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Prognostic Significance of Cigarette Smoking in Association with Histologic Subtypes of Resected Lung Adenocarcinoma

Jung Hoon Yi, M.D., Pil Jo Choi, M.D., Ph.D., Sang Seok Jeong, M.D., Jung Hee Bang, M.D., Jae Hwa Jeong, M.D., Joo Hyun Cho, M.D.

Department of Thoracic and Cardiovascular Surgery, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Korea

Background: Smokers with lung adenocarcinoma have a worse prognosis than those who have never smoked; the reasons for this are unclear. We aimed to elucidate the impact of smoking on patients' prognosis and the association between smoking and clinicopathologic factors, particularly histologic subtypes. **Methods:** We reviewed the records of 233 patients with pathologic stage T1-4N0-2M0 lung adenocarcinomas who underwent surgery between January 2004 and July 2015. The histologic subtypes of tumors were reassessed according to the 2015 World Health Organization classification. **Results:** In total, 114 patients had a history of smoking. The overall survival probabilities differed between never-smokers and ever-smokers (80.8% and 65.1%, respectively; p=0.003). In multivariate analyses, the predominant histologic subtype was an independent poor prognostic factor. Smoking history and tumor size >3 cm were independent predictors of solid or micropapillary (SOL/MIP)-predominance in the logistic regression analysis. Smoking quantity (pack-years) in patients with SOL/MIP-predominant tumors was greater than in those with lepidic-predominant tumors (p=0.000). However, there was no significant difference in smoking quantity between patients with SOL/MIP-predominant tumors and those whose tumors had non-predominant SOL/MIP components (p=0.150). **Conclusion:** Smoking was found to be closely associated with SOL/MIP-predominance in lung adenocarcinoma. Greater smoking quantity was related to the presence of a SOL/MIP component.

Key words: 1. Smoking
2. Adenocarcinoma
3. Lung neoplasms

Introduction

Several decades ago, lung cancer emerged as the most common cancer worldwide [1]. In developed countries, the incidence of lung cancer and deaths from lung cancer have been steadily declining as a result of the implementation of comprehensive tobacco control programs to reduce tobacco use. However, lung cancer is still the leading cause of cancer-related death worldwide because of the high fatality associated with the disease [1].

The decline in the prevalence of tobacco smoking has been accompanied by notable changes in the histologic subtypes of lung cancer. Squamous cell carcinoma was previously the most prevalent histologic subtype, but it has been gradually replaced by ad-

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Corresponding author: Pil Jo Choi, Department of Thoracic and Cardiovascular Surgery, Dong-A University Hospital, 26 Daesingongwon-ro, Seo-gu, Busan 49201, Korea
(Tel) 82-51-240-5195 (Fax) 82-51-253-5195 (E-mail) pjchoi@dau.ac.kr

enocarcinoma since the mid-1970s [2]. In 2011, a new classification of adenocarcinoma was proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS). In this classification, 5 distinct subtypes of invasive adenocarcinoma were defined: the lepidic (LEP) subtype (low grade, favorable prognosis), the acinar (ACN) and papillary (PAP) subtypes (intermediate grade and prognosis), and the solid (SOL) and micropapillary (MIP) subtypes (high grade, poor prognosis). The associations between the predominant subtypes and prognoses have been validated by several studies [3].

Smoking is a well-established causative factor of all types of lung cancer. In addition to describing the link between smoking and carcinogenesis, previous studies showed that among individuals with non-small cell lung cancer, those with a history of smoking had poorer survival than never-smokers [4]. Smoking is most strongly linked with squamous cell carcinoma and small cell lung cancer, while adenocarcinoma is the predominant type of lung cancer in lifelong never-smokers [5]. Nevertheless, a small number of influential studies reported that smoking had a prognostic impact on adenocarcinoma, and some authors proposed a relationship between smoking and the histologic subtypes of adenocarcinoma as a mechanism to explain the poorer outcomes of adenocarcinoma patients with a history of smoking [6]. However, those studies used the previous classification (bronchioloalveolar carcinoma) or did not include all 5 major subtypes of invasive adenocarcinoma, having been performed and reported before the new IASLC/ATS/ERS classification.

