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Clinical Research

Prognostic Impact of Postoperative Complications in High-Risk Operable Non-small Cell Lung Cancer

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Background: Patients with high-risk (HR) operable non-small cell lung cancer (NSCLC) may have unique prognostic factors. This study aimed to evaluate surgical outcomes in HR patients and to investigate prognostic factors in HR patients versus standard-risk (SR) patients.
Methods: In total, 471 consecutive patients who underwent curative lung resection for NSCLC between January 2012 and December 2017 were identified and reviewed retrospectively. Patients were classified into HR (n=77) and SR (n=394) groups according to the American College of Surgeons Oncology Group criteria (Z4099 trial). Postoperative complications were defined as those of grade 2 or higher by the Clavien-Dindo classification.
Results: The HR group comprised more men and older patients, had poorer lung function, and had more comorbidities than the SR group. The patients in the HR group also experienced more postoperative complications ($p \leq 0.001$). More HR patients died without disease recurrence. The postoperative complication rate was the only significant prognostic factor in multivariable Cox regression analysis for HR patients but not SR patients. HR patients without postoperative complications had a survival rate similar to that of SR patients.
Conclusion: The overall postoperative survival of HR patients with NSCLC was more strongly affected by postoperative complications than by any other prognostic factor. Care should be taken to minimize postoperative complications, especially in HR patients.

Keywords: Lung neoplasms, Non-small-cell lung carcinoma, Postoperative care, Prognosis, Surgery

Introduction

Lung cancer is the leading cause of cancer-related death in Korea and worldwide [1,2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers [3]. Surgery is the mainstay of treatment for early-stage NSCLC, and lobectomy has been accepted as the standard treatment. Sublobar resection, such as segmentectomy or wedge resection, is recommended in selected patients with poor pulmonary reserve or other major comorbidities and in those with smaller tumors [4].

The pathologic tumor-node-metastasis (TNM) stage is known to be the most important prognostic factor for surgically treated patients with NSCLC [5]. However, patient comorbidities are also important prognostic factors for survival [6-8]. Age and smoking are strongly associated with comorbidities such as chronic obstructive pulmonary disease and cardiovascular disease, which commonly coexist with NSCLC [9]. These comorbidities may have independent negative impacts on survival, and they also influence the outcomes of NSCLC treatment such as surgery or adjuvant therapy. Therefore, the presence of several comorbidities may have a greater impact than the cancer stage on the prognosis of high-risk (HR) patients with NSCLC.

Because cardiopulmonary assessments such as pulmonary function tests or exercise tests, are closely related to postoperative outcomes, these evaluations are essential in selecting appropriate treatments for HR patients with early-stage NSCLC [10]. Although algorithms exist for determining the risk associated with lung resection, the identification of patients for whom lobectomy poses a HR is complicated and remains a clinical decision [10,11]. Due to advances in surgical and anesthetic techniques, such as minimally invasive techniques, lobectomy may be performed safely with acceptable outcomes in some HR patients [12]. This study aimed to investigate the surgical outcomes of HR patients who underwent surgical treatment for NSCLC and to identify prognostic factors in these patients.

High-risk criteria	Standard-risk criteria
• Meet ≥1 major criteria - FEV1 ≤50% predicted - DLCO ≤50% predicted • Meets ≥2 minor criteria - Age ≥75 yr - FEV1 51%–60% predicted - DLCO 51%–60% predicted - RVSP ≥40 mm Hg - LVEF ≤40% - Exercise SpO_2 ≤88%	• No major criteria met • Meet ≤1 minor criteria

Fig. 1. Schema of high-risk criteria from the American College of Surgeons Oncology Group (ACOSOG) Z4099 trial. FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monxide; RVSP, right ventricular systolic pressure; LVEF, left ventricular ejection fraction; SpO_2, oxygen saturation.

Methods

Patients

This retrospective study was approved by the Institutional Review Board of Ajou University School of Medicine (approval no., AJIRB-MED-MDB-21-216), and the need for informed consent was waived. By reviewing electronic medical records, we identified patients with NSCLC who underwent curative lung resection between January 2012 and December 2017. Patients who had a history of lung

