World J Surg (2019) 43:1857–1866
https://doi.org/10.1007/s00268-019-04982-4

ORIGINAL SCIENTIFIC REPORT

Competing Risk Analysis in Lung Cancer Patients Over 80 Years Old Undergoing Surgery

Haruaki Hino[1] · Takahiro Karasaki[2] · Yukihiro Yoshida[3] · Takeshi Fukami[4] · Atsushi Sano[5] · Makoto Tanaka[6] · Yoshiaki Furuhata[7] · Kosuke Kashiwabara[8] · Junji Ichinose[2] · Mitsuaki Kawashima[2] · Jun Nakajima[2]

Published online: 1 April 2019

Abstract

Background This study aimed to analyze cause-specific mortality in lung cancer patients over 80 years old undergoing surgery.

Methods This retrospective, multi-institutional analysis included patients aged ≥ 80 years who underwent radical surgery for primary lung cancer from January 1998 to December 2015. Preoperative clinical data, surgical results, survival, and cause of death were evaluated. Competing risk analysis for cause-specific mortality was performed.

Results Of the 337 patients (median age 82 years) enrolled and analyzed, 68.1% were male. There were 52 and 44 cancer-specific and non-cancer-specific deaths, respectively. On competing risk regression analysis, non-cancer-specific deaths were significantly associated with male sex (hazard ratio [HR]: 3.06, 95% confidence interval [CI]: 1.02–9.12, $p = 0.046$), coronary artery disease (HR: 2.49, 95% CI: 2.49 [1.14–5.47], $p = 0.02$), interstitial pneumonia (HR: 3.58, 95% CI: 1.73–7.40, $p < 0.001$), and pathological stage III (HR: 3.83, 95% CI: 1.44–10.13, $p = 0.007$). In contrast, cancer-specific deaths were significantly associated with limited resection (HR: 1.99, 95% CI: 1.02–3.89, $p = 0.04$) and pathological stage III (HR: 3.13, 95% CI: 1.44–6.80, $p = 0.004$). The 5-year cumulative incidences of lung cancer-specific and non-cancer-specific deaths were 18.0% and 15.9%, respectively.

Conclusions Prognostic factors for non-cancer-specific death were different from those of cancer-specific death, except for pathological stage. Each prognostic factor should be considered when deciding surgical indication and procedure and monitoring for pulmonary events during outpatient follow-up.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00268-019-04982-4) contains supplementary material, which is available to authorized users.

✉ Jun Nakajima
nakajima-tho@h.u-tokyo.ac.jp

Haruaki Hino
haruakihino@gmail.com

Takahiro Karasaki
karasakit-sur@h.u-tokyo.ac.jp

Yukihiro Yoshida
yyoshida-tky@umin.ac.jp

Takeshi Fukami
fukami-ths@umin.net

Atsushi Sano
sanoa-tky@umin.ac.jp

Makoto Tanaka
makoto1020@hotmail.com

Yoshiaki Furuhata
furuhata_yoshiaki@med.jrc.or.jp

Introduction

The number of elderly lung cancer patients older than 80 years has been increasing recently [1, 2]. According to previous retrospective analyses of lung cancer surgery in octogenarians, morbidity and mortality rates were 8.4–48.0% and 0–6.3%, respectively, and the 5-year overall survival rate was 27.0–57.5% [3–7]. Recently, Japanese studies have demonstrated more acceptable morbidity and mortality rates of 27.7–34.0% and 1.1–1.6%, respectively [8, 9]. Previously, we conducted a retrospective multi-institutional analysis of 337 lung cancer operations in patients older than 80 years and revealed that male sex, Glasgow Prognostic Score (GPS), Charlson comorbidity index (CCI), and pathological stage (P-stage) were associated with long-term survival using Cox proportional hazards analysis [10]. In that dataset, the rate of non-cancer-specific death ($n = 44$, 13.1%) was relatively higher than that of cancer-specific death ($n = 52$, 15.4%). A previous subset analysis of cause-specific mortality after lung cancer surgery in patients older than 75 years showed that non-cancer-specific cumulative incidence of death (CID) at 5 years was 9.0% compared with 13.2% for lung cancer-specific CID [11, 12]. However, few competing risk regression analysis studies have focused on elderly lung cancer patients. Therefore, the aim of this study was to analyze prognostic factors for cause-specific death, i.e., cancer-specific and non-cancer-specific deaths in patients older than 80 years undergoing surgery for lung cancer in a Japanese multi-institutional cohort.

Materials and methods

This study included lung cancer patients older than 80 years who underwent radical surgery at any of the seven institutions from January 1998 through December 2015 (Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, The University of Tokyo Graduate School of Medicine, Asahi General Hospital, National Hospital Organization Tokyo National Hospital, Chigasaki Municipal Hospital, JR Tokyo General Hospital, and Japanese Red Cross Medical Center). Data on clinical characteristics, including age, sex, Brinkman index, body mass index, pulmonary function, GPS, preoperative comorbidity, operative procedure, postoperative complications, tumor histology, P-stage, survival, and cause of death, were retrospectively collected from patient charts. The preoperative examination for cancer staging included chest and upper abdomen computed tomography (CT), CT or magnetic resonance imaging of the brain, and bone scintigraphy or F-18 fluorodeoxyglucose positron emission tomography. Preoperative mediastinoscopy was not performed. The tumor stage was determined according to the 7th edition of the TNM staging system of the International Union against Cancer [13]. The histologic tumor type was determined according to the 3rd edition of the World Health Organization classification [14]. Operative indication was determined based on the following factors at the discretion of the surgeons at each institute: performance status, 0 to 1; clinical stage, I to IIIA expected to be completely resectable; and mental status, not senile. Video-assisted thoracic surgery (VATS) was the operative method of choice. Open thoracotomy was performed in patients contraindicated for VATS, such as those with pulmonary artery plasty or chest wall construction. CCI was scored according to 19 preoperative comorbidities according to Charlson et al. [15]. Briefly, previous disease was scored between 1 and 6, with the total score ranging from 0 to 8. GPS was defined as follows: 0, albumin $\geq$ 3.5 mg and C-reactive protein (CRP) $<$ 0.5; 1, albumin $<$ 3.5 mg or CRP $\geq$ 0.5; 2, albumin $<$ 3.5 mg and CRP $\geq$ 0.5. This was similar to the definition of MacMilan et al. [16]. Survival was calculated