In the present study, we reassessed the predominant histologic subtypes according to the new IASLC/ATS/ERS classification and investigated (1) the prognostic impact of smoking and (2) the association between smoking status and histologic subtypes in patients with completely resected adenocarcinoma.

Methods

1) Patients and eligibility criteria

We searched the thoracic surgical database of Dong-A University Hospital and identified 261 patients who underwent surgical resection with curative intent for pathologic stage I–III adenocarcinomas from January 2004 to July 2015. The standard surgical treatment was lobectomy with hilar and mediastinal lymph node dissection. However, in 20 cases, segmentectomy was performed as an optional strategy when a peripheral tumor (less than 2 cm and without nodal involvement) was resected completely with appropriate surgical margins. If any lymph node involvement was detected in frozen section biopsy specimens, the procedure was converted to lobectomy.

The following exclusion criteria were applied: (I) N3 or M1 disease, (II) residual tumor or involved resection margin, (III) preinvasive lesions including atypical adenomatous hyperplasia and adenocarcinoma *in situ* (AIS), (IV) neoadjuvant chemotherapy or radiation therapy, (V) sublobar resection due to poor lung function, (VI) death from early complications within 30 days of the operation. The records of the 233 eligible patients with pathologic T1-4N0-2M0 adenocarcinomas were evaluated. The institutional review board at Dong-A University Hospital approved this retrospective study with a waiver of informed consent, because the patients' personal data had been secured (IRB No., DAUHIRB-19-177).

2) Clinicopathologic information

We obtained clinicopathologic information from the patients' medical records. Cigarette smoking status was based on self-reported smoking behavior, using values obtained during clinical encounters that were closest in time to the date of the lung cancer operation. The amount of smoking was quantified in pack-years (PY), which were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the patient had smoked. Patients were classified into an ever-smoking group and a non-smoking group based on their history. The ever-smoking group included both current smokers and ex-smokers. A non-smoker was defined as someone who has not smoked in her lifetime. A current smoker was a patient who had smoked and continued to smoke until the time of diagnosis. An ex-smoker was defined as someone who had smoked at any point in his or her life but had not smoked in the last 28 days.

Charlson comorbidity index (CCI) scores were used to estimate the severity of comorbidities. As all patients had a malignancy, weights were not assigned

to the cancer diagnosis. Age was also not included in the score because it was used as an independent variable.

The disease stages of all resected tumors were re-assessed according to the eighth edition of the TNM classification system. Following the 2015 World Health Organization classification of lung tumors, pathologists reviewed all of the tumor slides using comprehensive histologic subtyping to make a semi-quantitative estimate of the different histologic patterns present in 5% increments. The predominant subtype was defined as the pattern involving the largest proportion of the tumor, and the tumors were categorized into 3 subgroups based on the grading system: (I) LEP-predominant, (II) ACN or PAP (ACN/PAP)-predominant, or (III) SOL or MIP (SOL/MIP)-predominant.

All patients were followed-up through routine office visits or by telephone contacts. For the first 2 years, they received physical examinations, plain chest X-rays, and chest computed tomography scans at 6-month intervals. Thereafter, they were examined every 6 months or annually. Overall survival (OS) was calculated from the date of initial surgery to the date of death from any cause. Recurrence-free survival (RFS) was defined as the time interval between surgery and clinical or pathological recurrence. Patients without death or recurrence were censored at the end of the follow-up period for OS or RFS, respectively.

The clinicopathologic data included age, sex, smoking status (never or ever), CCI (0–1 or ≥2), carcinoembryonic antigen (CEA) level (cutoff at the upper limit of normal, 5 ng/mL), forced expiratory volume in 1 second (FEV1; ≥70% or <70%), procedure (lobectomy or segmentectomy), adjuvant treatment (no or yes), pathologic tumor size (≤3 cm or >3 cm), tumor laterality (right or left), lobar location (upper/middle or lower), nodal status (N0 or N1–2), visceral pleural invasion (VPI; absent or present), lymphovascular invasion (LVI; absent or present), and predominant subtype (LEP, ACN/PAP, or SOL/MIP).