Table 1. Baseline characteristics

Characteristic	Total (n=471)	HR (n=77)	SR (n=394)	p-value
Age (yr)	64.09±9.9	72.6±7.0	62.4±9.6	<0.001
Sex				0.001
Male	304 (64.5)	63 (81.8)	241 (61.2)	
Female	167 (35.5)	14 (18.2)	153 (38.8)	
Smoking				0.017
Nonsmoker	252 (53.5)	31 (40.3)	221 (56.1)	
Ex-smoker	131 (27.8)	31 (40.3)	100 (25.4)	
Current smoker	88 (18.6)	15 (19.5)	73 (18.5)	
Age-adjusted CCI	3.0 (2.0–4.0)	4.0 (2.0–7.0)	3.0 (0.0–5.0)	<0.001
FEV1 (% predicted)	91.51±16.9	80.2±20.2	93.8±15.2	<0.001
DLCO (% predicted)	74.85±21.0	47.7±12.8	80.4±17.8	<0.001
Approach				0.073
VATS	305 (64.7)	43 (55.8)	262 (66.5)	
Thoracotomy	166 (35.3)	34 (44.2)	132 (33.5)	
Operation				0.089
Sublobar resection	61 (12.9)	15 (19.5)	46 (11.7)	
Lobectomy	379 (80.5)	55 (71.4)	324 (82.2)	
Extended resection	31 (6.6)	7 (9.1)	24 (6.1)	
Pathology				<0.001
SqCC	132 (28.1)	42 (54.5)	90 (22.8)	
Adenocarcinoma	314 (66.6)	32 (41.6)	282 (71.6)	
Other NSCLC	25 (5.3)	3 (3.9)	22 (5.6)	
Pathologic stage				0.470
I	298 (63.2)	44 (57.1)	254 (64.5)	
II	91 (19.3)	17 (22.1)	74 (18.8)	
III	82 (16.1)	16 (20.8)	66 (16.8)	
Adjuvant treatment	137 (49.4)	14 (18.2)	123 (31.2)	0.030

Values are presented as mean±standard deviation, number (%), or median (interquartile range), unless otherwise stated.
HR, high-risk patient; SR, standard-risk patient; CCI, Charlson comorbidity index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monoxide; VATS, video-assisted thoracoscopic surgery; SqCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer.

cancer or previously received neoadjuvant treatment were excluded. We identified 471 patients who met the inclusion criteria, and classified them into HR (n=77) and standard-risk (SR) groups (n=394) according to the American College of Surgeons Oncology Group (ACOSOG) criteria (Z4099 trial) (Fig. 1) [13]. The ACOSOG Z4099 trial was a

Table 2. Postoperative morbidity and mortality

Variable	Total (n=471)	HR (n=77)	SR (n=394)	p-value
Any complication	123 (26.1)	39 (50.6)	84 (21.3)	<0.001
Pulmonary complication	104 (22.1)	37 (48.1)	67 (17.0)	<0.001
Pneumonia	49 (10.4)	24 (31.2)	25 (6.3)	<0.001
Prolonged air leakage	54 (11.5)	14 (18.2)	40 (10.2)	0.039
Pleural effusion	5 (1.1)	3 (3.9)	2 (0.5)	0.033
Bleeding	8 (1.7)	2 (2.6)	6 (1.5)	0.853
Chylothorax	3 (0.8)	0	3 (0.8)	1.000
Arrhythmia	13 (2.7)	3 (3.9)	10 (2.5)	0.776
Cerebrovascular accident	2 (0.5)	0	2 (0.5)	1.000
Hospital stay (day)	10.4±10.5	16.4±16.6	9.2±8.4	<0.001
30-day mortality	8 (1.6)	3 (3.9)	5 (1.3)	<0.001
90-day mortality	16 (3.3)	8 (10.4)	8 (2.1)	<0.001

Values are presented as number (%) or mean±standard deviation.
HR, high-risk patient; SR, standard-risk patient.

