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Development and validation of a prognostic model for non-lung cancer death in elderly patients treated with stereotactic body radiotherapy for non-small cell lung cancer

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ABSTRACT

This study sought to develop and validate a prognostic model for non-lung cancer death (NLCD) in elderly patients with non-small cell lung cancer (NSCLC) treated with stereotactic body radiotherapy (SBRT). Patients aged ≥65 diagnosed with NSCLC (Tis-4N0M0), tumor diameter ≤5 cm and SBRT between 1998 and 2015 were retrospectively registered from two independent institutions. One institution was used for model development (arm D, 353 patients) and the other for validation (arm V, 401 patients). To identify risk factors for NLCD, multiple regression analysis on age, sex, performance status (PS), body mass index (BMI), Charlson comorbidity index (CCI), tumor diameter, histology and T-stage was performed on arm D. A score calculated using the regression coefficient was assigned to each factor and three risk groups were defined based on total score. Scores of 1.0 (BMI ≤18.4), 1.5 (age ≥ 5), 1.5 (PS ≥2), 2.5 (CCI 1 or 2) and 3 (CCI ≥3) were assigned, and risk groups were designated as low (total ≤ 3), intermediate (3.5 or 4) and high (≥4.5). The cumulative incidences of NLCD at 5 years in the low, intermediate and high-risk groups were 6.8, 23 and 40% in arm D, and 23, 19 and 44% in arm V, respectively. The AUC index at 5 years was 0.705 (arm D) and 0.632 (arm V). The proposed scoring system showed usefulness in predicting a high risk of NLCD in elderly patients treated with SBRT for NSCLC.

Keywords: non-cancer death; non-small cell lung cancer (NSCLC); stereotactic body radiotherapy (SBRT)

INTRODUCTION

Lung cancer is the leading cause of death from cancer worldwide. For localized lung cancer without regional lymph node metastasis or distant metastasis, the optimal approach for curative intent is either surgery or stereotactic body radiotherapy (SBRT). Surgery is the standard of care for medically operable patients, whereas SBRT is appropriate for medically inoperable patients or those who refuse surgery. Thus, the population treated with SBRT is typically represented by the elderly patients who frequently have comorbidities which might affect their prognosis. In the JCOG 0403 trial assessing the efficacy and safety of SBRT in patients with T1N0M0 non-small cell lung cancer (NSCLC), 55 out of 100 inoperable patients with a median age of 78 years died during the follow-up period (median: 47 months), and 38 (69%) patients died of causes other than lung cancer [1]. Several investigators have performed a comparison between surgery and SBRT [2]. The results have been inconsistent, with some in favor of SBRT and others in favor of surgery. Given that planned phase 3 trials experienced early closure due to poor accrual, retrospective studies with real-world data have become increasingly important for a better evaluation of these two treatment approaches.

Due to technical improvements in SBRT and less invasive surgical approaches, an increasing number of patients are eligible for both SBRT and surgery. Research into early lung cancer has frequently focused on overall survival (OS). OS is the most rigorous endpoint in assessing treatment effectiveness under the conditions which minimize the impact of confounders or selection bias such as randomized control

trials. Conversely, patient background inherently differs in the setting of retrospective studies with real-world data. In the context of the treatment of early lung cancer, several clinical guidelines recommend considering surgery first, followed by other modalities as second-line treatments. Such selection bias can lead to a discrepancy in non-lung cancer death (NLCD) between the treatment modalities. In this situation, OS is not an optimal index to compare treatment effects between the modalities. By considering the NLCD risk, we can characterize the two treatments and compare their effectiveness.

The risk classification of NLCD also provides a helpful perspective in clinical practices. When a patient suffering from a disease with a poor prognosis develops early-stage NSCLC, the predicted risk of NLCD is relatively high compared with that of lung cancer death (LCD). Data on the estimated risk of NLCDs would help patients and clinicians share their thoughts on prognosis after SBRT and develop a consensus on the choice of treatment.

In this study, we sought to establish a model for the prediction of NLCD risk in patients with early or localized NSCLC who are eligible for SBRT. To confirm the predictive performance of the model, we undertook external validation using independent patient data from another institution.

MATERIALS AND METHODS

Source of data and participants

This study was designed as a retrospective cohort study and was approved by the Institutional Review Board of Kyoto University Hospital (approval number, R2140) and Ofuna Chuo Hospital (2019-014). Medical records were reviewed at Kyoto University Hospital and Ofuna Chuo Hospital, both of which function as secondary and tertiary care centers. Data from Kyoto University Hospital was used as the development data set (arm D), while data from Ofuna Chuo Hospital was used as the validation data set (arm V). The accrual period was from January 1998 to December 2015 in arm D and from January 2005 to December 2015 in arm V. The start date of accrual period was decided to be as early as possible for each institution, thus it differed between the two institutions. The end of follow-up was May 2018 in arm D and June 2019 in arm V. The eligibility criteria were as follows: (i) age $\geq$ 65 years, (ii) clinically diagnosed or pathologically proven NSCLC, either primary or postoperative local recurrence, (iii) tumor diameter $\leq$ 50 mm, (iv) SBRT was performed as the definitive treatment for the tumor, and (v) prescribed dose was $\geq$40Gy in 4-10 fractions. If a patient underwent several courses of SBRT for lung cancer during the accrual period, the first course was used for the analysis. Patients who lacked data on pretreatment body mass index (BMI) were excluded from this study. Although biopsy was the preferred method for the diagnosis of lung cancer if it was medically acceptable and approved by the patient, clinical diagnosis of cancer based on the radiologic findings was permitted when biopsy was not applicable.