3) Statistical analysis

Differences in variables were evaluated using the chi-square test, Student t-test, and linear-by-linear associations. Survival probability was estimated from Kaplan-Meier curves, and the log-rank test was used to assess the significance of differences. Univariate and multivariate analyses were performed using Cox proportional hazards models to identify independent factors associated with OS or RFS. Clinical predictors for SOL/MIP-predominant tumors were identified by logistic regression analysis. Multivariate analyses were performed with variables demonstrating a p-value <0.2 in the univariate analysis. A 2-sided p-value <0.05 was considered to indicate statistical significance. All statistical analyses were conducted using IBM SPSS Statistics ver. 20.0 (IBM Corp., Armonk, NY, USA).

Results

1) Patient characteristics according to smoking status and overall survival and recurrence-free survival analyses

The median follow-up period was 47 months (range, 3–158 months). During follow-up, 75 deaths (32.2%) occurred, and 84 patients (36.1%) experienced recurrence. Among the 233 patients, 119 (51.1%) were non-smokers and 114 (48.9%) were ever-smokers. Of the 114 ever-smokers, 61 were current smokers and 53 were ex-smokers. The clinicopathologic characteristics according to smoking status are presented in Table 1. The majority (84.2%) of the ever-smokers were male (p=0.000), and ever-smoker status was significantly associated with a high CEA level (p=0.008), low FEV1 (p=0.038), VPI (p=0.004), and the SOL/MIP-predominant subtype (p=0.001). A significant difference was found in the OS probability between non-smokers and ever-smokers (p=0.003); their 5-year OS rates were 80.8% and 65.1%, respectively. Although the difference in their RFS probabilities was not significant (p=0.162), there was a trend for shorter RFS in ever-smokers than in non-smokers.

The univariate analyses of OS identified sex, smoking status, CEA, FEV1, tumor size, nodal status, VPI, LVI, and predominant subtype as significant prognostic factors. The univariate analyses of RFS identified CEA, tumor size, nodal status, VPI, LVI, and predominant subtype as significantly associated with shorter RFS. In the multivariate analyses, the presence of LVI and predominant subtypes remained statistically significant as independent prognostic factors of both OS and RFS (Table 2).

Table 1. Clinicopathologic characteristics of patients according to smoking status

Characteristic	Total (n=233)	Never-smoker (n=119)	Ever-smoker (n=114)	p-value
Sex				0.000
Male	118 (50.6)	22 (18.5)	96 (84.2)	
Female	115 (49.4)	97 (81.5)	18 (15.8)	
Age (yr)	63.6±9.4	63.8±8.9	63.4±9.8	0.749
Charlson comorbidity index				0.861
0–1	181 (77.7)	93 (78.2)	88 (77.2)	
≥2	52 (22.3)	26 (21.8)	26 (22.8)	
Carcinoembryonic antigen (ng/mL)				0.008
≤5	138 (72.3)	74 (81.3)	64 (64.0)	
>5	53 (27.7)	17 (18.7)	36 (36.0)	
Unknown	42			
Forced expiratory volume in 1 second (%)				0.038
≥70	220 (94.4)	116 (97.5)	104 (91.2)	
<70	13 (5.6)	3 (2.5)	10 (8.8)	
Pathologic stage				0.139
1	127 (54.5)	72 (60.5)	55 (48.2)	
2	55 (23.6)	23 (19.3)	32 (28.1)	
3	51 (21.9)	24 (20.2)	27 (23.7)	
Procedure				0.535
Lobectomy	214 (91.8)	108 (90.8)	106 (93.0)	
Segmentectomy	20 (8.2)	11 (9.2)	8 (7.0)	
Adjuvant treatment				0.902
No	144 (61.8)	74 (62.2)	70 (61.4)	
Yes	89 (38.2)	45 (37.8)	44 (38.6)	
Tumor size (cm)				0.612
≤3	157 (67.4)	80 (67.2)	73 (64.0)	
>3	76 (32.6)	39 (32.8)	41 (36.0)	
Tumor laterality				0.498
Right	142 (60.9)	70 (58.8)	72 (63.2)	
Left	91 (39.1)	49 (41.2)	42 (36.8)	
Lobar location				0.492
Upper/middle	144 (61.8)	71 (59.7)	73 (64.0)	
Lower	89 (38.2)	48 (40.3)	41 (36.0)	
Nodal status				0.608
N0	153 (65.7)	80 (67.2)	73 (64.0)	
N1–2	80 (34.3)	39 (32.8)	41 (36.0)	
Visceral pleural invasion				0.004
Absent	160 (68.7)	92 (77.3)	68 (59.6)	
Present	73 (31.3)	27 (22.7)	46 (40.4)	
Lymphovascular invasion				0.620
Absent	169 (72.5)	88 (73.9)	81 (71.1)	
Present	64 (27.5)	31 (26.1)	33 (28.9)	
Predominant subtype				0.001
Lepidic	52 (24.6)	33 (31.1)	19 (18.1)	
Acinar/papillary	72/46 (55.9)	61 (57.5)	57 (54.3)	
Solid/micropapillary	38/3 (19.4)	12 (11.3)	29 (27.6)	
Variant	22			

