

Original Article

Postoperative complications and open gastrectomy affect non-cancer-related death and shorten life expectancy in elderly patients with gastric cancer

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Abstract: Postoperative complications contribute to recurrences and poor long-term outcomes for gastric cancer patients, especially among the elderly. However, the prognostic effect of postoperative complications on non-cancer-related death in elderly patients with gastric cancer has not been reported. Two hundred and twenty elderly (> 75 years of age) patients with stage I gastric cancer were retrospectively identified from consecutive admissions between 1995 and 2020. Non-cancer-related death following gastrectomy occurred in 13.6% (30/220) of patients. Non-cancer-related death was associated with respiratory disease in 46.7% (14/30) of cases. Although there was no association with any preoperative comorbidities, postoperative complications [$P < 0.001$, HR 4.16 (95% CI: 1.91-9.02)] and open gastrectomy [$P=0.002$, HR 3.87 (95% CI: 1.54-9.66)] were independently associated with a poorer prognosis for non-cancer-related death. Poor nutritional status [$P=0.028$, OR 4.25 (95% CI: 1.17-15.4)] was an independent risk factor for postoperative complications. Postoperative complications shortened life expectancy from 8.8 years to 6.1 years. Specifically, postoperative complications shortened life expectancy from 6.7 years to 3.9 years in elderly patients over 80 years of age. Postoperative complications and open gastrectomy affected the incidence of non-cancer-related death among elderly patients with gastric cancer, primarily attributed to respiratory disease. Efforts should be made to perform minimally invasive surgery, improve preoperative nutrition, and avoid postoperative complications.

Keywords: Non-cancer-related death, postoperative complication, prognosis, risk factor, gastric cancer

Introduction

Gastric cancer is the fifth most common type of cancer and the third-leading cause of death worldwide [1-3]. Recent developments in diagnostic technology, clinical collaboration, and an established evidence base have enhanced detection rates and drastically improved early and long-term outcomes for gastric cancer patients. However, gastric cancer remains a global health problem with various clinical issues complicating the selection of appropriate treatments [4-7]. Especially in elderly patients, the effects of surgical stress on physiological status and putative decreases in life expectancy following gastrectomy are pivotal clinical issues to be resolved.

There is a high incidence (12.8% to 14%) of postoperative complications following curative

gastrectomy [8-10]. Several studies have confirmed that postoperative complications following gastrectomy lead to poor oncological prognosis [11-14]. Namely, patients with postoperative complications may be at increased risk of hyperinflammation and hypercytokinemia, resulting in poor immune function and a high incidence of cancer recurrence [15-17]. However, the prognostic effect of postoperative complications on non-cancer-related death and the life expectancy of elderly patients have not been reported. It is foreseeable that excessive surgical stress and postoperative complications might have a negative physiological effect and shorten life expectancy due to non-cancer-related death.

In this study, we firstly investigated the most common cause of non-cancer-related death in gastric cancer. Next, the independent prognos-

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Table 1. Common reasons for non-cancer-related death

Reasons for non-cancer-related death	n=30
Respiratory-related death	14 (47%)
Senility	3 (10%)
Cardiovascular-related death	3 (10%)
Infection-related death	2 (7%)
Liver-related death	2 (7%)
Accidental death	1 (3%)
Renal-related death	1 (3%)
Nerve-related death	1 (3%)
Unknown	3 (10%)

tic factors of non-cancer-related death were examined, and we further investigated the putative risk factors affecting these prognostic factors. Finally, we elucidated the effect of these factors on life expectancy. The results of this study may provide clear evidence of an association between gastrectomy and non-cancer-related death in patients with gastric cancer.

Methods

Patients and procedures

The study was institutionally approved by the Kyoto Prefectural University of Medicine, and each participant provided written informed consent. A total of 220 patients who underwent gastrectomy for pathological stage I gastric cancer (stage IA and IB according to the Japanese guidelines for the treatment of gastric cancer [18, 19]) at Kyoto Prefectural University of Medicine between 1995 and 2020 were included in this study. Only stage I gastric cancer patients were included to remove the influence of cancer-related death from the analysis. Patients underwent preoperative assessments, including gastric endoscopy, computed tomography (CT) scans, and laboratory tests. Based on the preoperative diagnosis, all patients were scheduled for curative gastrectomy and lymphadenectomy, according to the Japanese guidelines for treating gastric cancer. Patients with clinical T1 and N0 tumors underwent D1 or D1+ lymphadenectomy, while patients with more advanced tumors underwent D2 or D2+ lymphadenectomy. In D2 dissections, peri-gastric lymph nodes and all second-tier lymph nodes were completely retrieved. Combined resection was

defined as the resection of the other organ involved in direct tumor invasion or concurrent cancer [19, 20].

