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ORIGINAL SCIENTIFIC REPORT

Postoperative Long-Term Outcomes in Elderly Patients with Gastric Cancer and Risk Factors for Death from Other Diseases

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Abstract

Background Elderly patients with gastric cancer are frequently treated surgically in current clinical practice. Although several studies have investigated short-term outcomes after gastrectomy in elderly patients, most did not evaluate long-term outcomes.

Methods We analyzed 1154 consecutive patients who underwent curative gastrectomy for gastric cancer between 2001 and 2013. We classified them into two groups: the elderly group (n = 241), consisting of patients aged ≥75 years, and the non-elderly group (n = 913), consisting of patients aged <75 years, and compared the short- and long-term outcomes between the two groups. The risk factors for death from other diseases in elderly patients were also examined.

Results Although the incidence of postoperative pneumonia was significantly higher in the elderly group ($P < 0.001$), the proportion of overall postoperative complications did not differ significantly between the two groups ($P = 0.097$). The disease-specific survival was similar between the two groups ($P = 0.743$), whereas the overall survival in the elderly group was significantly shorter than that in the non-elderly group ($P < 0.001$) because of a higher incidence of death from other diseases throughout all gastric cancer stages. Multivariate analysis revealed that a low preoperative prognostic nutrition index (PNI) and multiple comorbidities were significant risk factors for death from other diseases within 5 years in the elderly group.

Conclusions Despite acceptable short-term outcomes, long-term outcomes in elderly patients with gastric cancer were poor due to the high incidence of death from other diseases. Indications for surgery in elderly patients with a low PNI or multiple comorbidities should be considered carefully.

Introduction

Gastric cancer is the third leading cause of cancer-related death and the fifth most commonly diagnosed cancer worldwide [1]. In recent years, as the aging of society has progressed, the ages of patients with various cancers, including gastric cancer, have increased as well [2]. Surgery for elderly patients with gastric cancer is frequently performed at many Japanese institutions, and postoperative morbidity and mortality are a major source of concern in the management of this population [3–5]. In addition, postoperative long-term outcomes, including death from

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various causes, are important to consider when deciding treatment strategies. Several retrospective studies investigated postoperative short-term outcomes, and some reported that gastrectomy for elderly patients with gastric cancer was acceptable if patients were appropriately selected [6, 7]. Meanwhile, other studies reported that elderly patients with gastric cancer experienced a higher incidence of postoperative complications than non-elderly patients [8, 9]. In a previous analysis, we identified only total gastrectomy as a significant risk factor for postoperative complications in elderly patients [10].

On the other hand, few studies have evaluated long-term outcomes after gastrectomy in elderly patients [11, 12]; furthermore, few have focused on death from other diseases in this population. Generally, elderly patients have poor physical or nutritional status and some degree of frailty and are likely to die from other diseases even if gastric cancer can be cured by gastrectomy. Against this background, it is necessary to determine the treatment strategy for elderly patients with gastric cancer considering both curability and the possibility of death from other diseases. This study aimed to evaluate the short- and long-term outcomes after gastrectomy in elderly patients with gastric cancer, and to elucidate the risk factors for death from other diseases.

Patients and methods

Patients

We retrospectively analyzed the data of 1154 consecutive patients who underwent curative gastrectomy for gastric cancer between January 2001 and December 2013. We excluded patients who had distant metastasis (Stage IV) or multiple cancers, and those who underwent non-curative resection (R1/2). We classified the patients into two groups: the elderly group, consisting of patients aged 75 years or older, and the non-elderly group, consisting of patients younger than 75 years. All tumors were histologically diagnosed as adenocarcinoma of the stomach. In principle, all patients were treated according to the Japanese Gastric Cancer Treatment Guidelines [13]. Classification of pT, pN, and pStage was performed according to the 14th edition of the Japanese classification of gastric carcinoma [14]. This study got approval of the Institutional Review Board of the Osaka University Hospital (Approval number: 17368).

