Original Article

How long is cessation of preoperative smoking required to improve postoperative survival of patients with pathological stage I non-small cell lung cancer?

Toshiyuki Shima[1,2], Tomonari Kinoshita[1,2], Mao Uematsu[1], Naomichi Sasaki[1], Yusuke Sugita[1], Reiko Shimizu[1], Masahiko Harada[1], Tsunekazu Hishima[3], Hirotoshi Horio[1]

[1]Department of Thoracic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; [2]Division of General Thoracic Surgery, Department of Surgery, Keio University School of Medicine, Tokyo, Japan; [3]Department of Pathology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

Contributions: (I) Conception and design: T Shima, T Kinoshita; (II) Administrative support: M Harada, T Hishima, H Horio; (III) Provision of study materials or patients: T Kinoshita; (IV) Collection and assembly of data: M Uematsu, N Sasaki, Y Sugita, R Shimizu; (V) Data analysis and interpretation: T Shima, T Kinoshita; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tomonari Kinoshita. Department of Thoracic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. Email: kinotomo0415@gmail.com.

Background: Smoking can cause non-small cell lung cancer (NSCLC). However, the effects of preoperative smoking on tumor progression are not well-known. In addition, the duration of smoking cessation that can provide NSCLC patients with smoking history similar postoperative prognosis as that of nonsmokers remains unknown. This study aimed to investigate the period of smoking cessation that may "compensate" for past smoking history regarding postoperative survival in cases of resected pathological stage I NSCLC by examining the relationship between clinicopathological factors and preoperative smoking.

Methods: We retrospectively examined clinicopathological factors including preoperative smoking status and postoperative survival in 453 patients with pathologically proven stage I NSCLC at our Institute. Smoking status was evaluated using the following four parameters: cigarettes per day, number of years of smoking, pack-years, and number of years since smoking cessation.

Results: Pathological factors that reflect tumor invasiveness including vascular invasion (VI) and pleural invasion (PL) were associated with the degree of preoperative smoking in adenocarcinomas, particularly invasive diameters of 2–3 cm. Such a relationship was not identified for non-adenocarcinomas. Heavy smoking status was significantly related to PL in lepidic or papillary predominant adenocarcinomas and to VI in acinar or solid predominant adenocarcinomas. Former smokers who quit smoking for ≥10 years had similar postoperative survival as non-smokers for adenocarcinoma ≤3 cm.

Conclusions: Accumulative smoking habit correlated with VI and PL, particularly in 2–3 cm adenocarcinoma, whereas larger adenocarcinomas and non-adenocarcinomas of any size appear to grow and become invasive independent of preoperative smoking status. Longer smoking cessation ≥10 years can result in postoperative survival similar to that of non-smokers with adenocarcinomas ≤3 cm. Current smokers should quit smoking immediately to ensure longer survival even though they suffer from small-sized lung adenocarcinomas in the future.

Keywords: Smoking cessation; lung adenocarcinoma; pathological stage I

Introduction

The number of surgical cases of non-small cell lung cancer (NSCLC) is increasing worldwide due to the increasing use of computed tomography (CT) (1,2). However, despite complete resection for early-stage NSCLC, lung cancer has a high frequency of recurrence (3). Multiple studies have demonstrated that some perioperative clinicopathological factors, such as pleural invasion (PL), vascular invasion (VI), and lymphatic permeation (LY), were identified as predictive markers of tumor relapse in resected early stage NSCLC (4-6). Indeed, PL was confirmed as an upstaging factor of "T" in the seventh TNM staging of lung cancer (7). In other words, these factors as well as nodal metastasis are representative surrogate markers that can reflect tumor invasiveness in early stage NSCLC.

Non-adenocarcinomas, such as squamous cell carcinomas, are generally considered to be associated with heavy smoking (8). Low yield filter cigarettes with deeper and more frequent inhalation may result in increased delivery of carcinogens to the lung peripheries. This may contribute to an increased incidence of adenocarcinoma of the lung (9). Non-smokers with specific genetic features too can develop lung adenocarcinoma (10). Some reports have stated that preoperative smoking cessation can prevent perioperative complications, such as postoperative pneumonia (11,12). However, the influence of preoperative smoking on the progression and invasiveness of early stage NSCLC remains unclear.

Additionally, there is an increase in the number of smokers who quit smoking owing to the worldwide educational efforts regarding the importance of smoking cessation as a means of preventing lung as well as other cancers (8,13). Unfortunately, some ex-smokers may still be diagnosed with NSCLC. In order to encourage current smokers to quit smoking, we should be able to provide information regarding the duration of smoking cessation prior to the diagnosis of stage I NSCLC that may result in outcomes and prognosis in smokers similar to that in non-smokers. However, this information is currently unavailable.

In this study, we examined the relationship between prognostic factors and preoperative smoking status in cases of resected pathological stage I NSCLC. We also investigated the period of smoking cessation that would make up for the past smoking history in terms of postoperative survival.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi. org/10.21037/tlcr-20-465).

Methods

Patients

This study was approved by our institutional review board in March 2020 (approved number #2483). The requirement of informed consent was waived due to the retrospective design of the study and because no personally identifiable information was collected. Clinical data including smoking history were recorded by medical staff (nurses and/or doctors) and used for statistical analysis. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013)

Overall, 453 patients with pathological stage I NSCLC who underwent complete resection and systematic lymph node dissection at our Institute between January 2004 and December 2018 were enrolled in this study. The cases with invasive diameter >4 cm or lymph node metastasis were excluded based on pathological examinations. Segmentectomy with systematic lymphadenectomy was the procedure included as limited surgery in our retrospective study. Patients who underwent wedge resection and/or neoadjuvant chemotherapy were excluded. Patients with a follow-up of less than one year were excluded (*Table 1*, *Figure 1*).