Patients with postoperative complications, grade II or more according to the Clavien-Dindo classification system, were enrolled in this study. We defined non-cancer-related death as all-cause mortality, excluding deaths from primary gastric cancer and other cancers. After categorizing patients by sex, postoperative complications (with/without), and age (≥ 85 years), life expectancy was calculated using the expected years of postoperative survival.

Statistical analysis

All analyses were performed using R software (R Foundation for Statistical Computing). Pearson's chi-square (χ^2) test and Fisher's exact probability test were performed for categorical variables. Student's t-test and Mann-Whitney U tests were used to compare clinicopathological characteristics for unpaired continuous variables between the two groups. Survival curves were estimated using the Kaplan-Meier method, and statistical differences were examined using the log-rank test. The data were stratified for multivariate analysis using both forward and backward stepwise Cox regression procedures. A p -value of < 0.05 was considered statistically significant. Life expectancy was evaluated with the restricted mean survival time (RMST) method.

Results

Common reasons for non-cancer-related death

A total of 30 (13.6%) patients died from non-cancer-related causes. **Table 1** shows that 14 (47%) of these deaths were related to respiratory disease, three (10%) were attributed to senility, two (6.7%) were related to cardiovascular disease, and two (6.7%) patients died of infection. Non-cancer-related deaths from respiratory disease were most common and considered extremely high-risk in these gastric cancer patients.

Prognostic effects of postoperative complications on non-cancer-related death

Comparing elderly patients with or without postoperative complications, **Figure 1** shows the cumulative incidences of non-cancer-relat-

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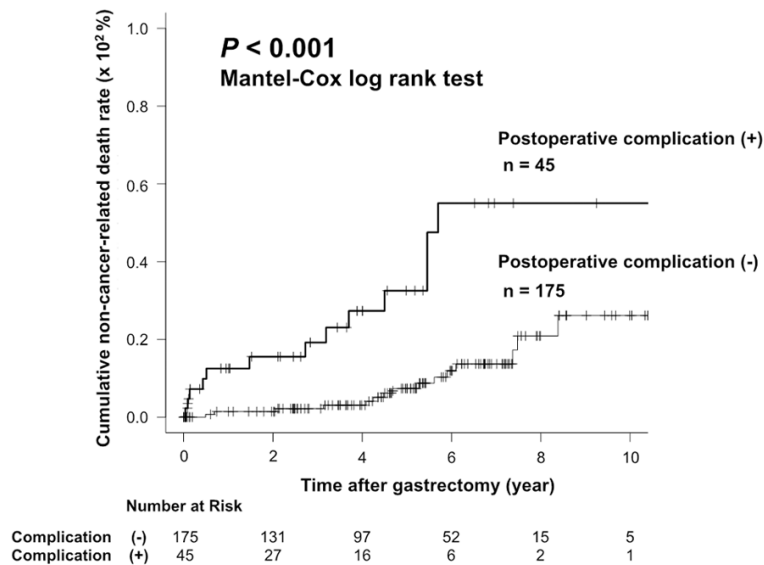


Figure 1. The cumulative incidence of non-cancer-related deaths among elderly patients with or without postoperative complications following gastrectomy, generated by the Mantel-Cox log-rank test method.

ed death and survival curves following gastrectomy. Elderly patients with postoperative complications had a significantly elevated cumulative incidence of non-cancer-related death and poorer long-term survival ($P < 0.001$). Univariate and multivariate analyses using Cox's proportional hazards model revealed that patients with postoperative complications [$P < 0.001$, HR 4.16 (95% CI: 1.91-9.02)] and having received open gastrectomy [$P=0.002$, HR 3.87 (95% CI: 1.54-9.66)] independently contributed to a poorer prognosis for non-cancer-related death (Table 2). There was no association between any preoperative comorbidities and non-cancer-related death. Among the reasons for non-cancer-related death, postoperative complications were significantly associated with respiratory-related deaths (Table 3).