Postoperative outcomes and statistical analysis

Postoperative complications were evaluated according to the Clavien–Dindo classification [15, 16], and we considered complications of Grade II or higher to be postoperative complications in the analysis of short-term outcomes. The number of preoperative comorbidities in each patient was counted based on the following categories, as previously reported: cardiac disease, pulmonary disease, liver disease, renal disease, cerebral disease, peripheral arterial disease, endocrine and metabolic disease, hypertension, connective tissue disease, and hematologic disease [17]. Regarding baseline characteristics, the prognostic nutrition index (PNI) was calculated using the following formula, as previously defined: $10 \times$ serum albumin (g/dl) $+ 0.005 \times$ total lymphocyte count (/mm^3) [18]. We compared the clinicopathological factors in the two groups using the Chi-squared test for categorical variables and the Mann–Whitney U test for continuous variables. Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause, and data were censored on the date of last follow-up. Disease-specific survival (DSS) was defined as the time from the date of surgery to the date of death from primary disease, and data were censored on the date of last follow-up or the date of death from other diseases. OS and DSS were estimated by the Kaplan–Meier method and tested with the log-rank test. Multivariate analyses were performed using logistic regression models. All variables with $P < 0.1$ in the univariate analysis were included in the multivariable models. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS Statistics software program, version 22 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Of the 1154 patients, 913 (79.1%) and 241 (20.9%) were classified into the non-elderly and elderly groups, respectively. Clinicopathological characteristics of the non-elderly and elderly groups are summarized in Table 1. The elderly group had a significantly lower preoperative body mass index (BMI), serum hemoglobin level, and PNI compared with the non-elderly group. In addition, significantly fewer patients in the elderly group underwent total gastrectomy or splenectomy compared with the non-elderly group. As for histology, the elderly group included more patients with differentiated-type carcinoma compared with the non-elderly group. There was no significant difference between the two groups regarding the distribution of pT status, pN status, and pStage. The proportions of patients who initiated adjuvant chemotherapy did not differ significantly between the two groups.

Table 1 Clinicopathological characteristics of the non-elderly and elderly groups

Factors	Non-elderly group (n = 913)	Elderly group (n = 241)	P value
Age (years)			
Median (range)	63 (29–74)	78 (75–98)	<0.001
Sex			
Male	633 (69.3%)	168 (69.7%)	0.91
Female	280 (30.7%)	73 (30.3%)	
Body mass index (kg/m^2)			
Median (range)	22.3 (12.9–33.8)	21.5 (13.3–33.1)	0.046
Serum hemoglobin level (g/dl)			
Median (range)	13.4 (6.9–17.8)	12.0 (5.9–16.3)	<0.001
PNI			
Median (range)	48.0 (24.3–64.9)	43.7 (24.1–67.8)	<0.001
Tumor location			
Upper	252 (27.6%)	52 (21.6%)	<0.001
Middle	360 (39.4%)	79 (32.8%)	
Lower	301 (33.0%)	110 (45.6%)	
Surgical approach			
Open	374 (41.0%)	109 (45.2%)	0.23
Laparoscopic	539 (59.0%)	132 (54.8%)	
Type of gastrectomy			
TG	283 (31.0%)	54 (22.4%)	0.009
DG or PG	630 (69.0%)	187 (77.6%)	
Lymph node dissection			
<D2	526 (57.6%)	152 (63.1%)	0.13
≥D2	387 (42.4%)	89 (36.9%)	
Splenectomy			
Not performed	805 (88.2%)	227 (94.2%)	0.001
Performed	108 (11.8%)	14 (5.8%)	
Histological type			
Differentiated	445 (48.7%)	164 (68.0%)	<0.001
Undifferentiated	468 (51.3%)	77 (32.0%)	
pT status			
pT1	557 (61.0%)	137 (56.8%)	0.33
pT2	102 (11.2%)	37 (15.4%)	
pT3	158 (17.3%)	40 (16.6%)	
pT4	96 (10.5%)	27 (11.2%)	
pN status			
pN0	645 (70.6%)	174 (72.2%)	0.91
pN1	112 (12.3%)	31 (12.9%)	
pN2	87 (9.5%)	18 (7.5%)	
pN3	69 (7.6%)	18 (7.5%)	
pStage			
pStage I	588 (64.4%)	155 (64.3%)	0.94
pStage II	178 (19.5%)	49 (20.3%)	
pStage III	147 (16.1%)	37 (15.4%)	
Adjuvant chemotherapy			
Yes	193 (21.1%)	39 (16.2%)	0.10