Values are presented as number (%) or mean±standard deviation.

Table 2. Multivariate analyses of overall survival and recurrence-free survival

Variable	Overall survival		Recurrence-free survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex			Not included	
Male	1.010 (0.434–2.353)	0.981		
Female	1			
Age	1.025 (0.993–1.058)	0.123	Not included	
Smoking				
Never	1		1	
Ever/current	2.332 (1.246–4.365)	0.008	1.580 (0.915–2.728)	0.101
Carcinoembryonic antigen (ng/mL)				
≤5	1		1	
>5	1.399 (0.776–2.525)	0.264	1.439 (0.822–2.518)	0.202
Forced expiratory volume in 1 second (%)			Not included	
≥70	1			
<70	3.530 (1.456–8.561)	0.005		
Procedure	Not included			
Lobectomy			1	
Segmentectomy			0.224 (0.030–1.659)	0.143
Adjuvant treatment				
No	1		1	
Yes	1.277 (0.693–2.353)	0.433	1.085 (0.544–2.166)	0.816
Tumor size (cm)				
≤3	1		1	
>3	1.216 (0.668–2.215)	0.522	0.798 (0.444–1.434)	0.451
Tumor laterality	Not included			
Right			1	
Left			0.983 (0.564–1.714)	0.951
Nodal status				
N0	1		1	
N1–2	0.793 (0.404–1.557)	0.500	1.424 (0.797–2.544)	0.233
Visceral pleural invasion				
Absent	1		1	
Present	0.705 (0.391–1.269)	0.244	1.300 (0.732–2.308)	0.371
Lymphovascular invasion				
Absent	1		1	
Present	2.727 (1.536–4.843)	0.001	2.033 (1.179–3.505)	0.011
Predominant subtype				
Lepidic	1	0.003	1	0.036
Acinar/papillary	1.479 (0.603–3.631)	0.393	1.165 (0.542–2.505)	0.696
Solid/micropapillary	3.812 (1.473–9.863)	0.006	2.438 (1.049–5.667)	0.038

Multivariate analyses were performed with variables demonstrating a p-value ≤0.2 in univariate analyses.
HR, hazard ratio; CI, confidence interval.

2) Patient characteristics according to histologic subtypes and analysis of clinical predictors of solid/micropapillary-predominant adenocarcinoma

The distribution of predominant subtypes demonstrated a significant difference according to smoking status (Table 1). Among the 3 subtypes, SOL/MIP-predominant tumors had the poorest outcomes for both survival (p=0.000) and recurrence (p=0.001). Therefore, we hypothesized a close correlation between smoking status and SOL/MIP-predominant adenocarcinoma. In the subsequent analysis of the