Treatment

All patients underwent SBRT with multiple X-ray beams, including non-coplanars, using a linear accelerator. The details of procedures in SBRT planning have been described in previous reports, for both arm D [3–6] and arm V [7–9]. In arm D, for peripheral lung tumors, 48 Gy (for tumor diameter $\leq$ 3 cm) or 56 Gy (>3 cm) in four fractions was prescribed to the isocenter until March 2014. A total of 60 Gy in eight fractions was prescribed to the isocenter for tumors adjacent to the mediastinum. The internal target volume (ITV) was contoured through slow-scan CT or four-dimensional CT. A margin of 5 mm was added to ITV for defining planning target volume (PTV). One hundred and ninety-one consecutive patients from 2004 to 2011 had a mean PTV volume of 37.1 cm^3 (range: 6.8-110.2) [5]. Since 2014, 50 Gy in four fractions was prescribed to the 70% isodose line of the maximal dose encompassing the PTV (@70%-isodose PTV) [6], due to a change in institutional protocol. Dose constraint of organs at risk was according to JCOG 0403 study [1]. Beam arrangement typically consisted of seven or eight X-ray beams with 6 MV to encompass the PTV.

In arm V, ITV was defined on slow-scan CT and enlarged by 6-8 mm to create PTV. For dose prescription to peripheral lesions, until 2011, 50 Gy was prescribed in 5 fractions (@80%-isodose PTV) [7, 8]. Since then, we have prescribed 50-60 Gy in five fractions (@60%-isodose PTV). For dose prescription to central lesions, until 2011, 40 Gy was prescribed in five fractions (@80%-isodose PTV). Between 2011 and 2015, the 40 Gy in five fractions (@60%-isodose PTV) was used. Since this time, we have prescribed 60 Gy in 10 fractions (@70%-isodose PTV). Radiotherapy was delivered by multiple dynamic conformal arcs before 2011. Since that time, volumetric-modulated arc therapy was introduced. The data of consecutive 237 patients from 2011 to 2017 shows that the median PTV size was 33.19 cm^3 and lung volume irradiated with $\geq$20Gy was 4.59%. The proportion of lung volume receiving 20 Gy to total lung was constraint to $\leq$15% [9].

A dose fractionation of 40 Gy in five fractions to 80% isodose line corresponds to 50 Gy in five fractions at isocenter, which is an equivalent biological effective dose (BED) of 100 Gy. Thus, all the radiotherapy prescription regimens in this study had the maximum dose with BED $\geq$100 Gy [10].

Outcome definition and assessment

The main outcome measure in the present study was NLCD. NLCD was defined as death from causes other than lung cancer, death from unknown causes without any evidence of lung cancer recurrence, or death from adverse events related to SBRT. When a patient died of a secondary lung cancer, the cause of death was defined as LCD. Information on survival and cause of death was acquired to the greatest extent possible from clinical records of our institutions or reliable information from the cooperating clinics. When they were not available, interviews with patients and/or their family were performed. Survival time was calculated as the period between the first day of SBRT and the date of death. Patients who experienced survival at the end of follow-up or those who were lost to follow-up were included as censored cases. LCD and NLCD were handled as competing risk factors for each other.

Predictive factors

Age, sex, Eastern Cooperative Oncology Group (ECOG)-performance status (PS), BMI, Charlson comorbidity index (CCI), tumor diameter, T stage according to the Union for International Cancer Control (UICC) 8th edition, and histology were evaluated as potential