Table 1 continued

Factors	Non-elderly group (n = 913)	Elderly group (n = 241)	P value
No	720 (78.9%)	202 (83.8%)	

TNM staging was according to the 14th edition of the Japanese classification of gastric carcinoma

PNI prognostic nutrition index, *TG* total gastrectomy, *DG* distal gastrectomy, *PG* proximal gastrectomy

Postoperative short-term outcomes

The postoperative short-term outcomes are summarized in Table 2. There was no significant difference between the two groups in the proportion of overall postoperative complications (21.0% in the non-elderly group vs. 26.1% in the elderly group, $P = 0.097$). Among the postoperative complications, only the incidence of pneumonia was significantly higher in the elderly group ($P < 0.001$). There was no significant difference between the two groups in terms of hospital death rate (0.3% in the non-elderly group vs. 0.8% in the elderly group, $P = 0.28$).

Postoperative long-term outcomes and causes of death

We evaluated DSS at the median follow-up duration for all censored patients of 62.4 months (Fig. 1). There was no significant difference in DSS between the two groups (HR = 1.09; 95% CI 0.55–1.53; log-rank $P = 0.74$). The result was similar for pStage I (HR = 1.91; 95% CI 0.49–7.41; log-rank $P = 0.34$), pStage II (HR = 1.24; 95% CI 0.48–3.24; log-rank $P = 0.65$), and pStage III (HR = 1.15; 95% CI 0.58–2.26; log-rank $P = 0.69$). We also evaluated OS at the median follow-up duration for all censored patients of 64.4 months (Fig. 2). OS in the elderly group was significantly shorter than that in the non-elderly group (HR = 2.91; 95% CI 2.20–3.83; log-rank $P < 0.001$). The result was similar for pStage I (HR = 6.08; 95% CI 3.90–9.47; log-rank $P < 0.001$), pStage II (HR = 1.92; 95% CI 1.07–3.48; log-rank $P = 0.027$), and pStage III (HR = 1.66; 95% CI 1.01–2.74; log-rank $P = 0.044$).

Causes of death within 5 years after gastrectomy are summarized in Table 3. For all stages, the percentages of patients in the elderly group who died from primary disease were significantly lower compared with the non-elderly group. The causes of death from other diseases in the elderly group were as follows: other malignancies (22%), pneumonia (18%), cardiovascular disease (10%), cerebrovascular disease (10%), malnutrition (8%), liver cirrhosis (4%), and others/unknown.

Risk factors for death from other diseases

We performed univariate and multivariate logistic analyses to clarify the risk factors for death from other diseases in elderly patients with no recurrence within 5 years after surgery (Table 4). Multivariate analysis revealed that low preoperative PNI and multiple comorbidities were significant risk factors for death from other diseases. If patients had both risk factors, the odds ratio increased to 28.2 (95% CI 3.50–227). In addition, we evaluated associations between each comorbidity and the incidence of death from other diseases in elderly patients. Of ten comorbidity categories, cardiac disease ($P = 0.015$) and cerebral disease ($P = 0.016$) were significant risk factors for the death from other diseases, and pulmonary disease ($P = 0.064$), and liver disease ($P = 0.077$) were marginal.