Kosuke Kashiwabara
kashiwabara-tky@umin.ac.jp

Junji Ichinose
junji.ichi@gmail.com

Mitsuaki Kawashima
mitsuaki.kawashima@gmail.com

[1] Department of Thoracic Surgery, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2 Sakaecho Itabashi-ku, Tokyo 173-0015, Japan

[2] Department of Thoracic Surgery, The University of Tokyo Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

[3] Department of Thoracic Surgery, Asahi General Hospital, 1326 I Asahi-shi, Chiba 289-2511, Japan

[4] Department of Thoracic Surgery, National Hospital Organization Tokyo National Hospital, 3-1-1 Takeoka Kiyose-shi, Tokyo 204-8585, Japan

[5] Department of Thoracic Surgery, Chigasaki Municipal Hospital, 5-15-1 Honson Chigasaki-shi, Kanagawa 253-0042, Japan

[6] Department of Thoracic Surgery, JR Tokyo General Hospital, 2-1-3 Yoyogi Shibuya-ku, Tokyo 151-8528, Japan

[7] Department of Thoracic Surgery, Japanese Red Cross Medical Center, 4-1-22 Hiroo Shibuya-ku, Tokyo 150-8935, Japan

[8] Department of Biostatistics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

from the date of surgery to the time of death or last follow-up.

This study was approved by the Research Review Board at The University of Tokyo Graduate School of Medicine (approval no. 11146) and the respective ethics committees at the other six institutions in accordance with the Declaration of Helsinki.

Continuous and categorical variables were analyzed using the unpaired Student's t test and Chi-square test, respectively. We considered cancer-specific and non-cancer-specific deaths to be two competing outcomes in our cohort. CID curves for each death were compared using Gray's test, and a competing risk regression analysis was performed based on Fine and Gray's model [12]. In detail, univariate analysis was performed for each variable first; then, variables with p values less than 0.2 were selected. Finally, multivariate analysis was performed with those variables. A landmark analysis at the 15-month point was conducted to evaluate survival rate at the late phase after surgery. A competing risk analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [17]. A p value < 0.05 was considered statistically significant.

Results and discussion

Initially, 365 patients aged 80 years or older who underwent surgery for lung cancer were registered; however, 28 patients were excluded due to incomplete resection ($n = 15$), insufficient data ($n = 7$), multiple lesions ($n = 3$), and diagnosis of small cell carcinoma ($n = 3$). The final analysis included 337 patients. Patient characteristics are shown in Table 1. Preoperative comorbidity based on CCI was noted in 207 patients (61.4%), which included malignant disease within 5 years (25.5%), diabetes mellitus (13.4%), and coronary artery disease (CAD: 13.1%). Postoperative complications and surgery-related death during the hospital stay occurred in 119 (35.3%) and 6 patients (1.8%), respectively. Thirty- and 90-day mortality rates were observed in 1.2% (4 patients) and 0.3% (1 patients), respectively, and the in-hospital mortality rate was 1.8% (6 patients). As for long-term outcome, during our observation time almost half of all patients were alive without cancer, and rates of non-cancer-specific deaths ($n = 44$, 14.1%) were closer to that of cancer-specific-deaths ($n = 52$, 15.4%). Pneumonia, cardiovascular disease, and other malignancies were the most common causes of death other than primary lung cancer (Table 2). Results of the competing risk regression analysis for cause-specific mortality based on Fine and Gray's model are shown in Table 3. Significant prognostic factors for non-cancer-specific death were male sex (hazard ratio [HR], 3.06; 95% confidence interval [CI]: 1.02–9.12, $p = 0.04$), CAD (HR, 2.49; 95% CI: 1.14–5.47, $p = 0.02$), interstitial pneumonia (HR, 3.58; 95% CI: 1.73–7.40, $p < 0.001$), and P-stage (P-stage III: HR, 3.83; 95% CI: 1.44–10.13, $p = 0.0069$). In contrast, cancer-specific death was significantly associated with limited resection (HR, 1.99; 95% CI: 1.02–3.89, $p = 0.04$) and P-stage (P-stage III: HR, 3.13; 95% CI: 1.44–6.80, $p = 0.004$). Next, we analyzed the variables without interstitial pneumonia, which were not included in the Charlson comorbidity index. The significant prognostic factors for non-cancer-specific death were male sex (HR, 4.02; 95% CI: 1.28–13.81, $p = 0.02$), CAD (HR, 2.74; 95% CI: 1.03–7.28, $p = 0.043$), P-stage (P-stage II: HR, 2.52; 95% CI: 1.02–6.23, $p = 0.046$), and (P-stage III: HR, 7.36; 95% CI: 2.70–20.01, $p < 0.001$) (Table 4). The prognostic factors for non-cancer-specific death became closer to those of overall survival. Then, we calculated the CID curve for both cancer-specific and non-cancer-specific deaths (Fig. 1). The CID of cancer-specific and non-cancer-specific deaths at 5 years was 18.0% (95% CI: 13.3–23.3%) and 15.9% (95% CI, 11.5–21.0%), respectively. The CID between cancer-specific and non-cancer-specific deaths was not significantly different by Gray's test ($p = 0.18$). The number of non-cancer-specific deaths up to 15 months after surgery was higher than that of cancer-specific deaths, a trend that was reversed at the end of the study period (Supplementary Figure 1).