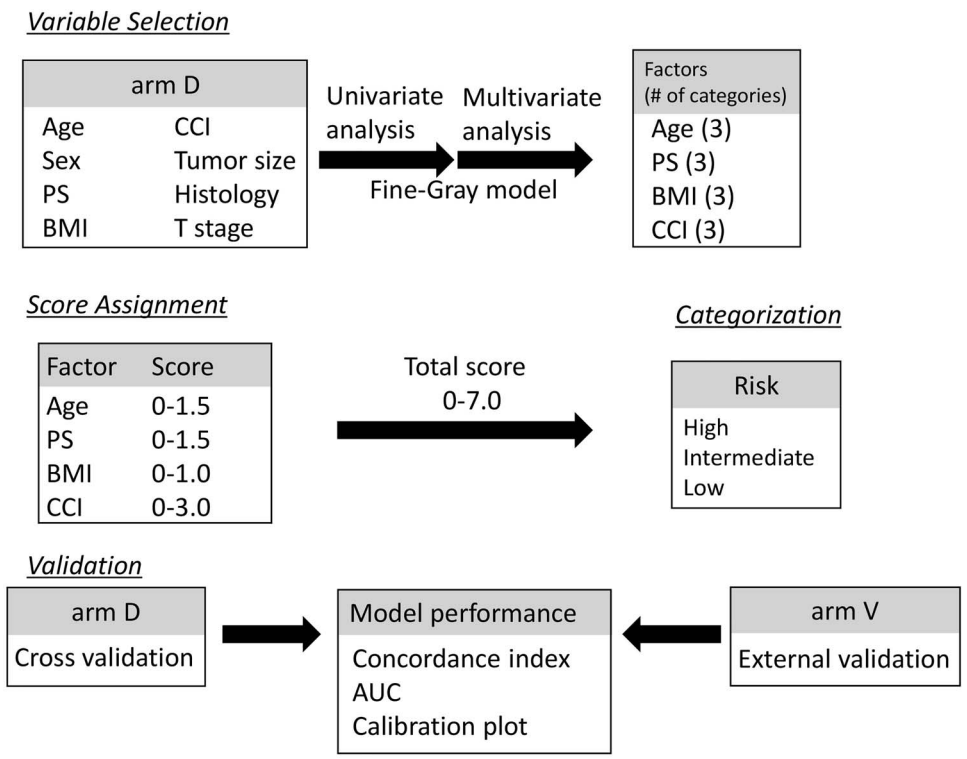

Fig. 1. Overview of model development and validation. PS, performance status; BMI, body mass index; CCI, Charlson comorbidity index; AUC, area under the curve.

prognostic factors for developing the predictive model for NLCD. Age, PS, BMI and CCI were assessed at the time of SBRT initiation. The thresholds in categorizing BMI into three levels were 18.5 and 25.0, according to the WHO definition of overweight and underweight. Tumor diameter and T stage were based on a diagnostic thin slice computed tomography (CT) scan just before the start of SBRT. Tumor diameter was defined as the longest tumor diameter among axial, sagittal and coronal views, including the surrounding ground glass opacity, if present. The sample size was not determined when planning this study.

Statistical analysis

OS was estimated using the Kaplan–Meier method. Age, BMI and CCI were converted to categorical variables. NCLD and LCD were considered as competing risks and the cumulative incidence was evaluated. A univariate analysis was first performed using Gray's test on the eight potential predictive factors described above. Gray's test is used to assess the statistical significance of covariates in a cumulative incidence analysis in the existence of competing events [11]. Then multivariate analysis using the Fine-Gray model was performed to determine the factors to include in the prognostic model using the significant factors in the univariate analysis. Fine-Gray model is a semiparametric proportional hazard model for the cumulative incidence function under the existence of competing risks [12]. The significance level was set to 0.05.

A prognostic model was developed as a scoring system. Scores were assigned to each factor based on a regression coefficient (the β value) which indicates the effect of the factor on the baseline subdistribution hazard function. Acquired β values were multiplied by a certain coefficient so that they were rounded to the nearest integer to determine the scores for the factors. From the sum of scores for all predictive factors, the patients were divided into three different risk groups. The discrimination of the cumulative incidence of NLCD among these three risk groups was estimated using Wolber's concordance index [13] and time-dependent area under the curve (AUC) [14]. Statistical analysis was performed using R software version 3.6.0. The 'crr' function in 'cmprsk' package was used for the regression modeling of subdistribution functions in competing risks.

RESULTS

Overview of the analytical procedure in this study is shown in Fig. 1.

Patients

We identified 353 cases in arm D and 401 cases in arm V who met the eligibility criteria. Patient characteristics in both arms are shown in Table 1. A number of significantly different characteristics between the two institutions were identified. Tumor histology was unproven in 30% of patients in arm D and 50% of patients in arm V. In arm V, the proportion of cases that were T3 or T4 was 7%. Since tumor diameter $\leq$ 50 mm was one of the eligibility criteria, classification as