Table 3. Clinicopathologic characteristics according to the predominant subtype

Variable	Other subtype-predominant tumors (n=170)	Solid/micropapillary-predominant tumors (n=41)	p-value
Sex			0.005
Male	79 (46.5)	29 (70.7)	
Female	91 (53.5)	12 (29.3)	
Age (yr)	63.2±9.1	65.4±10.0	0.178
Smoking			0.003
Never	94 (55.3)	12 (29.3)	
Ever/current	76 (44.7)	29 (70.7)	
Charlson comorbidity index			0.582
0–1	130 (76.5)	33 (80.5)	
≥2	40 (23.5)	8 (19.5)	
Carcinoembryonic antigen (ng/mL)			0.553
≤5	103 (73.6)	24 (68.6)	
>5	37 (26.4)	11 (31.4)	
Forced expiratory volume in 1 second (%)			0.720
≥70	160 (94.1)	38 (92.7)	
<70	10 (5.9)	3 (7.3)	
Pathologic stage			0.002
1	103 (60.6)	15 (36.6)	
2	37 (21.8)	11 (26.8)	
3	30 (17.6)	15 (36.6)	
Procedure			0.304
Lobectomy	153 (90.0)	39 (95.1)	
Segmentectomy	17 (10.0)	2 (4.9)	
Adjuvant treatment			0.243
No	108 (63.5)	22 (53.7)	
Yes	62 (36.5)	19 (46.3)	
Tumor size (cm)			
≤3	128 (75.3)	23 (56.1)	
>3	42 (24.7)	18 (43.9)	0.014
Tumor laterality			0.877
Right	110 (64.7)	26 (63.4)	
Left	60 (35.3)	15 (36.6)	
Lobar location			0.461
Upper/middle	110 (64.7)	24 (58.5)	
Lower	60 (35.3)	17 (41.5)	
Nodal status			0.055
N0	118 (69.4)	22 (53.7)	
N1–2	52 (30.6)	19 (46.3)	
Visceral pleural invasion			0.038
Absent	120 (70.6)	22 (53.7)	
Present	50 (29.4)	19 (46.3)	
Lymphovascular invasion			0.799
Absent	121 (71.2)	30 (73.2)	
Present	49 (28.8)	11 (26.8)	

Values are presented as number (%) or mean±standard deviation.

Table 4. Univariate and multivariate analyses of clinical predictors for the predominance of a solid or micropapillary subtype

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex				
Male	2.784 (1.332–5.818)	0.006	1.748 (0.663–4.612)	0.259
Female	1		1	
Age	1.027 (0.988–1.067)	0.178	1.023 (0.984–1.064)	0.256
Smoking				
Never	1		1	
Ever/current	2.989 (1.430–6.250)	0.004	2.908 (1.379–6.131)	0.005
Charlson comorbidity index				
0–1	1			
≥2	0.788 (0.337–1.843)	0.582		
Carcinoembryonic antigen (ng/mL)				
≤5	1			
>5	1.276 (0.570–2.858)	0.554		
Forced expiratory volume in 1 second (%)				
≥70	1			
<70	1.263 (0.331–4.813)	0.409		
Procedure				
Lobectomy	1			
Segmentectomy	0.462 (0.102–2.082)	0.732		
Tumor size (cm)				
≤3	1		1	
>3	2.385 (1.174–4.844)	0.016	2.296 (1.112–4.742)	0.025
Tumor laterality				
Right	1			
Left	1.058 (0.520–2.149)	0.877		
Lobar location				
Upper/middle	1			
Lower	1.058 (0.520–2.149)	0.877		

Multivariate analyses were performed with variables demonstrating a p-value ≤0.2 in univariate analyses.
OR, odds ratio; CI, confidence interval.

clinicopathologic data based on SOL/MIP predominance (Table 3), the presence of a SOL/MIP-predominant tumor was associated with male sex (p=0.005), smoking history (p=0.003), higher pathologic stage (p=0.002), a tumor size larger than 3 cm (p=0.014), and the presence of VPI (p=0.038). Univariate and multivariate analyses excluding pathologic variables identified smoking history (p=0.005) and tumor size larger than 3 cm (p=0.025) as independent clinical predictors of SOL/MIP predominance (Table 4).

3) Associations between smoking quantity and histologic subtypes

We examined the associations between smoking status and all histologic subtypes, including SOL/MIP-predominant tumors. Fig. 1A shows the proportion of smokers among patients according to the predominant subtype. The percentage of smokers was higher in the higher-grade group (p=0.001). The proportion of smokers was 36.5% (19 of 52) among patients with LEP-predominant tumors. In contrast, the proportion of smokers among patients with SOL/MIP-predominant tumors was 70.7% (29 of 41).

