0)	0.315

Continuous variables were presented with mean±standard deviation and compared with Student's t-test. Nominal variables were presented with a number (%) and compared with χ^2 analysis.
EldG = elderly group; nEldG = non-elderly group; PPG = pylorus-preserving gastrectomy.

Table 3. Details of complications between the EldG and nEldG in the matched population

Variables	All complication			Clavien-Dindo ≥IIIa		
	nEldG (n=56)	EldG (n=56)	P	nEldG (n=56)	EldG (n=56)	P
Bleeding	1 (1.8)	4 (7.1)	0.170	1 (1.8)	2 (3.6)	0.558
Leakage	2 (3.6)	2 (3.6)	NS	2 (3.6)	2 (3.6)	NS
Intestinal obstruction	2 (3.6)	2 (3.6)	NS	1 (1.8)	1 (1.8)	NS
Wound complication	0 (0)	2 (3.6)	0.154	0 (0)	0 (0)	NS
Fluid collection or abscess	0 (0)	0 (0)	NS	0 (0)	0 (0)	NS
Iatrogenic injury	1 (1.8)	1 (1.8)	NS	1 (1.8)	1 (1.8)	NS
Delayed emptying	2 (3.6)	0 (0)	0.154	0 (0)	0 (0)	NS
Pulmonary complication	0 (0)	5 (8.9)	0.022	0 (0)	3 (5.4)	0.079
Other medical complication	1 (1.8)	0 (0)	0.315	0 (0)	0 (0)	NS

Nominal variables were presented with a number (%) and compared with χ^2 analysis.
EldG = elderly group; nEldG = non-elderly group; NS = not significant.

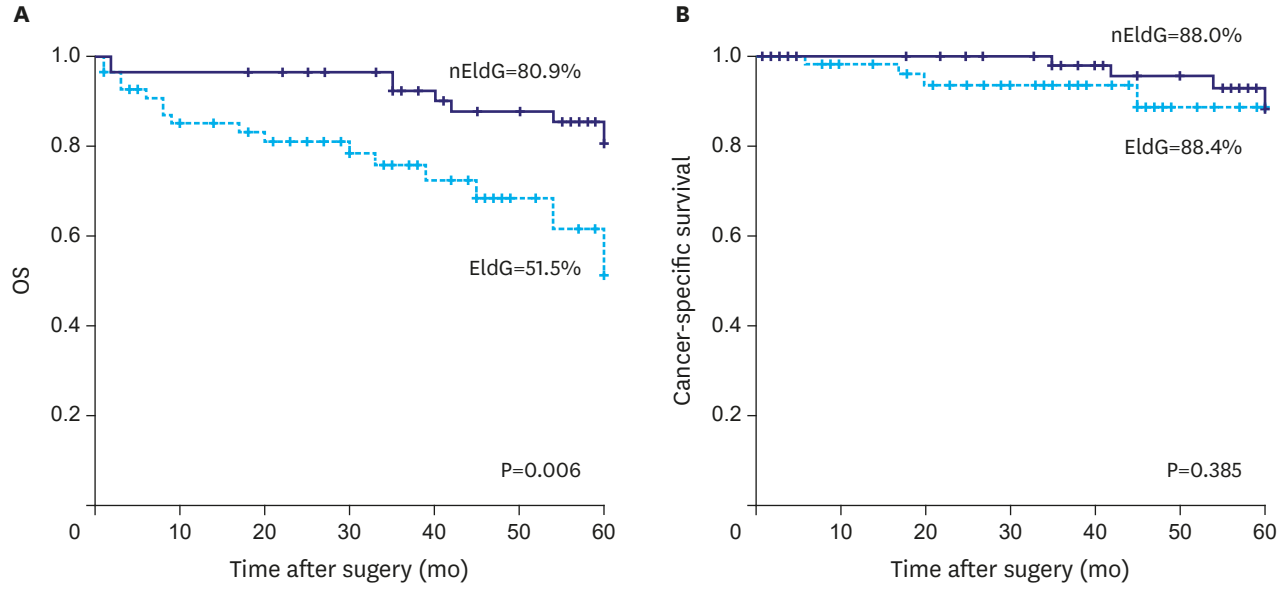

Fig. 1. Survival analysis between the EldG and nEldG: (A) OS, (B) cancer-specific survival.
EldG = elderly group; nEldG = non-elderly group; OS = overall survival.

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Table 4. Risk factor analysis for OS in matched groups

Variables	No.	OS (univariate)		OS (multivariate)	
		5-year survival (%)	P	Odd ratio (95% CI)	P
Age			0.006		0.017
nEldG	56	80.9		1.000	
EldG	56	51.5		3.540 (1.254–9.996)	
Sex			0.748		
Male	95	66.2			
Female	17	79.1			
BMI (kg/m^2)			0.659		
<25	77	72.7			
25–30	32	56.5			
≥30	2	-			
ASA			0.004		0.001
1	47	72.1		1.000	
2	53	70.1		2.655 (0.862–8.179)	
3	12	53.0		21.916 (3.957–121.382)	
Resection extent			0.094		0.700
Total gastrectomy	19	43.8		1.000	
Distal gastrectomy	85	75.5		0.705 (0.225–2.232)	
Proximal gastrectomy	8	-		0.393 (0.040–3.902)	
pTNM stage			<0.001		<0.001
Stage I	69	88.8		1.000	
Stage II	24	52.7		3.256 (1.052–10.081)	
Stage III	19	18.8		20.103 (6.046–66.842)	
Lymph node dissection			0.134		
D1 or D1+	48	81.2			
D2	64	59.4			
Combined resection			0.054		0.763
Yes	8	50.0		1.256 (0.284–5.549)	
No	104	71.9		-	
Complication			0.003		0.001
Yes	25	51.0		5.583 (2.084–14.954)	
No	87	75.2		-	

OS = overall survival; CI = confidence interval; EldG = elderly group; nEldG = non-elderly group; BMI = body mass index; ASA = American Society of Anesthesiologists; pTNM = pathologic tumor, node, metastasis.