Table 1. Patient characteristics

		Arm D (N = 353)	Arm V (N = 401)	*p* value
Age	Median (range)	78 (65–93)	79(65-91)	0.12
	65–74	106 (30%)	97 (24%)	
	75–84	200 (56%)	246 (61%)	
	≥85	47 (14%)	59 (15%)	
Sex	Male	259 (73%)	283 (71%)	0.44
	Female	94 (27%)	118 (29%)	
PS	0–1	320 (91%)	364 (91%)	0.94
	2	29 (8%)	34 (8%)	
	≥3	4 (1%)	3 (1%)	
BMI [kg/m^2]	Median (range)	21.4 (13.9–31.1)	21.2 (12.7–37.6)	0.56
	≤18.4	67 (19%)	83 (21%)	
	18.5–24.9	229 (65%)	264 (66%)	
	≥25.0	57 (16%)	54 (13%)	
CCI	median (range)	2 (0–8)	2 (0–10)	0.14
	0	50 (14%)	60 (15%)	
	1–2	197 (56%)	196 (49%)	
	≥3	106 (30%)	145 (36%)	
Tumor diameter [mm]	Median (range)	24 (7–50)	24 (7–50)	0.14
	≤20	144 (41%)	145 (36%)	
	21–30	117 (33%)	154 (38%)	
	≥31	92 (26%)	102 (26%)	
Histology	Ad	128 (36%)	113 (28%)	<0.01
	Sq	93 (26%)	61 (15%)	
	LC	3 (<0.1%)	2 (<0.1%)	
	NS	22 (6%)	24 (6%)	
	UK	107 (30%)	201 (50%)	
T stage	Tis	8 (2%)	25 (6%)	<0.01
	T1	250 (71%)	227 (57%)	
	T2	94 (27%)	120 (30%)	
	T3	0 (0%)	20 (5%)	
	T4	1 (<0.1%)	9 (2%)	

Abbreviations: BMI, body mass index; PS, Eastern Cooperative Oncology Group performance status; CCI, Charlson comorbidity index; Ad, adenocarcinoma; Sq, squamous cell carcinoma; LC, large cell carcinoma; NS, not specified; UK, unknown

T3 or T4 was due to invasion to the adjacent structures (i.e. pleura, mediastinum, vessels, or pulmonary metastasis). The flow diagram of participants through this study, including the number of patients with and without the primary outcome, is shown in Fig. 2. With a median follow-up of 6.5 years (arm D) and 7.3 years (arm V), the OS at 5 years was 45% in arm D and 51% in arm V (p = 0.66). The number (and proportion of all eligible patients) of NLCD was 80 (22%) in arm D and 148 (37%) in arm V. The number of cases with LCD was 120 (34%) in arm D and 87 (22%) in arm V. When focused on the cause of NLCD, both arms (arm D vs arm V) showed a similar distribution: respiratory diseases (32% vs 38%), other malignancies (15% vs 17%), heart failure (11% vs 15%) and stroke (7% vs 4%). No patient in arm D and four patients in arm V died of apparently secondly lung cancer. Respiratory diseases included acute exacerbation of chronic obstructive pulmonary disease (COPD), aspiration pneumonia and Grade 5 radiation pneumonitis (two patients in arm D and two in arm V). One patient died of bleeding as an adverse event of SBRT in arm V. The number of unknown causes of death (as proportion of NLCD) was 13 (16%) patients in arm D and 6 (4%) in arm V.

Model development

The results of univariate and multivariate analyses are shown in Table 2. Univariate analysis of the eight potential risk factors revealed that significant factors for NLCD were age, PS and CCI, with all of these having a p value <0.05. Sex and BMI were of borderline significant, with p values of 0.077 and 0.070, respectively. After multivariate analysis for the three significant and the two borderline significant factors with backward-stepwise variable selection, age, PS, CCI and BMI remained in the model, but sex didn't.

Acquired β values were multiplied by 2. Age ≥75,PS ≥ 2 and BMI <18.5 were given 1.5, 1.5 and 1.0 points, respectively. CCI 1 or 2 were given 2.5 points and CCI ≥3 was given 3.0 points. Categorization of risk group was determined by summation of the scores assigned to these four factors.