After a detailed analysis of CID rate in early and late phases after surgery by Gray's test, the results revealed that in the first 15 months after surgery, the CID rate of non-cancer-specific death and cancer-specific death was 5.1% and 4.8%, respectively, which was not significantly different ($p = 0.20$). A major cause of non-cancer-specific death during the early period was pneumonia ($n = 6$). After 15 months of surgery, the CID rate of non-cancer-specific death and cancer-specific death was 8.7% and 14.1%, respectively, which was not significantly different either ($p = 0.33$). The latter evaluation was conducted by a landmark analysis at the 15-month landmark point post-surgery. We believe that there might be a significant difference if the sample size was increased. In a previous report [11], the results of a competing risk analysis that included more than 600 lung cancer patients over 75 years of age appeared to show a significant difference in cancer-specific and non-cancer-specific death rates, in both early and late phases following surgery. Although there was no significant difference in CID between cancer-specific and non-cancer-specific deaths in early and late phase of survival, results of the CID curve suggest that we should be more cautious of non-cancer-specific deaths until

Table 1 Clinical characteristics of 337 lung cancer patients older than 80 years who underwent radical surgery

Clinical characteristics	*N* (%)
Age (years)	80–92 (median 82)
Sex	
Male	216 (64.1%)
Female	121 (35.9%)
Brinkman index	
0	120 (35.6%)
< 200	12 (3.6%)
< 600	41(12.2%)
≥ 600	158 (46.8%)
Unknown	6 (1.8%)
Body mass index	15.1–31.8 (mean 22.5)
%VC (%)	50.5–162.6 (mean 99.7)
FEV1/FVC (%)	31.0–98.7 (mean 69.0)
Glasgow Prognostic Score	
0	240 (71.2%)
1 or 2	80 (23.8%)
Unknown	17 (5.0%)
Charlson comorbidity index	
0 or 1	287 (85.2%)
≥ 2	50 (14.8%)
Preoperative comorbidity	
Yes	207 (61.4%)
No	130 (38.6%)
Cancer history	
Yes	86 (25.5%)
No	251 (74.5%)
Coronary artery disease	
Yes	44 (13.1%)
No	293 (86.9%)
Interstitial pneumonia	
Yes	30 (8.9%)
No	307 (91.1%)
Diabetes mellitus	
Yes	50 (14.8%)
No	287 (85.2%)
Lymph node dissection	
ND0	82 (24.3%)
ND1	105 (31.2%)
ND2	145 (42.0%)
Unknown, other	5 (1.5%)
Procedure	
Partial resection	66 (19.6%)
Segmentectomy	28 (8.3%)
Lobectomy	237 (70.3%)
Bilobectomy	5 (1.5%)
Pneumonectomy	1 (0.3%)
Postoperative complication	
Yes	119 (35.3%)
No	218 (64.7%)
Histology (Ad/Sq/others)	
Adenocarcinoma	217 (64.4%)
Squamous cell carcinoma	90 (26.7%)
Others	30 (8.9%)
Pathological stage	
I	239 (70.9%)
II	60 (17.8%)
III	38 (11.3%)
Observation time (months)	0.1–152.8 (median 29.9)

VC vital capacity, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *ND* lymph node dissection, *ND0* without any lymph node dissection, *ND1* hilar lymph node dissection, *ND2* hilar and mediastinal lymph node dissection

approximately 15 months of surgery; however, after that, we should be more concerned about cancer-related deaths.

We also calculated CID curves stratified by sex, interstitial pneumonia, CAD, and GPS (Figs. 2a–d, 3a–d), as well as procedure and P-stage (Fig. 4a–d). According to the results of Gray's test, the CID at 5 years for non-cancer-specific death was significantly higher in men (21.8% in men vs. 5.8% in women, $p < 0.001$), those with interstitial pneumonia (51.0% vs. 12.9%, $p < 0.001$) or CAD (27.9% vs. 11.1%, $p = 0.003$), and higher GPS (26.2% in GPS 1 or 2 vs. 12.5% in GPS 0, $p = 0.004$) and P-stage (27.9% in stages II and III vs. 11.1% in stage I, $p = 0.003$). In contrast, CID at 5 years for lung cancer-specific death was associated with limited resection (24.1% in limited resection vs. 16.6% in radical resection, $p = 0.03$) and P-stage

Table 2 Cause of non-lung-cancer death

Cause of death	*N* (%)
Pneumonia	10 (22.7%)
Cardiovascular disease	6 (13.6%)
Other malignancy	5 (11.4%)
Acute exacerbation of interstitial pneumonia	3 (6.8%)
Cerebrovascular disease	3 (6.8%)
Trauma	2 (4.5%)
Natural death	2 (4.5%)
Sepsis	1 (2.2%)
Renal failure	1 (2.2%)
Intestinal necrosis	1 (2.2%)
Unknown	10 (22.7%)
Total	44 (100%)

Table 3 Univariate and multivariate analyses using Fine and Gray's competing risk regression for the effect of non-cancer-specific and cancer-specific death on survival using all variables

	Non-cancer-specific death				Cancer-specific death			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	1.08 (0.97–1.22)	0.16	1.03 (0.88–1.22)	0.69	0.99 (0.77–1.06)	0.20		
Sex (male/female)	3.72 (1.69–8.15)	0.0011	3.06 (1.02–9.12)	0.046*	1.43 (0.79–2.57)	0.23		
Brinkman index (≥ 600/ < 600)	2.43 (1.33–4.45)	0.004	1.79 (0.76–4.23)	0.18	1.50 (0.86–2.58)	0.15	1.15 (0.61–2.18)	0.67
Body mass index	0.93 (0.85–1.01)	0.08	0.90 (0.79–1.03)	0.13	1.01 (0.92–1.10)	0.90		
%VC	0.99 (0.97–1.01)	0.21			0.99 (0.97–1.00)	0.13	0.99 (0.98–1.01)	
FEV1sec/FVC	1.02 (0.99–1.05)	0.14	1.01 (0.98–1.04)	0.60	0.98 (0.95–1.00)	0.054	0.98 (0.96–1.00)	
GPS (1 or 2/0)	2.24 (1.23–4.07)	0.01	1.51 (0.66–3.45)	0.33	1.51 (0.81–2.81)	0.19	1.84 (0.93–3.65)	0.08
CCI (≥ 2/0 or 1)	1.68 (0.98–2.90)	0.06	1.28 (0.66–2.49)	0.46	1.72 (1.01–2.95)	0.047	1.38 (0.56–3.39)	0.48
Cancer history	1.24 (0.68–2.26)	0.49			1.67 (0.94–2.96)	0.08	1.54 (0.61–3.87)	0.37
Coronary artery disease	2.30 (1.15–4.59)	0.02	2.49 (1.14–5.47)	0.02*	1.13 (0.52–2.44)	0.75		
Interstitial pneumonia	5.13 (2.63–10.00)	< 0.001	3.58 (1.73–7.40)	< 0.001*	1.29 (0.51–3.22)	0.59		
Diabetes mellitus	1.06 (0.43–2.38)	0.89			0.70 (0.27–1.80)	0.46		
Procedure (limited/ radical)	0.56 (0.25–1.26)	0.16	0.77 (0.28–2.13)	0.62	1.97 (1.08–3.59)	0.03	1.99 (1.02–3.89)	0.047*
LN dissection (ND2/ND0 or 1)	0.96 (0.55–1.67)	0.89			0.96 (0.55–1.67)	0.89		
Surgical procedure (VATS/thoracotomy)	0.60 (0.35–1.05)	0.07	0.93 (0.46–1.86)	0.82	0.76 (0.43–1.36)	0.36		
Postoperative complication (yes/no)	1.52 (0.87–2.65)	0.14	1.05 (0.48–2.28)	0.90	0.82 (0.45–1.46)	0.49		
Pathology (non-Ad/Ad)	1.60 (0.92–2.79)	0.10	0.76 (0.33–1.75)	0.52	1.40 (0.80–2.43)	0.24		
P-stage (I, II, III)	P-stage I 1				P-stage I 1			
	P-stage II 2.47 (1.32–4.62)	0.005	1.99 (0.86–4.64)	0.11	P-stage II 1.38 (0.67–2.85)	0.38	1.52 (0.67–3.45)	0.31
	P-stage III 1.48 (0.99–2.22)	0.06	3.83 (1.44–10.13)	0.0069*	P-stage III 1.45 (1.03–2.04)	0.03	3.13 (1.44–6.80)	0.004*