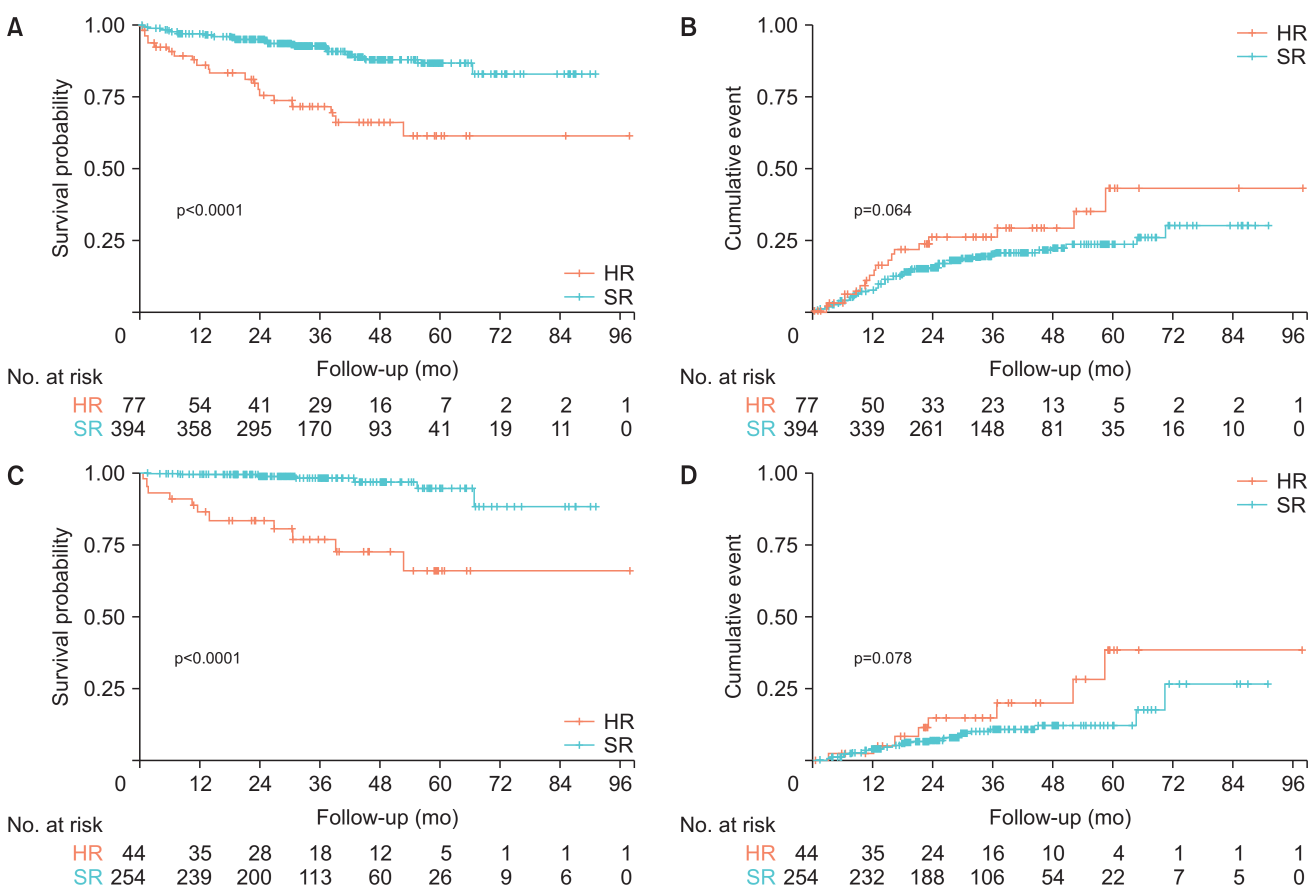

Fig. 2. Comparison of overall survival and cumulative incidence of recurrence. (A) Overall survival in all patients by risk. (B) Cumulative incidence of recurrence in all patients by risk. Overall survival of (C) stage 1 lung cancer patients, (E) stage 2 lung cancer patients, and (G) stage 3 lung cancer patients. Cumulative incidence of recurrence in (D) stage 1 lung cancer patients, (F) stage 2 lung cancer patients, and (H) stage 3 lung cancer patients. HR, high-risk; SR, standard-risk. (Continued on next page).