Clinicopathological factors affecting postoperative complications

Next, we compared clinicopathological factors between patients with and without postoperative complications (Table 4). By univariate analysis, postoperative complications were associated with poorer nutritional status (serum albumin (Alb) level < 3.5 mg/mL; $P=0.032$) and total gastrectomy ($P=0.038$). Multivariate analysis revealed that poorer nutritional status (Alb < 3.5 ; $P=0.028$, OR 4.25) was an independent risk factor for postoperative complications (Table 4).

Postoperative complications and life expectancy

Table 5 shows life expectancy according to the presence of postoperative complications. Postoperative complications shortened the life expectancy of elderly patients (≥ 75 years of age) following curative gastrectomy for gastric cancer. Life expectancy was 8.8 years for patients without postoperative complications, which was longer than the 6.1 years found among patients with postoperative complications. Specifically, patients aged 80 years or older without postoperative complications had 6.7 years life expectancy, whereas patients of the same age

group with postoperative complications had a life expectancy of only 3.9 years.

Discussion

Postoperative complications are known to impair oncological prognosis following gastrectomy [11-14]. However, there have been no studies of the prognostic effect postoperative complications and open gastrectomy have on non-cancer-related death in patients with gastric cancer. In this study, we demonstrated that postoperative complications and open gastrectomy independently affected a poorer prognosis for non-cancer-related death in elderly patients. Indeed, postoperative complications shortened life expectancy from 8.8 years to 6.1 years in elderly patients (≥ 75 years of age). Specifically, the life expectancy of patients 80 years or older with postoperative complications fell from 6.7 years to 3.9 years. Poor nutritional status proved to be an independent risk factor for postoperative complications in elderly gastric cancer patients. Respiratory disease was the most common cause of non-cancer-related death, accounting for 46.7% of cases. These novel findings provide pivotal clinical evidence imperative for managing elderly patients with gastric cancer.

Previous research has identified the common causes of non-cancer-related death from various cancers [21]. Newschaffer et al. reported

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Table 2. Univariate and multivariate analyses of clinical factors affecting non-cancer-related death using the Cox's proportional hazard model

	Variable			Univariate ^a		Multivariate ^b	
				p-value	HR ^c	95% CI ^d	p-value
Age	< 80		80 ≤	0.059			
Gender	Male	vs.	Female	0.064			
BMI	< 22	vs.	22 ≤	0.029		-	
Albumin	< 3.5	vs.	3.5 ≤	0.003		-	
Cardiovascular disease	(+)	vs.	No	0.440		-	
Digestive disease	(+)	vs.	No	0.622		-	
Endocrine and autoimmune disease	(+)	vs.	No	0.481		-	
Hepatic disease	(+)	vs.	No	0.600		-	
Malignant disease	(+)	vs.	No	0.369		-	
Neurological disease	(+)	vs.	No	0.544		-	
Renal and urologic disease	(+)	vs.	No	0.397		-	
Respiratory disease	(+)	vs.	No	0.326		-	
Total gastrectomy	(+)	vs.	No	0.087		-	
Surgical approach	(+)	vs.	No	0.001	4.21	1.70-10.4	< 0.001
Complication	Grade II ≤	vs.	< Grade II	< 0.001	4.98	2.36-10.5	< 0.001

^aKaplan-Meier method; significance was determined by log-rank test. ^bMultivariate survival analysis was performed using Cox's proportional hazard model. ^cHR: Hazard ratio. ^dCI: Confidence interval.