Table 2 Postoperative short-term outcomes in the non-elderly and elderly groups

	Non-elderly group (n = 913)	Elderly group (n = 241)	P value
Any complications	192 (21.0%)	63 (26.1%)	0.097
Pancreatic fistula	58 (6.4%)	10 (4.1%)	0.22
Intraperitoneal abscess	43 (4.7%)	16 (6.6%)	0.25
Anastomotic leakage	37 (4.1%)	12 (5.0%)	0.59
Bleeding	21 (2.3%)	6 (2.5%)	0.81
Pneumonia	7 (0.8%)	12 (5.0%)	<0.001
Bowel obstruction	14 (1.5%)	4 (1.7%)	0.78
Delayed gastric empty	7 (0.8%)	5 (2.1%)	0.14
Stenosis	8 (0.9%)	2 (0.8%)	1.000
Others	12 (1.3%)	5 (2.1%)	0.37
Hospital death	3 (0.3%)	2 (0.8%)	0.28

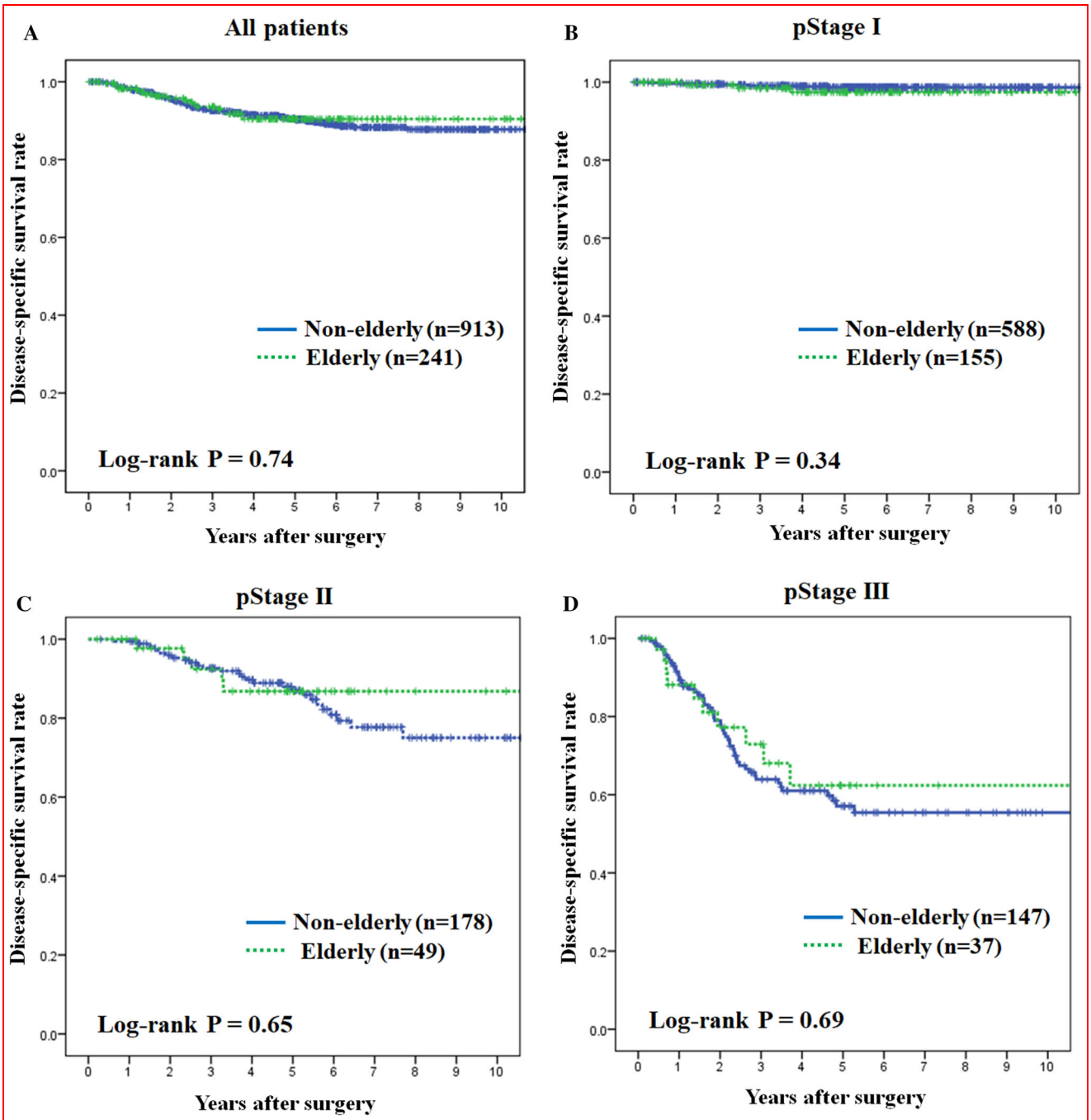

Fig. 1 Kaplan–Meier disease-specific survival in the elderly and non-elderly groups in all patients (**a**), and in those classified as pStage I (**b**), pStage II (**c**), and pStage III (**d**)

Discussion

In terms of postoperative complications, the incidence of pneumonia was higher in the elderly group than the non-elderly group; however, the incidence of overall complications did not differ significantly between the two groups, indicating that gastrectomy is considered to be feasible in elderly patients. Regarding long-term outcomes, although DSS was similar in both groups, OS in the elderly group was significantly shorter than that in the non-elderly group due to the high incidence of death from other diseases. This inconsistency between DSS and OS was observed for all pStages. Moreover, multivariate analysis revealed that low preoperative PNI and multiple comorbidities were