Ad adenocarcinoma, *CCI* Charlson comorbidity index, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *GPS* Glasgow Prognostic Score, *HR* hazard ratio, limited = limited resection including partial resection and segmentectomy, *radical* radical resection including lobectomy, bilobectomy and pneumonectomy, *LN* lymph node, *ND* lymph node dissection, *ND0* without any lymph node dissection, *ND1* hilar lymph node dissection, *ND2* hilar and mediastinal lymph node dissection, *P-stage* pathological stage, *VATS* video-assisted thoracoscopic surgery, *VC* vital capacity

*p value < 0.05 in univariate and multivariate analysis

(22.8% for P-stages II and III vs. 16.1% in P-stage I, $p = 0.07$).

The number of elderly lung cancer patients who undergo surgery has been increasing, reaching up to 12.1% in Japan [2]. A recent Japanese annual report found an overall mortality rate of 0.7%, and our previous study reported a rate of 1.8% in the elderly, which we, as general thoracic surgeons, considered an acceptable short-term result [2, 9].

Table 4 Univariate and multivariate analyses using Fine and Gray's competing risk regression for the effect of non-cancer-specific death on survival without interstitial pneumonia

	Non-cancer-specific death			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	1.08 (0.97–1.22)	0.16	1.10 (0.93–1.29)	0.26
Sex (male/female)	3.72 (1.69–8.15)	0.0011	4.20 (1.28–13.8)	0.02*
Brinkman index (≥ 600/< 600)	2.43 (1.33–4.45)	0.004	2.17 (0.85–5.49)	0.10
Body mass index	0.93 (0.85–1.01)	0.08	0.91 (0.80–1.04)	0.16
%VC	0.99 (0.97–1.01)	0.21		
FEV1sec/FVC	1.02 (0.99–1.05)	0.14	0.99 (0.99–1.04)	0.87
GPS (1 or 2/0)	2.24 (1.23–4.07)	0.01	2.20 (0.95–5.08)	0.07
CCI (≥ 2/0 or 1)	1.68 (0.98–2.90)	0.06	1.51 (0.75–3.01)	0.25
Cancer history	1.24 (0.68–2.26)	0.49		
Coronary artery disease	2.30 (1.15–4.59)	0.02	2.74 (1.03–7.28)	0.04*
Interstitial pneumonia	NA		NA	
Diabetes mellitus	1.06 (0.43–2.38)	0.89		
Procedure (limited/radical)	0.56 (0.25–1.26)	0.16	1.14 (0.36–3.60)	0.83
LN dissection (ND2/ND0 or 1)	0.96 (0.55–1.67)	0.89		
Surgical procedure (VATS/thoracotomy)	0.60 (0.35–1.05)	0.07	0.66 (0.32–1.36)	0.26
Postoperative complication (yes/no)	1.52 (0.87–2.65)	0.14	0.86 (0.38–1.93)	0.71
Pathology (non-Ad/Ad)	1.60 (0.92–2.79)	0.10	0.76 (0.33–1.75)	0.52
P-stage (I, II, III)	P-stage I 1			
	P-stage II 2.47 (1.32–4.62)	0.005	2.52 (1.02–6.23)	0.046*
	P-stage III 1.48 (0.99–2.22)	0.06	7.36 (2.70–20.01)	< 0.001*

Ad adenocarcinoma, *CCI* Charlson comorbidity index, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *GPS* Glasgow Prognostic Score, *HR* hazard ratio, *limited* limited resection including partial resection and segmentectomy, *radical* radical resection including lobectomy, bilobectomy and pneumonectomy, *LN* lymph node, *ND* lymph node dissection, *ND0* without any lymph node dissection, *ND1* hilar lymph node dissection, *ND2* hilar and mediastinal lymph node dissection, *P-stage* pathological stage, *VATS* video-assisted thoracoscopic surgery, *VC* vital capacity, *NA* not analysis