DISCUSSION

Elderly patients are known to develop more postoperative complications after major abdominal surgery, because of pre-existing comorbidities and low functional reserves [7-9]. Gastric cancer needs a major surgery to prevent metastasis. For decades, laparoscopic surgery has been generally adopted in every field of surgery. Randomized clinical trials, as well as many retrospective studies, have revealed advantages of laparoscopic gastrectomy over open gastrectomy in terms of early recovery, less pain, and fewer complications [5,10,11]. There have been several attempts to explore the feasibility of gastrectomy in elderly patients because of changes in the average lifespan globally [12-14]. Similar results for elderly patients, such as less blood loss and early recovery of the patients ≥80 years of age, have been reported. In addition, a meta-analysis comparing laparoscopic gastrectomy with open gastrectomy for elderly patients with gastric cancer revealed less blood loss, shorter hospital stays, and fewer postoperative complications in the laparoscopic group [15].

Once the benefits of laparoscopic gastrectomy for gastric cancer were fully established, many studies focused on comparing the short and long-term results between the elderly and non-elderly patients. The objective was to explore whether surgical treatment for specific elderly patients would be beneficial for their remaining lifespan. One study reported that

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non-cancer-specific deaths in elderly patients with clinical stage I gastric cancer could be negligible with laparoscopic gastrectomy [12]. In our study, 5 patients with stage I gastric cancer died of non-cancer-related reasons within a year of surgery. Considering the natural course of early gastric cancer, those patients might not have benefitted from the surgical treatment. However, ethical principles do not allow studies which include a surgical and a control groups (a group that does not undergo any treatment for a disease). Thus, to establish the safety or benefit of surgery, surgical results for the very elderly and non-elderly patients can be compared as an alternative. In this study design, the criteria for defining a patient as elderly is debatable because no specific age can exactly reflect the biological age criteria. Yoshida et al. [13] compared elderly and non-elderly patients who underwent laparoscopic distal gastrectomy, defining patients of 65 years of age and above as elderly, and showed a higher incidence of pulmonary complications, delirium, and lower OS in the elderly patients. In a Korean study, 71 elderly (≥70 years) patients were compared with non-elderly patients who underwent laparoscopic total gastrectomy [3]. This study reported that elderly patients were more vulnerable to grade III or higher complications. Another Japanese study, which used 75 years and older as the age for classifying elderly patients, showed no significant differences in the rate of complications between the EldG and nEldG [16]. In this report, age itself was not a significant risk factor for the development of post-operative complications, but ASA score and pre-operative comorbid conditions were important factors for the outcomes of surgery. Age criteria are defined by the individual principal investigators, and no definite criteria exist. Hence, we used the criterion of the average lifespan of the study population to reflect the patients' biologic status as precisely as possible. In addition, there is a definite gap in the average lifespan between men and women. This difference was also considered in this study setting.

In the present study, elderly and non-elderly patients in the entire cohort and in the matched population were compared. Matching was done to eliminate bias regarding sex, tumor stage, and type of resection. The most important difference was the higher ASA score and the higher number of comorbidities in the elderly patient group. Even under this condition, there was no significant difference in the occurrence of post-operative complication, except pulmonary complications, which showed a marginal difference. In this study, laparoscopic gastrectomy seems technically feasible for elderly patients with gastric cancer. In previous studies comparing the results of laparoscopic gastrectomy between elderly and non-elderly patients, age itself was not a significant factor that affected post-operative complications [17-19]. Although propensity matching was performed to minimize the bias, more patients with less extensive lymph node dissection were included in the EldG. This might be due to the surgeon's discretion during surgeries in the elderly patients. This could affect the results of comparison of post-operative morbidity and mortality between the 2 groups. However, there was no difference in cancer-specific survival between the groups, and this reflects real-life clinical settings.

The age of elderly patients was a significant independent risk factor for OS, but there was no difference in the disease-free survival between the 2 groups. We estimate that stage of the tumor might be the most powerful factor for OS in patients with gastric cancer. In addition, pre-operative status (ASA score or the number of comorbidities) and incidence of complications were important factors that influenced overall post-operative survival. In the Japanese study, although there was no difference in the recurrence-free survival between the groups, OS in the EldG was lower than that in the nEldG [13]. When assessing survival, we should also focus on the unexpected early mortality, which reflects the patients' general

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condition by the surgical procedure. The early mortality was found to be related to post-operative complications directly or indirectly. On multivariate analysis of risk factors related to OS, the incidence of complications, tumor stage, ASA score, and combined resection were independent risk factors. Although the development of complications may not affect the overall difference in survival in the entire matched population, it would deteriorate the health of elderly patients with low physiologic reserves compared to non-elderly patients. These events would affect each patient critically. Hence, a more meticulous and safe surgical approach for such elderly patients is necessary.

This study has several limitations. First, the study cohorts were selected from a database retrospectively and may have potential selection bias. To overcome this problem, we performed a propensity-matching analysis. In addition, there is no quality of life data available because of the retrospective design. Second, as the most interesting clinical question is whether laparoscopic surgery is better compared to no surgery in elderly patients who are in average lifespan age or older, this study design has technical limitations. The real valuable study should analysis between surgery group and an observational group among only elderly patients.

In conclusion, laparoscopic gastrectomy can be safely adopted in very elderly patients with gastric cancer who have outlived the average lifespan of the Korean population. However, the survival benefit is still questionable, and meticulous patient selection is highly recommended.

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