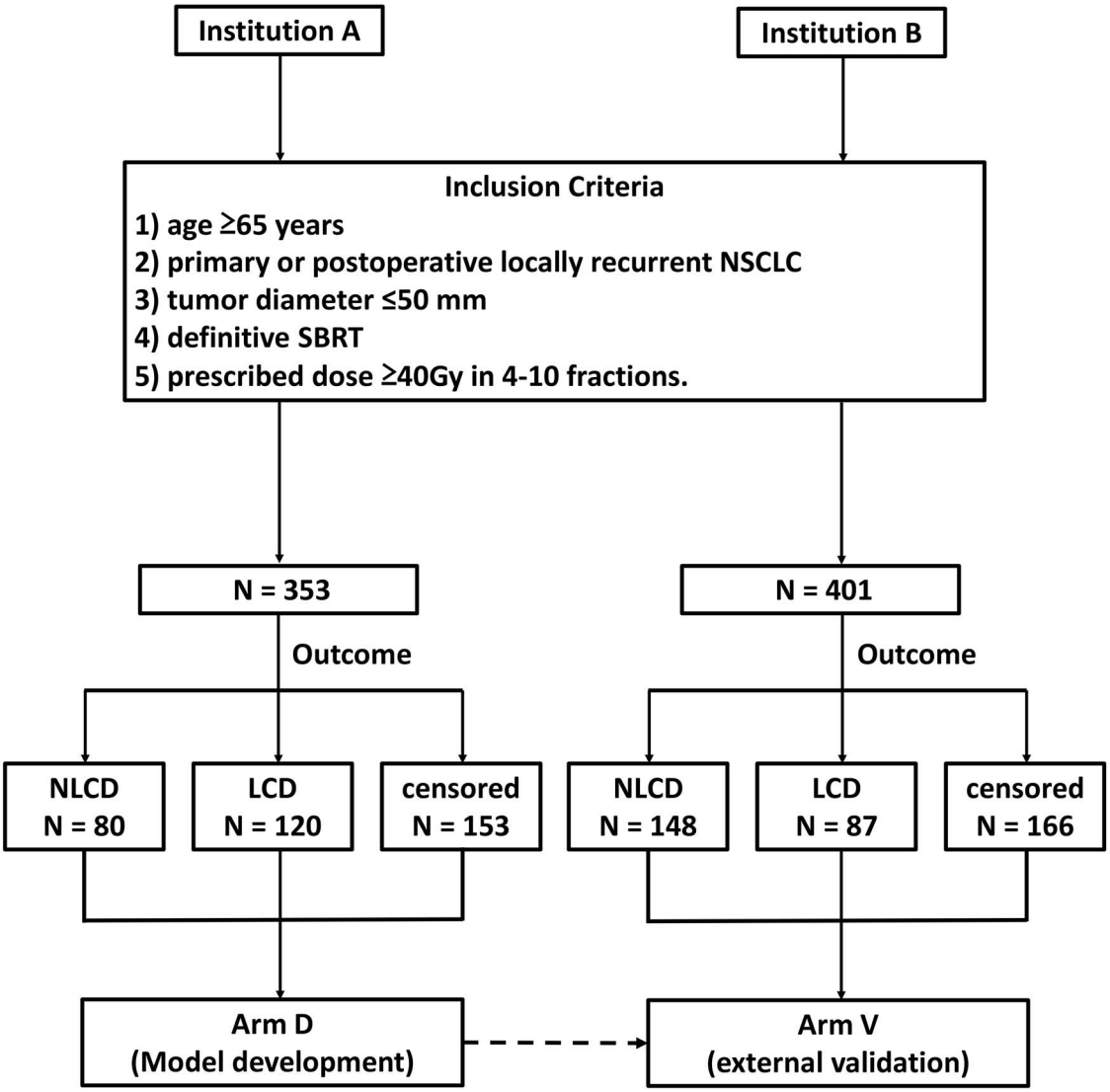

Fig. 2. Flow diagram of the patients included in this study. Institution A is Kyoto University Hospital and Institution B is Ofuna Chuo Hospital. The patients from Institution A are in the arm D, whereas those from Institution B are in the arm V.

The cumulative incidence of NLCD for the whole cohort in arm D was 22.7% at 5 years. So, we aimed to differentiate the patients with higher and lower incidence from those with average incidence. The thresholds were determined to be 3.0 and 4.0 based on tertiles of the total score in arm D. Consequently, three risk groups were defined: low-risk group (LR, total score ≤ 3.0), intermediate-risk group (IR, total score 3.5 or 4.0) and high-risk group (HR, total score ≥ 4.5). The established risk score system is shown in Table 3. The proportion of patients who were categorized as LR, IR and HR was 32, 37 and 31%, respectively, in arm D and 31, 29 and 40%, respectively, in arm V.

Model performance

Fig. 3 shows the cumulative incidence of NLCD and LCD in both arms. In arm D, the cumulative incidence of NCLD at 5 years was 6.8% in the LR group, 23% in the IR group and 40% in the HR group ($p < 0.01$). After confirming that Wolber's concordance index at 1, 3 and 5 years was 0.68, 0.66 and 0.67, respectively, through cross-validation with 1000 bootstrap samples, we performed external validation with arm V. In arm V, the cumulative incidence of NCLD at 5 years was 23% for the LR group, 19% for the IR group and 44% for the HR group. In both arms, the separation between the three groups was significant ($p < 0.01$). Arm D tended to distinguish between the three risk groups 3 years after SBRT, while IR and LR remained similar for at least 5 years in arm V. In both arm D and arm V, the HR group showed clear separation from the other groups and the cumulative incidence was almost equivalent between the two arms. In arm V, Wolber's concordance index at 1, 3 and 5 years was 0.63, 0.62 and 0.61, respectively.

Fig. 4 illustrates the calibration plots and the time-dependent AUC curve for both arms. The calibration plot of arm V indicated lower

Table 2. Result of univariate and multivariate analysis on Fine-Grey model in arm D