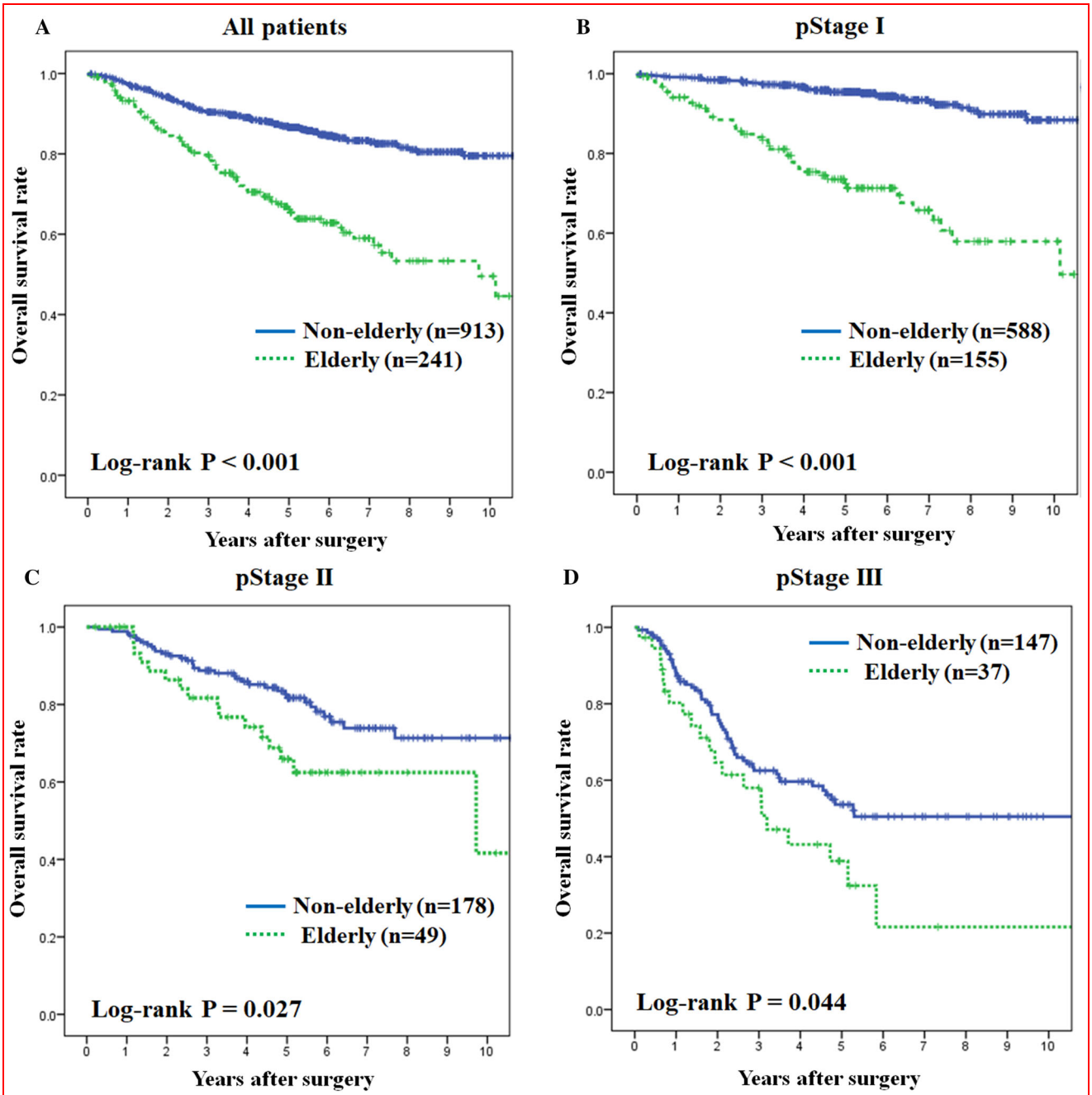

Fig. 2 Kaplan–Meier overall survival in the elderly and non-elderly groups in all patients (**a**), and in those classified as pStage I (**b**), pStage II (**c**), and pStage III (**d**)

significant risk factors for death from other diseases in elderly patients.

In terms of overall postoperative complications, the short-term outcomes in elderly patients were thought to be acceptable in this study. This result is presumably due to improvements in surgical techniques and perioperative management, as well as the less invasive surgical approaches used in elderly patients. We previously reported that total gastrectomy was a significant risk factor for postoperative complications in elderly patients with gastric cancer [10]. In this study, total gastrectomy, splenectomy, and extended lymph node dissection were performed in a lower proportion of elderly patients than non-elderly patients, which might have led to the lower surgical complication rate observed in the former group. In terms of postoperative complications, only the incidence of pneumonia was

Table 3 Causes of death within 5 years after gastrectomy

Causes of death	Non-elderly group	Elderly group	*P* value
pStage I (*n* = 743)	(*n* = 588)	(*n* = 155)	
Primary disease	7 (1.2%)	3 (1.9%)	0.030
Other disease	17 (2.9%)	33 (21.3%)	
pStage II (*n* = 227)	(*n* = 178)	(*n* = 49)	
Primary disease	19 (10.7%)	5 (10.2%)	0.047
Other disease	9 (5.1%)	9 (18.4%)	
pStage III (*n* = 184)	(*n* = 147)	(*n* = 37)	
Primary disease	52 (35.4%)	10 (27.0%)	0.001
Other disease	5 (3.4%)	9 (24.3%)	

significantly higher in the elderly group. This is consistent with several previous studies that reported that the incidence of non-surgical complications such as pneumonia was higher in elderly patients than in non-elderly patients [19, 20]. Risk factors for postoperative pneumonia after gastrectomy include older age, postoperative respiratory malfunction, diabetes, and blood transfusion [21]. Elderly patients usually have worse nutritional status and respiratory function, which are consistent with the low preoperative serum hemoglobin levels and PNI in the elderly group in this study; these factors likely contributed to the higher incidence of post-gastrectomy pneumonia in the elderly group compared with the non-elderly group. This severe complication can be prevented by perioperative respiratory rehabilitation, oral care, and early mobilization programs for elderly patients [22]. We should address patients' preoperative respiratory and nutritional status and consider introducing perioperative interventions to increase the safety of gastrectomy in elderly patients.