Among the 114 smokers, the smoking quantity of all but 1 was identified. In ever-smokers, the median value of smoking quantity was 30 PY (range, 0.2–144.5 PY). When the distribution of predominant subtypes was analyzed based on a threshold of 30 PY (Fig. 1B), the proportion of LEP-predominant tumors was significantly higher in patients with a

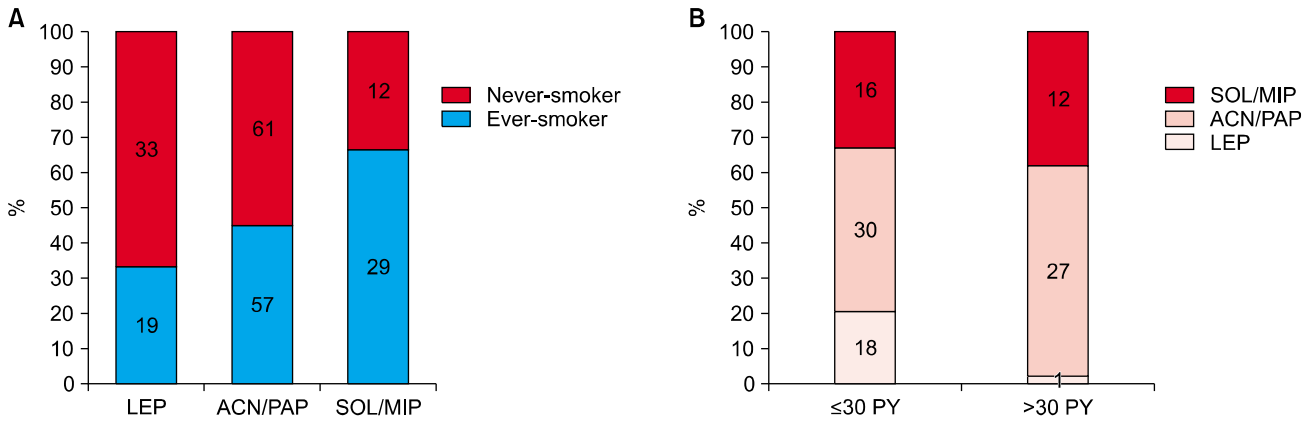

Fig. 1. Associations between predominant subtype and smoking status. (A) Proportion of smokers according to the predominant subtype (p=0.001). (B) Distribution of predominant subtypes according to a smoking amount of 30 PY (p=0.023). The number on the graph is the number of patients. LEP, lepidic; ACN, acinar; PAP, papillary; SOL, solid; MIP, micropapillary; PY, pack-years.