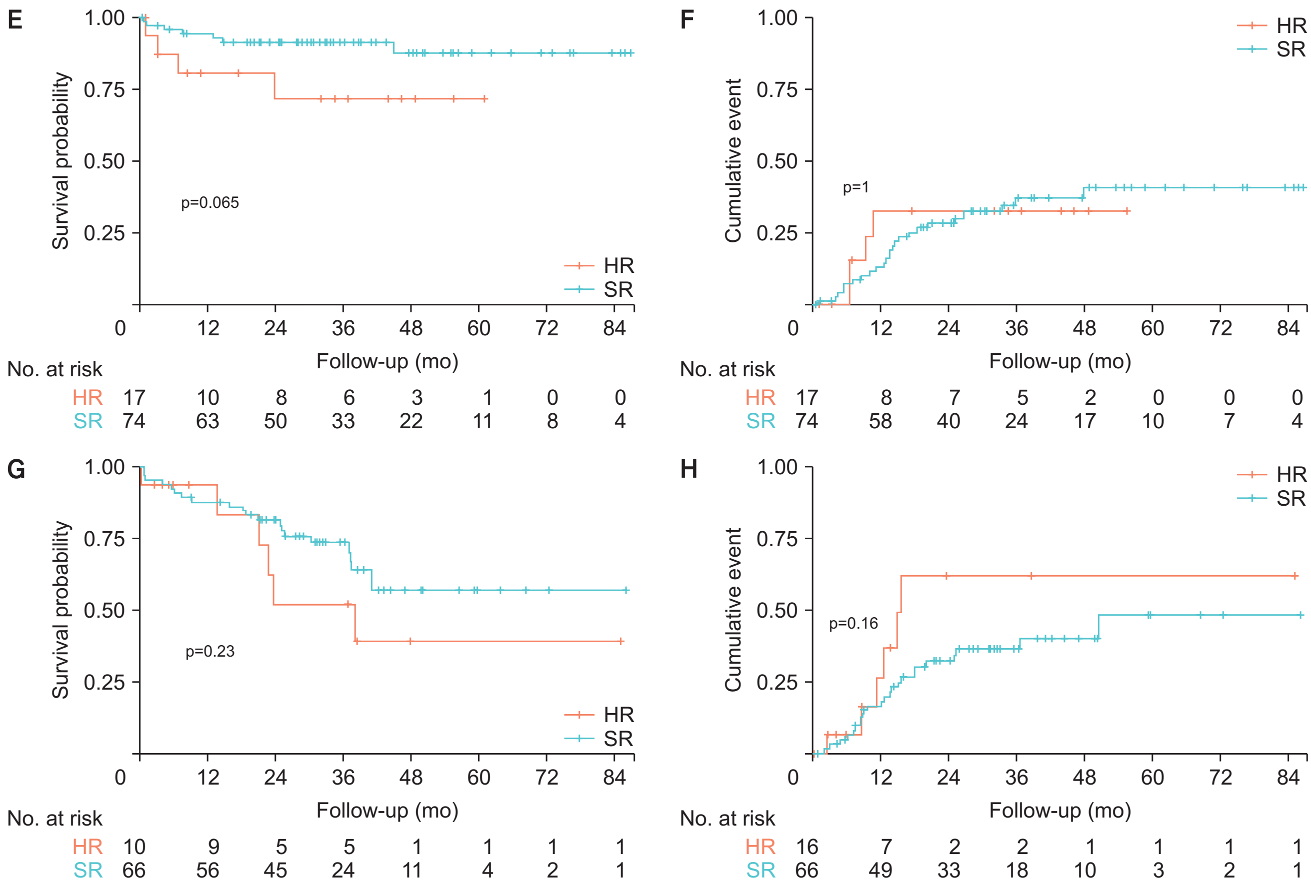

Fig. 2. (Continued; caption shown on previous page).

randomized study of sublobar resection versus stereotactic body radiation therapy (SBRT) for HR stage I NSCLC. Patients were categorized as HR when they met more than 1 major enrollment criterion (preoperative forced expiratory volume in 1 second [FEV1] or diffusing capacity for carbon monoxide [DLCO] <50% of the predicted value) or 2 minor criteria (age, ≥75 years; pulmonary hypertension, ejection fraction ≤40%; or exercise partial pressure of oxygen ≤55 mm Hg or oxygen saturation ≤88%).

Data collection

Patients' demographic and clinical characteristics included age, sex, smoking status, age-adjusted Charlson comorbidity index (CCI) [14], pulmonary function, echocardiography findings, tumor histology, pathological stage, type of surgery, and history of adjuvant therapy. Pathological staging was determined using the eighth edition of the TNM classification [15]. The extent of surgery was classified as sublobar resection, lobectomy, or extended resection, which included bilobectomy and pneumonectomy. Postoperative complications (PCs) were defined as those of grade 2 or higher, according to the Clavien-Dindo classification, that occurred during hospitalization or readmission up to and including 30 days postoperatively [16].

Statistical analyses

Continuous variables were compared using the Student t-test or the Mann-Whitney U-test. Categorical variables were compared using the chi-square test or the Fisher exact test. Survival and cumulative incidence of recurrence by risk group were analyzed using Kaplan-Meier curves, and comparisons were made using the log-rank test. Univariable and multivariable analyses were conducted using a Cox proportional hazards regression model to identify prognostic factors that may affect survival. Risk factors for PCs were analyzed using binary logistic regression. Variables with a p-value ≤0.1 were included in the multivariable analyses. A p-value ≤0.05 was considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA)

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and R ver. 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

Results

Baseline characteristics

The baseline characteristics of the 471 patients included in the study are described in Table 1. The mean±standard deviation age of patients was 64.09±9.9 years, and 304 (64.5%) were men. The HR group was older, had a higher proportion of men, had more patients with a history of smoking, had higher CCI scores, and had lower FEV1 and DLCO than the SR group. Adenocarcinoma was the most common overall histological type in all study patients; however, squamous cell carcinoma (SqCC) was the predominant histology observed in the HR group. The HR group underwent more thoracotomies and sublobar resections, but without statistically significant differences from the SR group. Although there was no significant difference in pathologic stage between the groups, fewer adjuvant treatments were performed in the HR group.