Considering long-term outcomes, the fact that both groups in this study had a similar incidence of death from primary disease indicated that most patients in each group were cured by standard radical gastrectomy. Similar proportions of patients who initiated adjuvant chemotherapy between the two groups might explain why there was no difference in DSS. However, many elderly patients then died of other diseases. A multivariate analysis revealed that low preoperative PNI and multiple comorbidities were significant risk factors for death from other diseases. We previously reported that higher numbers of preoperative complications were associated with worse postoperative outcomes [17]; thus, we examined the number of preoperative complications using the same method in this study. The findings suggested that elderly patients were more likely to succumb to death from other diseases, due to their preexisting comorbidities or poor nutritional status. Indeed, elderly patients often have at least one comorbid disease, and the number of comorbidities probably reflects a patient's systemic condition. Frailty, which is a state of vulnerability to poor resolution of homoeostasis after a stressor event, is caused by functional deterioration associated not only with aging but also with comorbidities [23]. Multiple comorbidities and poor nutritional status are likely to be associated with frailty and dysfunction of numerous organ systems, which in turn increase the

Table 4 Univariate and multivariate logistic analyses for death from other diseases within 5 years after gastrectomy in the elderly patients

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex				
Male	1.26 (0.56–2.82)	0.57		
Body mass index				
<18.5 kg/m^2	2.44 (0.87–6.85)	0.090	2.55 (0.68–9.52)	0.17
Serum hemoglobin level				
<10.0 g/dl	2.88 (1.04–7.94)	0.041	3.05 (0.87–10.6)	0.082
PNI				
<40.0	5.56 (2.14–14.5)	<0.001	5.41 (1.77–16.7)	0.003
Surgical approach				
Open	1.33 (0.64–2.75)	0.45		
Type of gastrectomy				
TG	1.98 (0.73–5.36)	0.18		
Number of comorbidities				
≥2	3.39 (1.54–7.47)	0.003	5.58 (2.13–14.7)	<0.001
pStage				
II–III	1.17 (0.53–2.58)	0.70		

PNI prognostic nutrition index, *TG* total gastrectomy, *OR* odds ratio, *95% CI* 95% confidence interval

likelihood of death from other diseases, such as other malignancies caused by immune dysfunction or pneumonia caused by dysphagia and muscle weakness. Accordingly, we should try to prevent frailty and malnutrition in elderly patients with multiple comorbidities or poor nutritional status. From this point of view, it can be considered valid to avoid performing invasive surgery such as total gastrectomy, which was reported to be associated with decreased postoperative oral intake and poor nutritional status [24, 25]. In addition, perioperative rehabilitation or nutritional support may be effective in improving patients' performance status, leading to better prognosis. Moreover, preoperative screening may be useful to reduce the possibility of death from other malignancies because elderly patients undergoing gastrectomy may have undiagnosed malignancies at the time of surgery.

This study has several limitations. First, this was a retrospective study performed at a single institution. Although we collected large-scale data of consecutive cases, a certain degree of selection bias could not be avoided. Second, we adopted a threshold of 75 years of age to define elderly patients, although no standard threshold exists [26–28]. However, the Japan Gerontological Society and the Japan Geriatrics Society currently proposes redefining the elderly as aged 75 years and older [29]; therefore, the threshold we adopted is considered to be appropriate.

This is the first large-scale study to examine both short- and long-term outcomes in elderly patients after total gastrectomy, including the cause of death. In conclusion, despite acceptable short-term outcomes, long-term outcomes in elderly patients with gastric cancer were poor due to a high incidence of death from other diseases. Careful preoperative risk evaluation is strongly recommended in elderly patients with gastric cancer, and indications for surgery in elderly patients with low PNI or multiple comorbidities should be considered carefully.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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