*p value < 0.05 in univariate and multivariate analysis

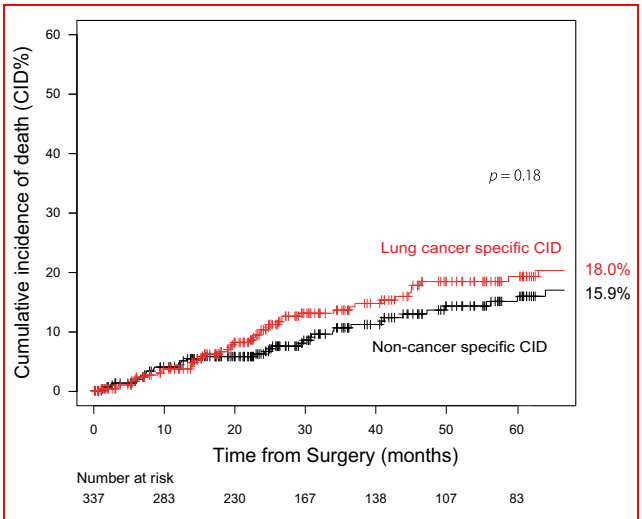

Fig. 1 Cumulative incidence of death (CID) curve stratified by all 337 cases, lung cancer-specific and non-cancer-specific deaths. The CID of lung cancer-specific and non-cancer-specific deaths was 18.0% and 15.9%, respectively ($p = 0.18$)

As for long-term results, the elderly cohort had a considerable rate of non-lung-cancer-specific deaths ($n = 44$, 13.1%) compared to lung cancer-specific deaths ($n = 52$, 15.4%). We considered that this substantial number of non-lung-cancer-specific deaths had an impact not only on overall survival but also on lung cancer-specific death. Therefore, we set out to analyze the effects of cause-specific mortality on long-term survival via competing risk regression analysis (Fine and Gray's model) [12, 18]. Recently, competing risk analyses of cause-specific mortality have been performed for various non-lung cancer malignancies, such as prostate cancer, renal cell carcinoma, thyroid cancer, head and neck carcinoma, and breast cancer [19–23]. Similarly, mortality in patients with cardiovascular disease has been recently analyzed using this approach [24, 25]. The prognostic factors for cancer-specific and non-cancer-specific deaths appear to differ based on the organ, malignant potential, patient age, and cause of death. According to a clinical study concerning

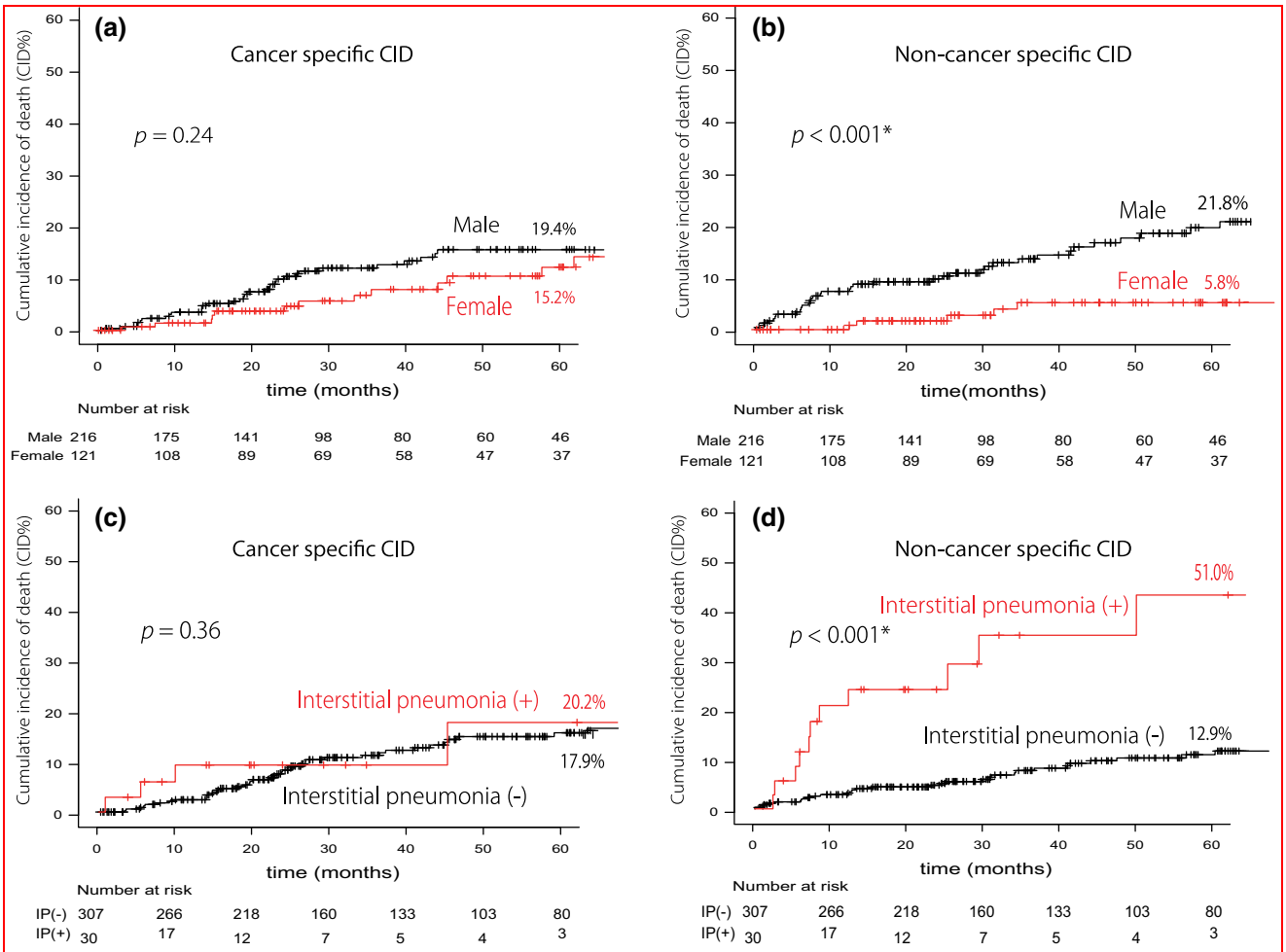

Fig. 2 Cancer-specific and non-cancer-specific CID stratified by sex and interstitial pneumonia. The number of non-cancer-specific deaths was significantly higher than that of cancer-specific deaths in male sex ($p < 0.001$) and interstitial pneumonia ($p < 0.001$). Cancer-specific and non-cancer-specific CID classified by sex (**a**, **b**), interstitial pneumonia (**c**, **d**). *CID* cumulative incidence of death

cause of death, cancer patients were nearly 50% more likely to die of non-cancer causes than the general population [26]. In particular, lung cancer patients had a more than fourfold increased risk of dying from non-cancer causes than the general population [26]. Therefore, prognostic factors for non-cancer death should be carefully considered before deciding on surgery or specific treatment approach in elderly lung cancer patients.