Postoperative morbidity and mortality

A higher proportion of patients experienced PCs in the HR group than in the SR group (HR group, 50.6% versus SR group, 21.3%). Pneumonia was the most frequent complication in HR patients, and its incidence was significantly higher than that in SR patients (p<0.001). In contrast, persistent air leakage was the most common complication in SR patients. Hospital stays were significantly longer in the HR group than in the SR group (p<0.001). The 30- and 90-day mortality rates were higher in the HR group than in the SR group (p<0.001) (Table 2).

Comparison of overall survival and cumulative incidence of recurrence

The overall survival of HR patients was significantly

Table 3. Prognostic factors for overall survival using a Cox regression model in all patients

Variable	Univariable		Multivariable	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (yr)	1.040 (1.011–1.071)	0.008	0.982 (0.942–1.025)	0.408
Female (vs. male)	0.359 (0.181–0.712)	0.003	0.718 (0.347–1.484)	0.371
Smoking				
Nonsmoker	1		-	
Ex-smoker	1.401 (0.768–2.556)	0.272	-	
Current smoker	1.484 (0.748–2.943)	0.259	-	
FEV1 (% predicted)	0.973 (0.959–0.988)	<0.001	-	
DLCO (% predicted)	0.958 (0.944–0.973)	<0.001	0.970 (0.946–0.994)	0.015
Age-adjusted CCI	1.201 (1.035–1.394)	0.016	1.131 (0.900–1.421)	0.289
VATS (vs. open)	0.406 (0.237–0.696)	0.001	0.824 (0.455–1.492)	0.523
Operation				
Sublobar resection	1		1	
Lobectomy	0.977 (0.419–2.330)	0.977	0.485 (0.191–1.232)	0.128
Extended resection	0.017 (1.250–9.491)	0.017	0.836 (0.258–2.715)	0.766
Histology				
SqCC	1		1	
Adenocarcinoma	0.252 (0.146–0.434)	<0.001	0.686 (0.349–1.348)	0.274
Other NSCLC	0.256 (0.061–1.068)	0.062	0.616 (0.134–2.836)	0.534
Pathologic stage				
I	1		1	
II	2.110 (0.996–4.471)	0.051	1.589 (0.704–3.586)	0.265
III	6.401 (3.524–11.630)	<0.001	7.956 (3.528–17.940)	<0.001
Postoperative complication	3.776 (2.232–6.386)	<0.001	3.090 (1.733–5.509)	<0.001
HR (vs. SR)	0.274 (0.160–0.472)	<0.001	1.112 (0.484–2.553)	0.803
Adjuvant treatment	1.675 (0.978–2.868)	0.060	0.595 (0.283–1.250)	0.171

CI, confidence interval; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monoxide; CCI, Charlson comorbidity index; VATS, video-assisted thoracoscopic surgery; SqCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; HR, high-risk patient; SR, standard-risk patient.

worse than that of SR patients (p≤0.001). Three- and 5-year survival rates of SR patients were 92.5% and 86.3%, respectively, and those of HR patients were 71.8% and 61.4%, respectively (Fig. 2A). HR patients seemed to have a higher recurrence; however, the difference was not statistically significant (p=0.064) (Fig. 2B).

Prognostic factors for overall survival using a Cox regression model

Prognostic factors for overall survival were investigated using Cox regression analysis in the entire cohort (Table 3). In the univariable analysis, age, sex, FEV1, DLCO, CCI, surgical technique, operation extent, tumor histology and pathologic stage, PCs, risk group, and history of adjuvant treatment were significantly associated with overall survival. Variables with p-values <0.1 were included in the multivariable analysis to exclude confounding factors. Since FEV1 and DLCO were strongly correlated (Pearson correlation coefficient of 0.396; p≤0.001), only DLCO was included in the multivariate analysis. DLCO, pathologic stage, and PCs were revealed as independent significant prognostic factors for overall survival (Table 3). We also performed subgroup analyses in the HR and SR groups. Pathologic stage was a significant prognostic factor in SR patients (Table 4), while PCs were a significant prognostic factor in HR patients (Table 5).