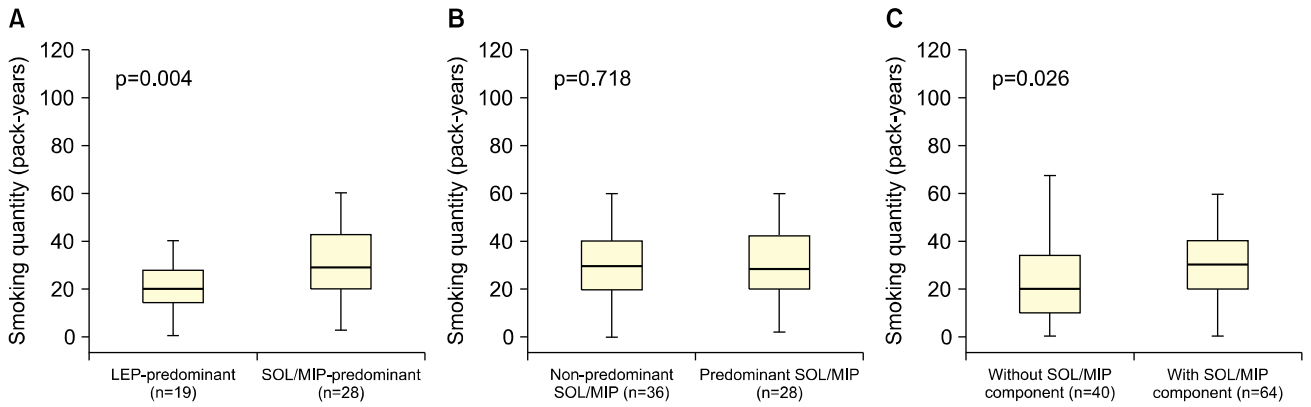

Fig. 2. Comparisons of smoking quantity based on the histologic subtype among ever-smokers. (A) LEP-predominant tumors versus SOL/MIP-predominant tumors. (B) Tumors with non-predominant SOL/MIP components versus SOL/MIP-predominant tumors. (C) Tumors without SOL/MIP components versus tumors with SOL/MIP components, regardless of the predominance. The mean value of smoking quantity in each group is presented. LEP, lepidic; SOL, solid; MIP, micropapillary.

smoking history of 30 PY or less. Conversely, the proportion of SOL/MIP-predominant tumors was higher in patients with over 30 PY (p=0.023).

Smoking quantity was also compared across the different subtypes (Fig. 2). Patients with higher-grade predominant tumors also had a greater smoking quantity in terms of PY. The 28 ever-smokers with SOL/MIP-predominant tumors (32.7±19.9 PY) tended to have smoked more than the 19 ever-smokers with LEP-predominant tumors (19.1±10.6 PY) (p=0.004). No significant difference in smoking quantity was found between the 36 ever-smokers with non-predominant SOL/MIP components (31.0±16.5 PY) and the 28 ever-smokers with predominant SOL/MIP components (32.7±19.9 PY) (p=0.718). However, a significant difference in smoking quantity was found when comparing groups defined by the presence of a SOL/MIP component (31.7±17.9 PY versus 23.7±17.2 PY), while ignoring predominance (p=0.026).

Discussion

Similar to previous studies, patients with adenocarcinoma who had a history of smoking had a poorer prognosis in our study. Several clinical and epidemiological inferences may be drawn from this association. Because smoking is a well-known risk factor for postoperative complications, it is possible that complications may contribute in part to the unfavorable prognosis of patients with a history of

smoking. However, our study eliminated this possibility by excluding patients who died from postoperative complications. Smoking is also associated with many other diseases, such as cardiovascular disease, pulmonary disease, diabetes, and infections. Although we conducted a multivariate analysis to offset the influence of comorbidities on survival, the adverse effect of smoking remained significant. Almost all patients stopped smoking after surgery; however, the cumulative effect of smoking may have led to death or recurrence by inducing second cancers or promoting the aforementioned chronic diseases during the follow-up period. In this and previous studies, the smokers were predominantly male. In the large retrospective study of Tseng et al. [7], male sex was an independent poor prognostic factor for OS regardless of epidermal growth factor receptor (EGFR) mutation status.

The molecular and genomic characteristics of adenocarcinoma differ between patients who have never smoked and those with a history of smoking. Mutations in the p53 gene are present in all lung cancers, whereas mutations in the *KRAS* gene are predominantly present in adenocarcinomas in individuals who have a history of smoking [8]. *KRAS* mutations generally mark a poor prognosis and are associated with intrinsic EGFR tyrosine kinase inhibitor (TKI) resistance. Never-smokers have demonstrated better therapeutic responses to EGFR TKIs, probably due to the higher occurrence of EGFR mutations in never-smokers [9]. Several studies have proposed mechanisms of resistance to EGFR TKIs related to smoking. Smoking induces the activation of cytochrome CYP 1A1 [10] and the release of reactive oxidative stress species, while promoting autophosphorylation [11]. Smoking also involves the activation of Src, the inhibition of which restored TKI sensitivity [12].

Several authors have reported a relationship between the predominant histologic subtype and prognosis in lung adenocarcinoma [4]. While LEP-predominant invasive adenocarcinomas have a better prognosis, SOL/MIP-predominant tumors show a worse prognosis than the other 3 subtypes. In an effort to determine the underlying biology, several research groups have correlated histologic subtypes with the mutational status of the tumors, but no specific or consistent correlation has been found between histologic subtypes and oncogenic driver mutations [13]. In our study, SOL/MIP-predominant tumors were not significantly associated with CEA, LVI, or nodal metastasis, which have been identified as prognostic factors in previous studies. Nonetheless, these tumors were associated with poorer outcomes of survival and recurrence than tumors with other predominant subtypes.