		Univariate		Multivariate		
		sHR (95% CI)	*p* value	sHR (95% CI)	coefficient β	*p* value
Age [y]	65–74	1 (ref)	0.049	1 (ref)	0 (ref)	0.011
	75–84	2.01 (1.15–3.52)		2.24 (1.28–3.93)	0.81	
	≥85	1.88 (0.89–3.98)		2.55 (1.19–5.43)	0.93	
Sex	Female	1 (ref)	0.077			
	Male	1.64 (0.95–2.84)				
PS	0	1 (ref)	0.003	1 (ref)	0 (ref)	0.058
	1	1.37 (0.85–2.21)		1.20 (0.74–1.95)	0.18	
	2–3	3.00 (1.59–5.66)		2.26 (1.15–4.42)	0.82	
BMI [kg/m^2]	≤18.4	1.82 (1.09–3.04)	0.070	1.86 (1.12–3.10)	0.62	0.053
	18.5–24.9	1 (ref)		1 (ref)	0 (ref)	
	≥25.0	1.18 (0.65–2.14)		1.10 (0.62–1.96)	0.09	
CCI	0	1 (ref)	0.007	1 (ref)	0 (ref)	0.006
	1–2	4.68 (1.47–14.9)		4.02 (1.27–12.7)	1.39	
	≥3	6.37 (1.96–20.7)		6.02 (1.88–19.3)	1.80	
Tumor diameter [mm]	≤20	1 (ref)	0.928			
	21–30	0.93 (0.57–1.53)				
	31–50	0.90 (0.51–1.59)				
Histology	Ad	1 (ref)	0.870			
	Sq	1.24 (0.72–2.12)				
	Lc	1.47 (0.26–8.58)				
	NS	0.75 (0.26–2.19)				
	UN	1.11 (0.64–1.93)				
T stage	Tis	1 (ref)	0.577			
	T1	1.66 (0.28–9.83)				
	T2	0.49 (0.31–11.34)				
	T4	NA				

Coefficient β was used in deciding score assigned to each factor
Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; PS, Eastern Cooperative Oncology Group performance status; sHR = subdistribution hazard ratio; Ad, adenocarcinoma; Sq, squamous cell carcinoma; LC, large cell carcinoma; NS, not specified; UK, unknown; NA, not available
sHR for T4 in univariate analysis was not available because the only one patient didn't have the event as non-lung cancer death.

observed frequencies of IR than the estimated probabilities. There was also an inversion in observed frequencies between LR and IR at 1 and 5 years. When looking at time-dependent AUC curve, the AUC of arm D reached nearly 0.7 to 0.8 at 3 to 5 years. In arm V, the AUC was lower than 0.6 within 6 months following SBRT, after which it remained 0.6 to 0.7.

In contrast, the difference in cumulative incidence of LCD at 5 years among the three risk groups was not significant in either arm. It was 29.0 in the LR group, 38.0 in the IR group and 27.5% in the HR group in arm D and 17.4 in the LR group, 20.4 in the IR group and 18.7% in the HR group for arm V ($p = 0.835$).

DISCUSSION

In this study, we demonstrated that age, PS, BMI and CCI were effective predictors of NLCD in patients with NSCLC treated with SBRT. To the best of our knowledge, this study is the first to propose a scoring system for predicting the risk of NLCD in elderly NSCLC patients. One of the strengths of our study is the existence of external validation in over 400 cases.

The scoring system proposed here is useful in several ways. It provides helpful information for the selection of treatment. Shared decision-making is crucial for patient satisfaction. According to a report by Mokhles *et al.*, in choosing between surgery or SBRT for early-stage NSCLC, approximately 20% of patients lacked knowledge on the advantages and disadvantages of each treatment, and a minority of patients received information on prognosis from their physicians [15]. If information on the predicted risk of NLCD is available in addition to information on expected cancer-specific survival and treatment-related toxicities, patients can refer to their own values, leading to fewer conflicts over decision-making.

Furthermore, our results can potentially be applied to future studies investigating the comparison between surgery and SBRT. Recently, SBRT has been compared with surgery in the setting of propensity