When analyzing survival, we should keep in mind whether there is a competing event in the cohort. In general, the Kaplan–Meier method is indicated for calculating survival time for an independent event, i.e., recurrence, death, or a cardiac event. However, if there is a competing relationship with the other events, the result might overestimate the absolute risk of the event of interest [27]. When extending the discussion to missing data bias, if a cohort has 10% or more competing events against the primary event during Cox regression analysis, the results are assumed to be invalid [28]. In our series, therefore, we used Fine and Gray's competing risk regression analysis, which could adjust for and balance the risk of each competing event and determine accurate risk factors and mortality rates [12].

Concerning the prognostic factors, our competing risk analysis revealed that the prognostic factors for non-cancer-specific death were male sex, interstitial pneumonia, CAD, and P-stage, while those of cancer-specific death were limited resection and P-stage. A competing risk analysis excluding the variable of interstitial pneumonia revealed the same tendency compared to the prognostic factors for overall survival of male sex, Glasgow Prognostic Score, Charlson comorbidity index, and P-stage, which we had reported previously (Table 4) [10]. The prognostic factors of non-cancer-specific death became closer to that of overall survival. In the results regarding prognostic factors for non-cancer-specific death, males had

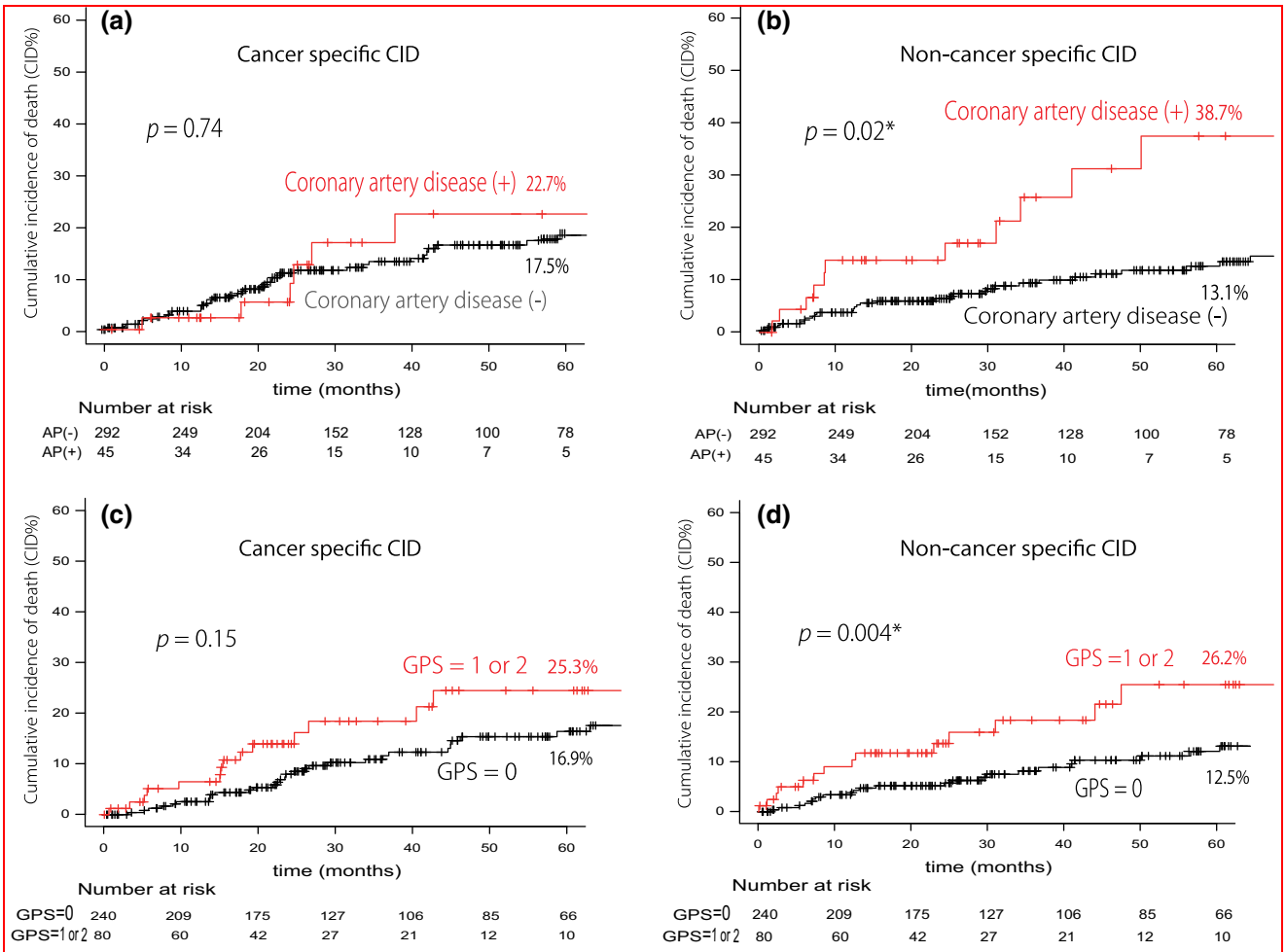

Fig. 3 Cancer-specific and non-cancer-specific CID stratified by coronary artery disease and GPS. Coronary artery disease ($p = 0.02$) and GPS = 1 or 2 ($p = 0.004$) significantly exceeded in the number of non-cancer-specific death than cancer-specific death. Cancer-specific and non-cancer-specific CID classified by coronary artery disease (**a**, **b**) and GPS = 0/1 or 2 (**c**, **d**). *CID* cumulative incidence of death, *GPS* Glasgow Prognostic Score