Overall survival and cumulative incidence of recurrence in accordance with risk group and postoperative complication

Patients with PCs had significantly poorer overall long-term survival than those without PCs in both groups (SR, p=0.018; HR, p=0.001). HR patients without complications showed comparable survival to SR patients with or without complications (p=0.502 and p=0.458, respectively). However, HR patients with complications had significantly poorer survival than SR patients with or without complications (p≤0.001) (Fig. 3A). HR patients without PCs had a higher recurrence rate than SR patients without PCs (p=0.014). However, there were no significant differences

Table 4. Prognostic factors for overall survival using a Cox regression model in standard-risk patients

Variable	Univariable		Multivariable	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (yr)	1.037 (0.999–1.077)	0.058	1.007 (0.962–1.054)	0.765
Female (vs. male)	0.517 (0.242–1.104)	0.088	0.874 (0.397–2.096)	0.749
Smoking				
Nonsmoker	1		-	
Ex-smoker	0.460 (0.208–1.015)	0.055	-	
Current smoker	0.595 (0.241–1.466)	0.259	-	
FEV1 (% predicted)	0.968 (0.946–0.990)	0.005	-	
DLCO (% predicted)	0.961 (0.938–0.984)	0.001	0.974 (0.947–1.002)	0.064
Age-adjusted CCI	1.204 (0.990–1.465)	0.063		
VATS (vs. open)	0.253 (0.123–0.519)	<0.001	0.557 (0.241–1.286)	0.171
Operation				
Sublobar resection	1		1	
Lobectomy	1.654 (0.392–6.983)	0.494	0.598 (0.130–2.760)	0.510
Extended resection	8.642 (1.830–40.803)	0.006	0.982 (0.164–5.876)	0.985
Pathology				
SqCC	1		1	
Adenocarcinoma	0.193 (0.097–0.382)	<0.001	0.539 (0.222–1.308)	0.172
Other NSCLC	0.149 (0.020–1.114)	0.064	0.349 (0.043–2.817)	0.323
Pathologic stage				
I	1		1	
II	3.438 (1.204–9.820)	0.021	2.205 (0.669–7.268)	0.194
III	12.916 (5.488–30.398)	<0.001	13.986 (4.293–45.568)	<0.001
Postoperative complication	2.337 (1.177–4.641)	0.015	1.695 (0.784–3.665)	0.180
Adjuvant treatment	2.265 (1.166–4.403)	0.016	0.516 (0.203–1.312)	0.165

CI, confidence interval; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monoxide; CCI, Charlson comorbidity index; VATS, video-assisted thoracoscopic surgery; SqCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer.

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Table 5. Prognostic factors for overall survival using a Cox regression model in high-risk patients

Variable	Univariable		Multivariable	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (yr)	0.958 (0.906–1.013)	0.130		
Female (vs. male)	0.171 (0.023–1.284)	0.086	0.280 (0.036–2.168)	0.223
Smoking				
Nonsmoker	1		-	
Ex-smoker	0.885 (0.359–2.182)	0.791	-	
Current smoker	0.429 (0.094–1.958)	0.274	-	
FEV1 (% predicted)	0.997 (0.977–1.017)	0.735	-	
DLCO (% predicted)	0.954 (0.907–1.003)	0.065	0.969 (0.919–1.021)	0.242
Age-adjusted CCI	0.891 (0.665–1.194)	0.440	-	
VATS (vs. open)	1.166 (0.489–2.780)	0.728	-	
Operation				
Sublobar resection	1		-	
Lobectomy	0.981 (0.326–2.959)	0.974	-	
Extended resection	0.917 (0.168–5.020)	0.921	-	
Pathology				
SqCC	1		-	
Adenocarcinoma	0.867 (0.354–2.123)	0.755	-	
Other NSCLC	1.233 (0.159–9.547)	0.841	-	
Pathologic stage				
I	1		-	
II	1.164 (0.370–3.663)	0.795	-	
III	2.230 (0.817–6.086)	0.118	-	
Postoperative complication	5.539 (1.848–16.603)	0.002	4.255 (1.383–13.097)	0.012
Adjuvant treatment	1.454 (0.526–4.017)	0.470	-	

CI, confidence interval; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monoxide; CCI, Charlson comorbidity index; VATS, video-assisted thoracoscopic surgery; SqCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer.

in recurrence between HR patients with PCs and SR patients with or without PCs (p=0.502 and p=0.757, respectively) (Fig. 3B).

Risk factors for postoperative complications in high-risk patients

Risk factors for PCs were analyzed using binary logistic regression analysis in the HR group. In the multivariable analysis, lower DLCO and lobectomy were identified as significant risk factors for PCs (Table 6).