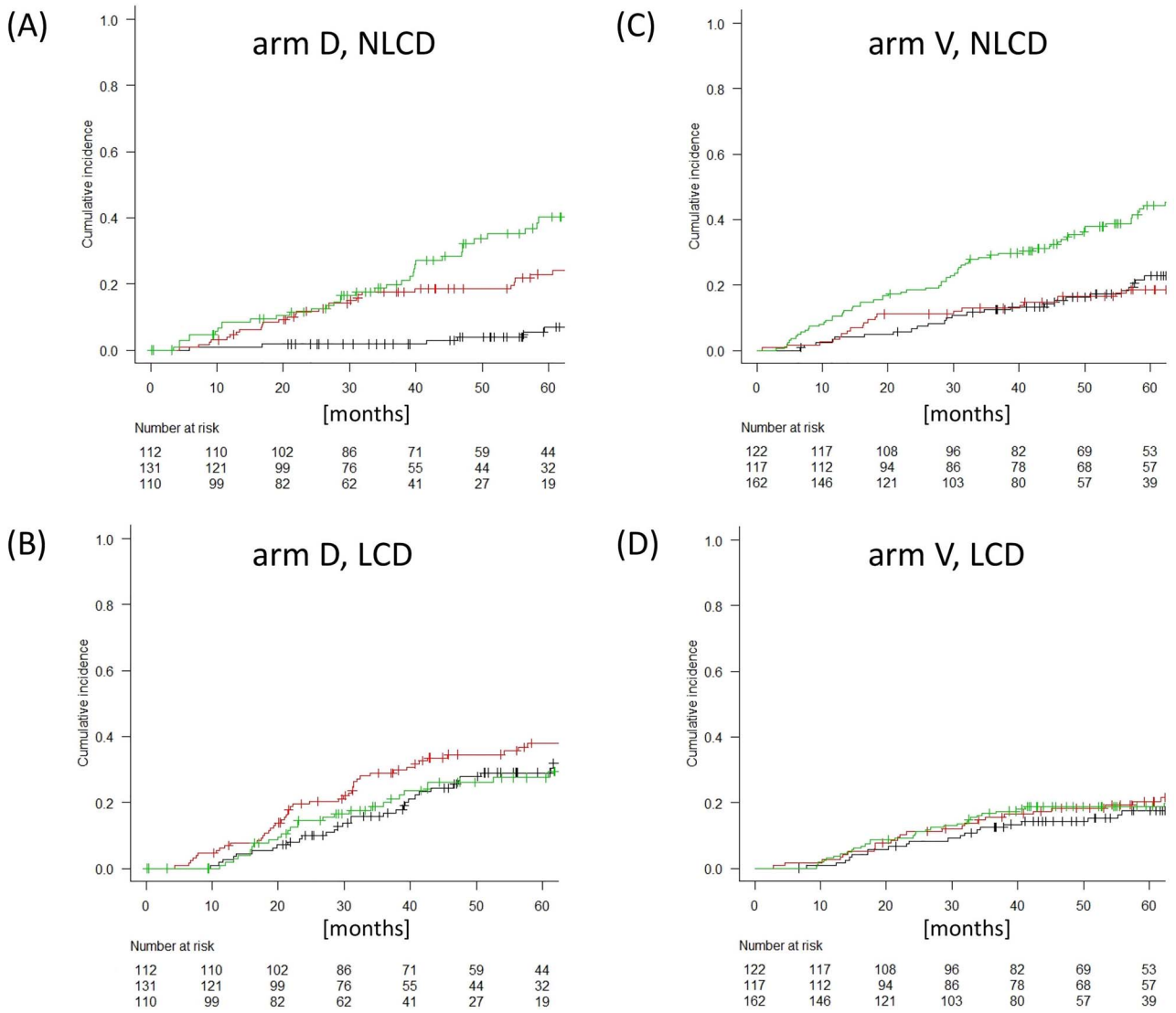

Fig. 3. Cumulative incidence of non-lung cancer death (NLCD) and non-lung cancer death (LCD) in both arms: (A) NLCD in arm D, (B) LCD in arm D, (C) NLCD in arm V, and (D) LCD in arm V. Green, red, and black lines indicate high-, intermediate-, and low-risk groups, respectively.

score matching or adjustment [16–20]. Factors that have been shown in this study to be significant are good candidates for creating propensity scores in such studies. CCI, first introduced by Charlson *et al.* in 1987 [21], includes factors such as age, myocardial infarction, chronic heart failure, peripheral vascular disease, cerebrovascular accident, dementia, COPD, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia, chronic kidney disease, history of solid tumor, leukemia/lymphoma and AIDS. CCI is also used in the description of comorbidities in malignancies [22] and has been analyzed as a prognostic factor after treatment. Since age was identified as an independent risk factor while validating CCI, age-adjusted CCI (aCCI) was proposed [23]. Despite its utility, CCI or aCCI has some disadvantages. It includes a limited number of comorbidities and ignores many important diseases that might affect patient life expectancy. Furthermore, CCI and aCCI are insufficient to quantify the severity of each comorbidity.

Studies have previously assessed the association between survival outcome and frailty or co-morbidity in the setting of SBRT for early-stage NSCLC [9, 24–26]. In this study, we used CCI rather than aCCI, to score comorbidities because age was independently investigated as a potential predictor. In our predictive model, CCI was a strong predictor for NLCD, with a higher score than those obtained for other factors. Previous studies reported that aCCI >5 was a significant predictor of OS after SBRT for early-stage NSCLC [9, 24].

Analysis that considers the existence of competing risks has emerged as a useful method to discuss cause-specific survival [27]. Eguchi *et al.* conducted the largest study, to our knowledge, which employed the SEER database and investigated cause-specific mortality