a threefold increased risk of non-cancer-specific death (Tables 3 and 4). We considered male lung cancer patients who underwent surgery had already exceeded the mean age of Japanese men compared with female patients; therefore, we believe that the threefold increased risk of non-cancer-specific death was an acceptable and reasonable result. Given these results, we should focus on the possibility and risks of non-cancer-specific death after lung cancer surgery, especially in male patients. Considering the relationship of the prognostic factors between cause-specific and overall survival, the considerable rate of non-cancer-specific deaths might influence not only cancer-specific deaths but also overall survival in an elderly cohort. Therefore, our results could help improve the survival of elderly lung cancer patients after undergoing surgery. In this study, P-stage had a significant impact on not only cancer-specific but also non-cancer-specific death. Patients with advanced lung cancer may have a poorer nutritional condition with weight loss and reduced immunity due to cancer metastasis and may be recovering from excessive surgical burden, all of which could contribute to the considerable number of non-cancer-specific deaths [29]. As for postoperative complications, they were not significant prognostic factors for non-cancer-specific death, probably because elderly patients have other preoperative comorbidities including coronary artery disease, interstitial pneumonia, and diabetes mellitus, all of which may have a greater impact on survival than postoperative complications. According to a prior competing risk analysis of lung cancer surgery, the prognostic factors for cancer-specific deaths were identical to those for overall survival [30]. Conversely, however, another similar study showed that the prognostic factors for overall survival had several commonalities with those of cancer-specific and non-

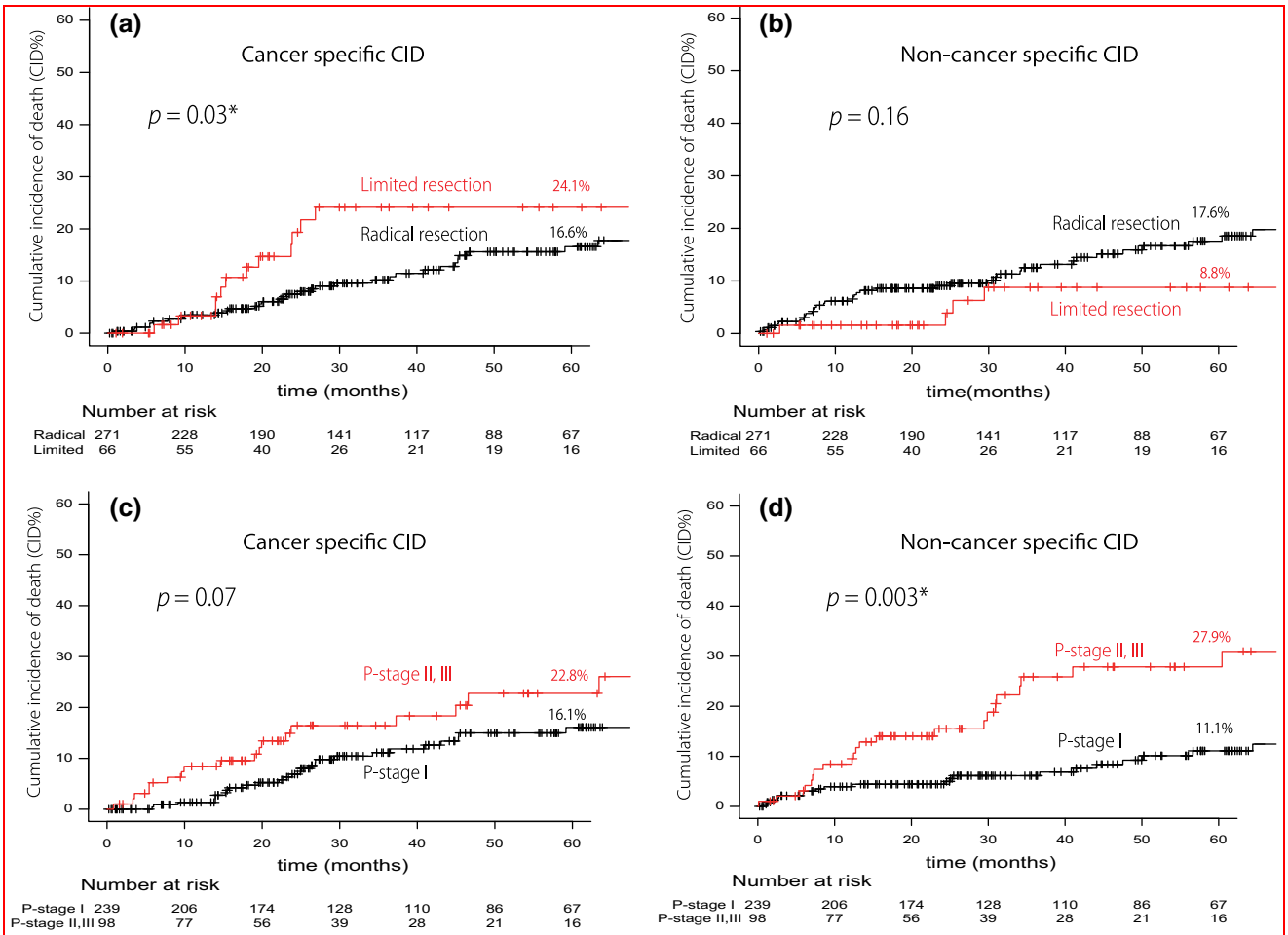

Fig. 4 Cancer-specific and non-cancer-specific CID classified by procedure and P-stage. Limited resection significantly augmented cancer-specific death than non-cancer-specific death ($p = 0.03$) (**a**, **b**). P-stages II and III had an influence on cancer-specific death with a nearly significant difference against P-stage I and significantly impact on non-cancer-specific death compared with P-stage I ($p = 0.07$ and $p = 0.003$, respectively) (**c**, **d**). *CID* cumulative incidence of death, *P-stage* pathological stage

cancer-specific deaths [11]. The differences in these prognostic factors were probably a reflection of the population and cause of death. Therefore, when considering the probability of long-term survival, especially in the elderly lung cancer population, we need to decide on the surgical indication and type of procedure based on the present prognostic factors.

As for the results of the CID curve, the rate of non-cancer-specific deaths exceeded those of cancer-specific death during the first 15 months after surgery, which can be assumed to be a form of "delayed" surgical mortality; however, the latter eventually exceeded the former (Fig. 1). Considering our results and similar prior results, we should pay increased attention to possible causes of non-cancer-specific death during outpatient follow-up, not only in the long-term course but also in the first 15 months after surgery, especially pulmonary events [11].