Table 3. Comparison of the incidences in each reason for non-cancer-related death according to the presence of postoperative complications

Reason for non-cancer death	n	Postoperative complications				p-value
		(+)	(n=45)	(-)	(n=175)	
Respiratory-related death	14	7	(15.6%)	7	(4%)	0.011
Senility	3	1	(2.2%)	2	(1.1%)	0.498
Cardiovascular-related death	3	2	(4.4%)	1	(0.6%)	0.498
Infection-related death	2	1	(2.2%)	1	(0.6%)	0.368
Liver-related death	2	1	(2.2%)	1	(0.6%)	0.368
Accidental death	1	0	(0%)	1	(0.6%)	1.000
Renal-related death	1	0	(0%)	1	(0.6%)	1.000
Nerve-related death	1	0	(0%)	1	(0.6%)	1.000
Unknown	3	2	(4.4%)	1	(0.6%)	0.107

that non-cancer-related death from prostate cancer was most commonly attributed to heart disease, followed by cerebrovascular disease [22]. Similarly, Afifi et al. also reported that heart disease and cerebrovascular disease were the first and second most common causes of non-cancer-related deaths in breast cancer patients within ten years of diagnosis [23]. On the contrary, non-cancer-related deaths among gastric cancer patients are most commonly caused by respiratory diseases, such as aspiration pneumonia. Sugawara et al. reported that preoperative restricted pulmonary dys-

function and total gastrectomy increased non-cancer-related death after gastrectomy and pneumonia was one of the most common death [24]. Patients with preoperative restricted pulmonary dysfunction have poor physical status, leading to a potential increase of non-cancer-related death after gastrectomy, especially respiratory-related death. Furthermore, the increased incidence of respiratory-related death may be caused by intestinal juice reflux following sub or total gastrectomy and adhesion, in addition to the impaired swallowing reflex in elderly patients. Previously, we reported that elderly gastric cancer patients have a higher risk of respiratory disease compared to their younger counterparts [13]. Therefore, it is important to bear in mind that respiratory-related disease is a pivotal cause of non-cancer-related death for gastric cancer patients.

Another striking and unexpected finding of this study was that open gastrectomy was an independent risk factor for non-cancer-related de-

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Table 4. Univariate and multivariate analyses to detect possible risk factors for postoperative complications

Variables		Postoperative complication		Univariate ^a p-value	Multivariate ^b		
		(+) (n=45)	(-) (n=175)		OR ^c	95% CI ^d	p-value
Age	< 80	24 (53%)	102 (58%)	0.613			
	≥ 80	21 (47%)	73 (42%)				
Gender	Female	15 (33%)	70 (40%)	0.493			
	Male	30 (67%)	105 (60%)				
BMI (kg/m ²)	< 22	17 (38%)	93 (53%)	0.094			
	≥ 22	28 (62%)	82 (47%)				
Nutritious status (Alb (g/dl))	≥ 3.5	40 (89%)	170 (97%)	0.032	1	4.25	1.17-15.4
	< 3.5	5 (11%)	5 (3%)				
Cardiovascular disease	(-)	23 (51%)	91 (52%)	1.000			
	(+)	22 (49%)	84 (48%)				
Digestive disease	(-)	33 (73%)	136 (78%)	0.555			
	(+)	12 (27%)	39 (22%)				
Endocrine and autoimmune disease	(-)	38 (84%)	141 (81%)	0.670			
	(+)	7 (16%)	34 (19%)				
Hepatic disease	(-)	42 (93.3%)	162 (93%)	1.000			
	(+)	3 (6.7%)	13 (7%)				
Malignant disease	(-)	30 (67%)	127 (73%)	0.462			
	(+)	15 (33%)	48 (27%)				
Neurological disease	(-)	39 (87%)	161 (92%)	0.257			
	(+)	6 (13%)	14 (8%)				
Renal and urologic disease	(-)	42 (93%)	169 (97%)	0.394			
	(+)	3 (7%)	6 (3%)				
Respiratory disease	(-)	42 (93%)	159 (91%)	0.394			
	(+)	3 (7%)	16 (9%)				
Surgical approach	Open	23 (51%)	77 (44%)	0.406			
	Laparoscopic	22 (49%)	98 (56%)				
Total gastrectomy ^e	(-)	33 (73%)	152 (87%)	0.038			
	(+)	12 (27%)	23 (13%)				

^aUnivariate analysis was assessed using Chi squared test and Fisher's exact probability test. ^bMultivariable logistic regression was used to assess the risk factors for severe complications. ^cOR: Odds ratio. ^dCI: confidence interval. ^eIncluding completion gastrectomy.