Our study also demonstrated an association of a history of ever smoking with SOL/MIP-predominant tumors, which may provide a partial explanation for the poorer prognosis in the smokers. A few other retrospective studies have explored this association, but most of them did not include all 5 major subtypes because they were reported before the development of the 2015 World Health Organization classification. Nearly all of them reported a positive association between smoking and high-grade subtypes. However, the mechanisms underlying this association are not fully understood, and additional studies are necessary to clarify this issue. In the case-control study of Bracci at al. [14], smoking status was positively associated with AIS risk, whereas the risk of AIS decreased with years since quitting smoking. In addition, patients with AIS were less likely to be ever-smokers or heavy smokers than those with other histologic subtypes. More recently, Lappi-Blanco et al. [15] reported that an altered MUC1 expression pattern was frequently observed in SOL-predominant adenocarcinomas and was correlated with reduced overall survival and smoking history. Similarly, Rokutan-Kurata et al. [16] found that MUC4-positive lung adenocarcinoma was correlated with male smokers, SOL subtype, HER2 expression, and a poorer prognosis.

Although several studies have reported encouraging results of sublobar resection for small, peripheral adenocarcinomas, sublobar resection may be less ideal for tumors with SOL/MIP components. Many studies identified that having non-predominant MIP/SOL components was a negative prognostic factor in patients who underwent even lobectomy [17]. When treated with sublobar resection, peripheral adenocarcinoma $\leq$2 cm with an MIP component of 5% or greater showed a higher cumulative incidence of recurrence [18]. Yeh et al. [19] reported that the presence of a SOL component was also found to correlate with locoregional recurrence, and that distant recurrence was correlated with the predominant his-

tologic subtype and the MIP component. Furthermore, occult lymph node metastasis was associated with non-predominant SOL/MIP components [20].

These studies raise the question of how to recognize SOL/MIP components preoperatively. Cha et al. [21] tried to predict the presence of SOL/MIP components by using radiological parameters including tumor size >2.5 cm, pure solidity, and maximum standardized uptake value ≥ 7. Similarly, our results demonstrated that smoking history and tumor size >3 cm were independent predictors of SOL/MIP-predominant tumors. In addition, a greater smoking quantity was associated with SOL/MIP predominance. However, the difference in smoking quantity was not significant between the tumors with SOL/MIP-predominant components and those with non-predominant SOL/MIP components. In our opinion, smoking history—and more specifically, greater smoking quantity—seems promising for use in a predictive model, and further studies with larger cohorts are needed.

Our study is limited by the relatively small sample size and the retrospective, single-institution study design. Additionally, our cohort included 20 cases of segmentectomy, although none of them experienced death or recurrence. Because smoking status and quantity were assessed based on patients' reports, without biochemical methods, those data might be biased. Although smoking status during the follow-up period was not taken into consideration in our analysis, almost all patients quit after surgery. We also did not assess exposure to secondhand smoke, air pollution, or occupational carcinogens due to the difficulty of objective quantification. Another limitation was the imbalance in the proportion of males and females in the never-smoker and ever-smoker groups.

In conclusion, our results show that smoking was closely associated with SOL/MIP-predominance in lung adenocarcinoma. A larger smoking quantity was associated with the presence of a SOL/MIP component, but may not be related to the predominant subtype. These associations between smoking and histologic subtype suggest a possible mechanism underlying the poorer prognosis of patients with adenocarcinoma and history of smoking.

Conflict of interest

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

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ORCID

Jung Hoon Yi: https://orcid.org/0000-0002-6605-0807
Pil Jo Choi: https://orcid.org/0000-0003-0188-2423
Sang Seok Jeong: https://orcid.org/0000-0001-8390-4942
Jung Hee Bang: https://orcid.org/0000-0001-5442-7139
Jae Hwa Jeong: https://orcid.org/0000-0001-6182-8731
Joo Hyun Cho: https://orcid.org/0000-0001-9189-4203

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