There are some limitations to this study. There was selection bias due to its retrospective and multi-institutional design. In addition, cognitive function testing and clinical frailty assessment, which are useful indices in the elderly, were not included [9]. However, the information from numerous lung cancer patients older than 80 years who underwent radical surgery was collected, allowing a reasonably robust analysis of the prognostic factors of cause-specific mortality.

In conclusion, we conducted competing risk regression, showing that only P-stage was a common prognostic factor for both cancer-specific and non-cancer-specific deaths. In our cohort, the prognostic factors for non-cancer-specific deaths became closer to those of overall survival due to the population's advanced age. Considering that the CID curves show more non-cancer-specific than cancer-specific death in the first 15 months, clinicians should pay extra attention to non-cancer-specific pathogenesis during this

period. Doing so might contribute to the increased survival of elderly lung cancer patients.

Acknowledgements We are deeply grateful to *Editage* for English proofreading.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ministry of Health, Labour and Welfare. Vital Statistics Japan (2018). http://www.mhlw.go.jp/toukei/list/dl/81-1a2.pdf. Published 28 March 2018, Accessed 22 May 2018
2. Masuda M, Okumura M, Doki Y (2016) Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg 64:665–697
3. Dominguez-Ventura A, Allen MS, Cassivi SD et al (2006) Lung cancer in octogenarians: factors affecting morbidity and mortality after pulmonary resection. Ann Thorac Surg 82:1175–1179
4. Dominguez-Ventura A, Cassivi SD, Allen MS et al (2007) Lung cancer in octogenarians: factors affecting long-term survival following resection. Eur J Cardiothorac Surg 32:370–374
5. Okami J, Higashiyama M, Asamura H et al (2009) Pulmonary resection in patients aged 80 years or over with clinical stage I non-small cell lung cancer: prognostic factors for overall survival and risk factors for postoperative complications. J Thorac Oncol 4:1247–1253
6. Blanchard EM, Arnaoutakis K, Hesketh PJ (2010) Lung cancer in octogenarians. J Thorac Oncol 5:909–916
7. Fanucchi O, Ambrogi MC, Dini P et al (2011) Surgical treatment of non-small cell lung cancer in octogenarians. Interact CardioVasc Thorac Surg 12:749–753
8. Hino H, Murakawa T, Ichinose J et al (2015) Results of lung cancer surgery for octogenarians. Ann Thorac Cardiovasc Surg 21:209–216
9. Saji H, Ueno T, Nakamura H et al (2018) A proposal for a comprehensive risk scoring system for predicting postoperative complications in octogenarian patients with medically operable lung cancer: JACS1303. Eur J Cardiothorac Surg 53:835–841
10. Hino H, Karasaki T, Yoshida Y, Fukami T, Sano A, Tanaka M, Furuhata Y, Ichinose J, Kawashima M, Nakajima J (2018) Risk factors for postoperative complications and long-term survival in lung cancer patients older than 80 years. Eur J Cardiothorac Surg 53:980–986
11. Eguchi T, Bains S, Lee MC et al (2017) Impact of increasing age on cause-specific mortality and morbidity in patients with I non-small-cell lung cancer: a competing risks analysis. J Clin Oncol 35:281–290
12. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496–509
13. Sobin LH, Gospodarowicz MK, Wittekind C (2009) lung and pleural tumours. In: Sobin LH, Gospodarowicz MK, Wittekind C (eds) UICC International Union Against Cancer TNM Classification of malignant tumours, 7th edn. Wiley-Blackwell, Oxford, pp 138–146
14. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (2004) Pathology and genetics of tumours of the lung, pleura, thymus and heart. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. IARC Press, Lyon, pp 9–124
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
16. McMillan DC, Elahi MM, Sattar N, Angerson WJ, Johnstone J, McArdle CS (2001) Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. Nutr Cancer 41:64–69
17. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transpl 48:452–458
18. Scrucca L, Santucci A, Aversa F (2007) Competing risk analysis using R: an easy guide for clinicians. Bone Marrow Transpl 40:381–387
19. Albertsen PC, Hanley JA, Gleason DF, Barry MJ (1998) Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 280:975–980
20. Cai M, Wei J, Zhang Z et al (2012) Impact of age on the cancer-specific survival of patients with localized renal cell carcinoma: martingale residual and competing risks analysis. PLoS ONE 7:e48489
21. Yang L, Shen W, Sakamoto N (2013) Population-based study evaluating and predicting the probability of death resulting from thyroid cancer and other causes among patients with thyroid cancer. J Clin Oncol 31:468–474
22. Shen W, Sakamoto N, Yang L (2015) Cancer-specific mortality and competing mortality in patients with head and neck squamous cell carcinoma: a competing risk analysis. Ann Surg Oncol 22:264–271
23. Ferraz RO, Moreira-Filho DC (2017) Survival analysis of women with breast cancer: competing risk models. Cien Saude Colet 22:3743–3754
24. Bayliss EA, Reifler LM, Zeng C et al (2014) Competing risks of cancer mortality and cardiovascular events in individuals with multimorbidity. J Comorb 4:29–36
25. Austin Peter C, Lee Douglas S, Fine Jason P (2016) Introduction to the analysis of survival data in the presence of competing risks. Circulation 133:601–609
26. Baade PD, Royle JA, Joske DJ, Fritschi L (2011) Non-cancer mortality among people diagnosed with lymphohaematopoietic neoplasm in Australia. Cancer Causes Control 22:715–723
27. Tan KS, Eguchi T, Adusumilli PS (2017) Competing risks and cancer-specific mortality: why it matters. Oncotarget 9:7272–7273
28. Gillings D, Koch G (1991) The application of the principle of intention–to–treat to the analysis of clinical trials. Drug Inf J 25:411–424
29. Kiss Nicole (2016) Nutrition support and dietary interventions for patients with lung cancer: current insights. Lung Cancer (Auckl) 7:1–9
30. Bugge AS, Lund MB, Valberg M et al (2018) Cause-specific death after surgical resection for early-stage non-small-cell lung cancer. Eur J Cardiothorac Surg 53:221–227