Table 5. Postoperative complications and life expectancy

Age (years old)	Total*	Postoperative complications	
		(+)*	(-)*
All ages	all	8.3	8.8
Age < 75	male	7.7	8.2
	female	6.8	7.0
75 ≤ Age < 80	all	8.6	8.9
	male	8.2	8.3
	female	4.8	4.8
80 ≤ Age	all	6.1	6.7
	male	4.5	5.1
	female	6.7	7.0

*Year of life expectancy.

ath. In other words, less invasive laparoscopic gastrectomy independently reduced the occur-

rence of non-cancer-related death. Similarly, several recent studies have demonstrated that laparoscopic surgery reduced postoperative complications. Inokuchi et al. reported that laparoscopic gastrectomy reduced postoperative pneumonia and cardiac complications in high-risk (ASA-3 <) patients compared with open gastrectomy [25]. Lee et al. reported that laparoscopic distal gastrectomy for locally advanced gastric cancer was safe and showed important benefits, such as a lower complication rate, compared to open surgery [26]. Thus, laparoscopic surgery, including robotic surgery, may

be less disruptive to the abdominal wall than open surgery and thereby maintain postopera-

tive abdominal breathing, which prevents the decrease of vital capacity and reduce respiratory-related diseases such as pneumonia, particularly in the elderly. In addition, these procedures may reduce the long-term risk of respiratory-related death. Therefore, a less invasive surgical approach is recommended to reduce inflammation and postoperative complications and adhesions, as well as to extend life expectancy and long-term outcomes. Currently, a prospective study is underway to examine these potential benefits.

The present study was limited by its retrospective design with a small cohort. Additionally, the prolonged recruitment period over which the retrospective analysis was performed at a single institution may be influenced by possible variations in treatment strategies over time. Therefore, a prospective observational study with several large cohorts or a nationwide clinical database study may be needed to validate the significance of postoperative complications and open gastrectomy on non-cancer-related death among gastric cancer patients.

In conclusion, postoperative complications were shown to be associated with non-cancer-related death, particularly respiratory-related death, and decreased life expectancy in elderly patients with gastric cancer. Careful consideration should be given to patient nutrition and surgical approach (less invasive) to prevent non-cancer-related deaths.

Disclosure of conflict of interest

None.

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References

- [1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87-108.
- [2] The Foundation for Promotion of Cancer Research (FPCR). *Cancer Statistics in Japan* 2018; 2018.

- [3] Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A and Bray F. Cancer statistics for the year 2020: an overview. *Int J Cancer* 2021; [Epub ahead of print].
- [4] Zhang Q, Wang F, Chen ZY, Wang Z, Zhi FC, Liu SD and Bai Y. Comparison of the diagnostic efficacy of white light endoscopy and magnifying endoscopy with narrow band imaging for early gastric cancer: a meta-analysis. *Gastric Cancer* 2016; 19: 543-552.
- [5] Kitano S, Shiraishi N, Uyama I, Sugihara K and Tanigawa N. A multicenter study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan. *Ann Surg* 2007; 245: 68-72.
- [6] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J and Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; 376: 687-697.
- [7] Komatsu S and Otsuji E. Essential updates 2017/2018: recent topics in the treatment and research of gastric cancer in Japan. *Ann Gastroenterol Surg* 2019; 3: 581-591.
- [8] Yasunaga H, Horiguchi H, Kuwabara K, Matsuda S, Fushimi K, Hashimoto H and Ayanian JZ. Outcomes after laparoscopic or open distal gastrectomy for early-stage gastric cancer: a propensity-matched analysis. *Ann Surg* 2013; 257: 640-646.
- [9] Kim HH, Han SU, Kim MC, Hyung WJ, Kim W, Lee HJ, Ryu SW, Cho GS, Song KY and Ryu SY. Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case-control and case-matched Korean multicenter study. *J Clin Oncol* 2014; 32: 627-633.
- [10] Yu J, Hu J, Huang C, Ying M, Peng X, Wei H, Jiang Z, Du X, Liu Z, Liu H and Li G. The impact of age and comorbidity on postoperative complications in patients with advanced gastric cancer after laparoscopic D2 gastrectomy: results from the Chinese laparoscopic gastrointestinal surgery study (CLASS) group. *Eur J Surg Oncol* 2013; 39: 1144-1149.
- [11] Kubota T, Hiki N, Sano T, Nomura S, Nunobe S, Kumagai K, Aikou S, Watanabe R, Kosuga T and Yamaguchi T. Prognostic significance of complications after curative surgery for gastric cancer. *Ann Surg Oncol* 2014; 21: 891-898.
- [12] Tokunaga M, Tanizawa Y, Bando E, Kawamura T and Terashima M. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. *Ann Surg Oncol* 2013; 20: 1575-1583.