Discussion

In the present study, the incidence of PCs and 90-day mortality rate was 50.6% and 10.4%, respectively, in HR patients; the rates of both of these outcomes were significantly higher in HR patients than in SR patients. However, HR status was not an independent prognostic factor in the multivariable Cox regression analysis of all patients. PCs were the only significant prognostic factor in the multivariable Cox regression analysis of HR patients. HR patients with PCs had worse overall survival, but a similar recurrence rate, compared to SR patients. HR patients without PCs had a survival rate similar to that of SR patients. Undergoing lobectomy and having a lower DLCO were associated with PCs in HR patients.

The criteria for identifying HR patients were adopted from the ACOSOG Z4099 trial, wherein the prognosis of sublobar resection and SBRT were compared in HR patients with operable NSCLC [13]. The criteria for enrollment of the trial defined lung cancer patients as "HR" for surgery. The criteria (definition of "HR" status) were determined by expert consensus and with audit verification, rather than being based on empirical evidence. As demonstrated by Puri et al. [17], who safely performed lobectomy in HR lung cancer patients, disagreement can exist regarding the definition of HR for surgery. In this study, despite the operative risks, lobectomy was the most frequently performed procedure in the HR group (71.4%), which might be related to the high prevalence of SqCC and advanced stage in HR patients. SqCC comprised 54.5% of

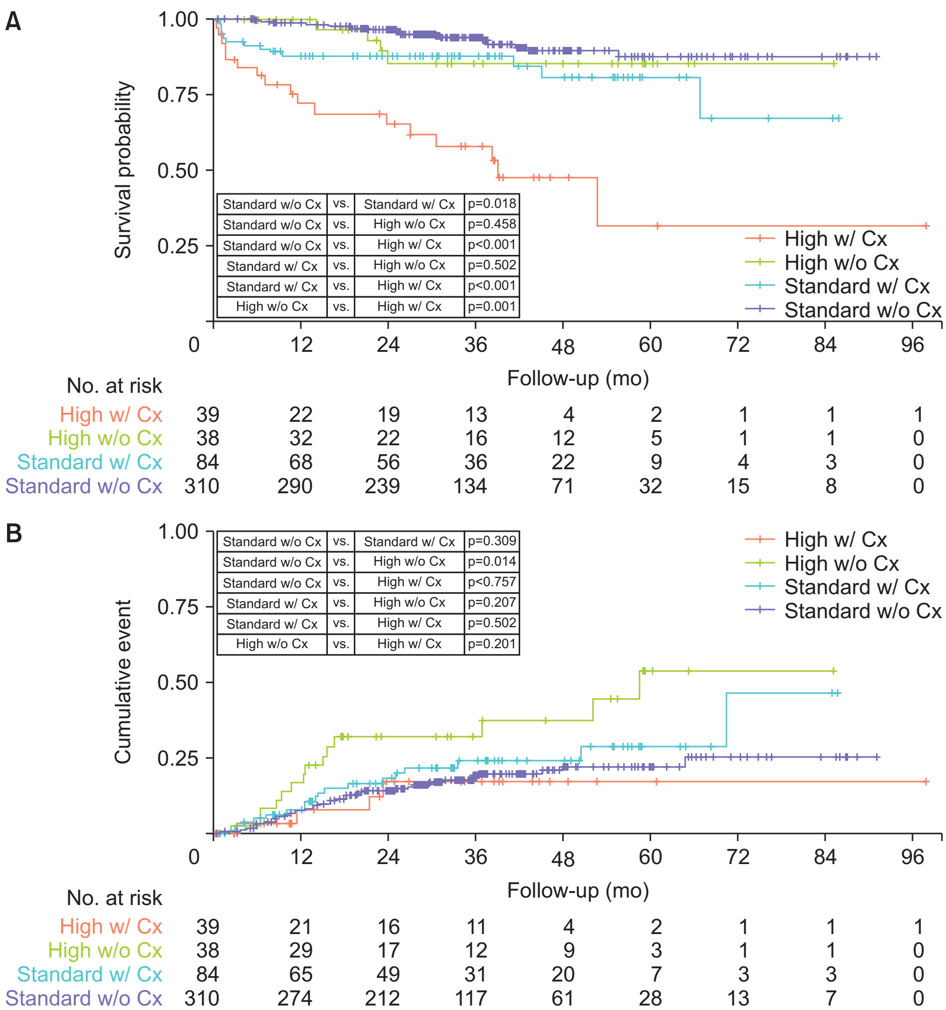

Fig. 3. (A) Overall survival and (B) cumulative incidence of recurrence according to risk group and postoperative complications. w/, with; w/o, without; Cx, complication.

histological cancer subtypes in the HR group. SqCCs are often centrally located and frequently need lobectomy for R0 resection. In addition, 42.9% of HR patients had NSCLC of stage II or greater. In the multivariable Cox model of all patients, lobectomy and HR were not independent prognostic factors. Taylor et al. [18] analyzed 1,259 consecutive patients who underwent lobectomy for NSCLC, and classified 206 patients as HR according to the ASCOG Z 4099 criteria. In their study, HR status was not an independent prognostic factor for major morbidity or survival [18].