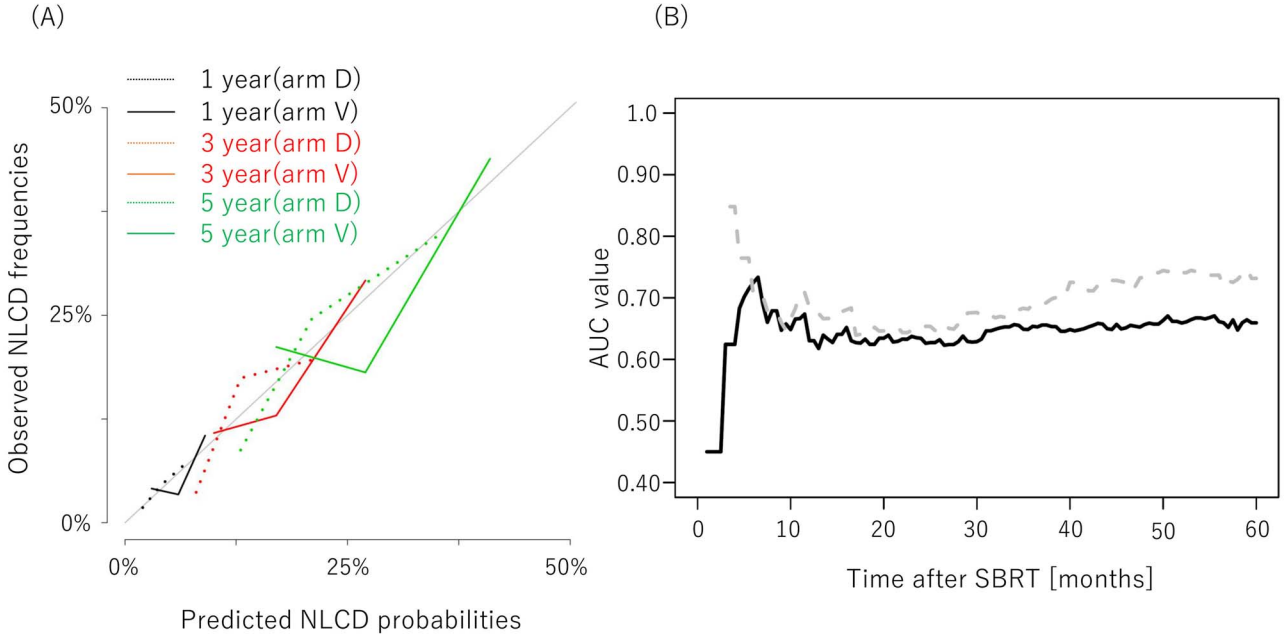

Fig. 4. Estimation of model performance. (A) calibration plot at 1 (black), 3 (red) and 5 (green) years in arm D (dotted) and V (solid). (B) time dependent AUC in the prediction of NLCD in arm D (dotted gray) and V (solid black).

Table 3. Risk scoring system of non-lung cancer death

Factor	Category	Score
Age	65–74	0
	75–84	1.5
	≥ 85	1.5
PS	0	0
	1	0
	2–3	1.5
BMI	≤18.4	1.0
	18.5–24.9	0
	≥25.0	0
CCI	0	0
	1–2	2.5
	≥3	3.0
Risk of non-lung cancer death	**Total score**	
Low	≤ 3.0	
Intermediates	3.5–4.0	
High	≥ 4.5	

The scoring system consists of four factors: age, performance status (PS), body mass index (BMI) and Charlson comorbidity index (CCI). The three risk groups are defined according to the sum of the scores.

in patients who underwent surgery for stage I NSCLC. Their results showed that age, sex, history of cardiovascular disease, diffusing capacity of the lung for carbon monoxide (DLCO) and surgical procedure (sublober lung resection [SLR] vs lobectomy) were significant predictive factors for NLCD. They further reported that the risk of NLCD was higher in the SLR group, a finding which they discussed because of the selection bias for SLR, which was applied to those who had lower pulmonary function tests and higher comorbidity status. In addition, in the subset of patients who underwent SLR, age was a prognostic factor for NLCD [28].

Interpretation of the present study requires some explanations. First, it is a valuable result that high-risk patients for NLCD could be well discriminated from others. For both arm D and arm V, cumulative incidence of NLCD reached nearly 40% at 5 years. The calibration plot supports the speculation that this prediction model fitted to arm V especially in high-risk patients. Secondly, the discrimination of low- and intermediate-risk groups was not satisfactory in arm V, reflecting the insufficient fitting ability of this model in these groups. A supplemental investigation was performed to search significant factors in predicting NLCD in arm V. Sex was a strong predictor of NLCD unlike in arm D. So modified model was experimented for improving the model performance by including sex as a factor. The model performance went worse in arm D. As an inherent trait of validation studies, the AUC of the established model usually lower in the validation arm [29].

Another limitation in this study is that respiratory function before SBRT was not included among the potential risk factors due to the lack of data in arm D. Previous studies have shown that postoperative pulmonary function was strongly associated with preoperative pulmonary function and affected the survival outcome [28].

In conclusion, we developed a risk scoring system that predicts NLCD in elderly NSCLC patients and validated this model in a large cohort. Although discrimination of intermediate- and low-risk patients was poor in the validation arm, the established model might help to predict high-risk patients for NLCD. It may prove to be useful for the purpose of shared decision-making with patients who are not eligible

for standard lobar resection. Further studies including additional clinical variables, such as pulmonary function, are warranted to improve this model.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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PRESENTATION AT A CONFERENCE

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