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- [13] Kiuchi J, Komatsu S, Ichikawa D, Kosuga T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H, Yasuda T and Otsuji E. Putative risk factors for postoperative pneumonia which affects poor prognosis in patients with gastric cancer. *Int J Clin Oncol* 2016; 21: 920-926.
- [14] Shimada H, Fukagawa T, Haga Y and Oba K. Does postoperative morbidity worsen the oncological outcome after radical surgery for gastrointestinal cancers? A systematic review of the literature. *Ann Gastroenterol Surg* 2017; 1: 11-23.
- [15] Thompson DA, Makary MA, Dorman T and Pronovost PJ. Clinical and economic outcomes of hospital acquired pneumonia in intra-abdominal surgery patients. *Ann Surg* 2006; 243: 547-552.
- [16] Hayashi T, Yoshikawa T, Aoyama T, Hasegawa S, Yamada T, Tsuchida K, Fujikawa H, Sato T, Ogata T, Cho H, Oshima T, Rino Y and Masuda M. Impact of infectious complications on gastric cancer recurrence. *Gastric Cancer* 2015; 18: 368-374.
- [17] Tokunaga M, Kurokawa Y, Machida R, Sato Y, Takiguchi S, Doki Y, Yabusaki H, Watanabe M, Hato S, Nakamori M, Ito S, Yoshikawa T and Terashima M. Impact of postoperative complications on survival outcomes in patients with gastric cancer: exploratory analysis of a randomized controlled JCOG1001 trial. *Gastric Cancer* 2021; 24: 214-223.
- [18] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; 24: 1-21.
- [19] Nakajima T. Gastric cancer treatment guidelines in Japan. *Gastric Cancer* 2002; 5: 1-5.
- [20] Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; 14: 101-112.
- [21] Zaorsky NG, Churilla TM, Egleston BL, Fisher SG, Ridge JA, Horwitz EM and Meyer JE. Causes of death among cancer patients. *Ann Oncol* 2017; 28: 400-407.
- [22] Newschaffer CJ, Otani K, McDonald MK and Penberthy LT. Causes of death in elderly prostate cancer patients and in a comparison non-prostate cancer cohort. *J Natl Cancer Inst* 2000; 92: 613-621.
- [23] Afifi AM, Saad AM, Al-Husseini MJ, Elmeharth AO, Northfelt DW and Sonbol MB. Causes of death after breast cancer diagnosis: a US population-based analysis. *Cancer* 2020; 126: 1559-1567.
- [24] Sugawara K, Yamashita H, Yajima S, Uemura Y, Okumura Y, Nishida M, Yagi K, Aikou S and Seto Y. Preoperative restrictive pulmonary dysfunction influences the survival after gastrectomy for elderly patients with gastric carcinoma. *Surg Today* 2020; 50: 1065-1073.
- [25] Inokuchi M, Kumamaru H, Nakagawa M, Miyata H, Kakeji Y, Seto Y and Kojima K. Feasibility of laparoscopic gastrectomy for patients with poor physical status: a retrospective cohort study based on a nationwide registry database in Japan. *Gastric Cancer* 2020; 23: 310-318.
- [26] Lee HJ, Hyung WJ, Yang HK, Han SU, Park YK, An JY, Kim W, Kim HI, Kim HH, Ryu SW, Hur H, Kong SH, Cho GS, Kim JJ, Park DJ, Ryu KW, Kim YW, Kim JW, Lee JH and Kim MC. Short-term outcomes of a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy with D2 lymphadenectomy to open distal gastrectomy for locally advanced gastric cancer (KLASS-02-RCT). *Ann Surg* 2019; 270: 983-991.