Lugg et al. [19] analyzed 670 patients who underwent lung resection to evaluate the long-term impact of postoperative pulmonary complications. Eighty-six patients (13%) had PCs. Compared to patients without PCs, more patients with PCs died from postoperative pulmonary complications (1% versus 10%, p<0.001) and non-cancer-related causes when excluding postoperative deaths (5% versus 11%, p=0.020). The presence of PCs, staging, age, and rates of readmission within 30 days of surgery were independent risk factors for late death in their study. In their study analyzing 129,893 patients who underwent surgery for NSCLC from the National Cancer Database, Puri et al. [20] additionally demonstrated that the rate of readmission within 30 days of surgery was an independent prognostic factor for long-term survival.

In our cohort, the presence of PCs was an independent prognostic factor in multivariable Cox analysis of all patients and in HR patients, unlike in SR patients. Pulmonary complications, which predominantly occurred in HR patients, comprised 94.8% (37 of 39) of the total PCs in HR patients. These results suggest that HR patients are more vulnerable to PCs and that PCs have a significant impact on survival. Furthermore, HR patients with PCs had poorer overall survival, but a similar recurrence rate, compared to SR patients. These suggest that HR patients with PCs died of treatment-related or non-cancer-related causes be-

Table 6. Risk factors for postoperative complications using a logistic regression model in high-risk patients

Variable	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (yr)	0.097 (0.914–1.043)	0.504	-	
Female (vs. male)	0.320 (0.080–1.067)	0.076	0.258 (0.058–0.977)	0.054
Body mass index (kg/m²)	0.904 (0.763–1.059)	0.225	-	
Smoking				
Nonsmoker	1		-	
Ex-smoker	1.476 (0.543–4.080)	0.446	-	
Current smoker	2.769 (0.788–10.760)	0.121	-	
Age-adjusted CCI	1 (0.729–1.371)	1	-	
FEV1 (% predicted)	1.002 (0.980–1.025)	0.812	-	
DLCO (% predicted)	0.957 (0.907–0.997)	0.067	0.951 (0.898–0.994)	0.049
VATS (vs. open)	1.600 (0.649–4.007)	0.309	-	
Operation				
Sublobar resection	1		1	
Lobectomy	3 (0.934–10.760)	0.073	4.407 (1.239–17.813)	0.027
Extended resection	0.333 (0.015–2.787)	0.364	0.352 (0.015–3.168)	0.400
Pathologic stage				
I	1		-	
II	1.125 (0.364–3.515)	0.837	-	
III	1 (0.314–3.182)	1	-	

OR, odds ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monxide; CCI, Charlson comorbidity index; VATS, video-assisted thoracoscopic surgery.

fore experiencing recurrence.

These results suggest that efforts to reduce PCs are critical when performing surgery in HR patients with operable NSCLC. Patients who need lobectomy rather than sublobar resection, and who have lower DLCO, should be managed with particular care, given that the risk of PCs may be higher in such patients. A careful preoperative assessment should be performed, including exercise and cardiopulmonary tests. Patients' comorbidities and their modifiable risk factors should be assessed meticulously, and management decisions should be made by multidisciplinary teams [21]. Emerging evidence suggests that perioperative rehabilitation and enhanced recovery after surgery (ERAS) protocols may reduce PCs after lung cancer surgery [22-24]. HR patients in particular may benefit from these approaches; however, further large-scale studies are needed to elucidate the benefits of ERAS protocols.

First, this study has inherent biases as we used retrospective data. Additionally, this was a single-center study with a small sample size, which may have caused type II error in the analyses. Second, patients with worse outcomes and more significant morbidities were not included in our study, as such patients would have undergone non-surgical treatment such as SBRT. HR patients who underwent surgical treatment were carefully selected, and our HR cohort is not representative of all HR patients with NSCLC. Therefore, we cannot exclude the possibility of selection bias, and our results are not generalizable to all HR patients with NSCLC. The overall postoperative survival of HR patients with NSCLC was affected more by PCs than by any other prognostic factor. Care should be taken to reduce PCs, especially in HR patients with NSCLC.

Conflict of interest

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

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