Pathological evaluation

All slides of resected specimens were evaluated. All specimens were fixed in 10% formalin and embedded in paraffin. Serial 4-µm-thick sections were stained with hematoxylin/eosin and Elastica van Gieson to assess the degree of PL and VI. When required, we also stained them with D2-40 to evaluate the extent of LY. All cases were reviewed according to the 4th edition of the World Health Organization histological classification and staged according to the 8th edition of the TNM classification of the Union for International Cancer Control (14,15). Invasive size confirmed by pathologists was used as tumor size according to the current TNM staging.

Follow-up assessments

Patients were followed-up at our outpatient department quarterly in the first 2 years after resection and semi-annually thereafter. CT scans of the chest and upper

Table 1 Characteristics of the enrolled patients

Factors	n=453
Sex, male/female	242/211
Age, median (range)	71 [34–88]
Observation period, mean months (range)	58.7 [12-193]
Smoking, ever/never	289/164
COPD, present/absent	103/350
Surgery, lobectomy/segmentectomy	396/57
Histological type, AD/SQ/ADSQ/others	325/97/10/21
Lymphatic permeation, present/absent	65/388
Vascular invasion, present/absent	154/299
Pleural invasion, present/absent	111/342
Invasive size, ≤3 cm/>3 cm	365/88
T stage, 1mi/1a/1b/1c/2a	59/45/102/88/159

COPD, chronic obstructive pulmonary disease; AD, adenocarcinoma; SQ, squamous cell carcinoma; ADSQ, adenosquamous carcinoma.
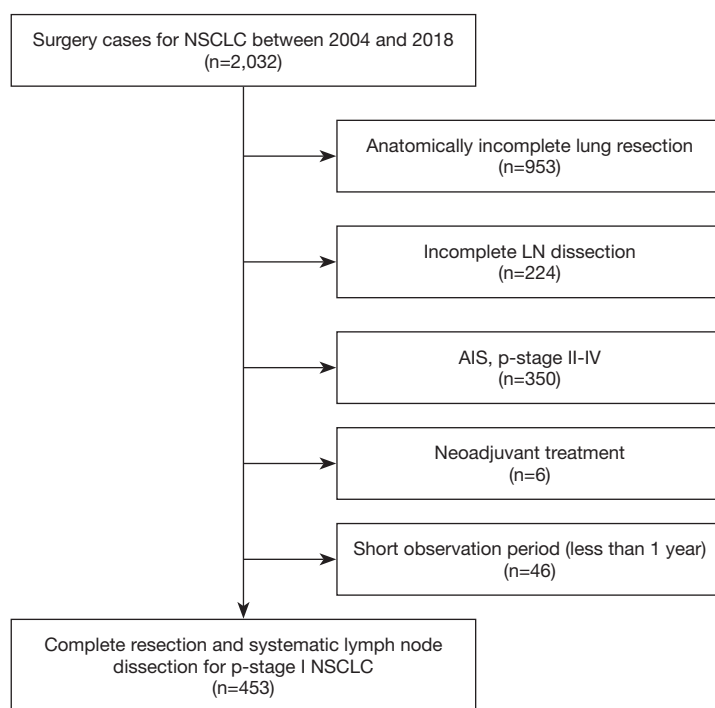
Figure 1 Study flow chart. NSCLC, non-small cell lung cancer; LN, lymph node; AIS, adenocarcinoma in situ.

abdomen were routinely performed at every scheduled outpatient department visit during the follow-up. Additionally, CT scans or magnetic resonance imaging of the brain were also routinely performed in the same schedule. The period of overall survival (OS) was defined as the interval between the date of surgical resection and the date of death or the last follow-up. The length of recurrence-free survival (RFS) was defined as the interval between the date of surgical resection and the date of the diagnosis of initial metastasis, death, or the last follow-up. Disease-specific survival (DSS) was defined as the period between the date of surgery and the date of lung cancer-associated death or the date of the last follow-up.

Statistical analyses

Survival curves were plotted using the Kaplan-Meier method. The log-rank test was used to compare the postoperative survival. For survival analyses, univariate and multivariate analyses were performed using the Cox proportional hazards model. All variables with P<0.1 on univariate analysis were entered into the multivariate forward-backward stepwise model. Two-category comparisons were performed using chi-square or Fisher's exact test, and Mann-Whitney U-test for quantitative data. All tests were two-sided, and statistical significance was defined as P<0.05. All analyses were performed using SPSS v25 (IBM Inc., Armonk, NY, USA).

Results

Pathological factors that would promote tumor progression in pathological stage I NSCLC

In the survival analyses of 453 patients, median survival period was 137 months (95% confidence interval, 130–144 months). Five- and 10-year survival rates were 84.9% and 68.4% for OS, and 75.8% and 62.6% for RFS, respectively. Among 325 adenocarcinoma patients, 49 patients (15.1%) died and 49 (15.1%) patients had recurrent tumors. In 128 non-adenocarcinoma patients, 34 (26.6%) died and 23 cases (18.0%) relapsed. The results of the univariate and multivariate analysis of OS, RFS, and DSS, according to histological types, are summarized in *Tables 2,3*. In univariate survival analyses of adenocarcinomas, larger invasive size and presence of LY, VI, and PL, in addition to smoking history, significantly correlated with unfavorable prognosis. VI and PL were identified as independent prognostic factors among

adenocarcinoma patients in multivariate analyses. Similar findings were observed in cases of non-adenocarcinoma. These findings indicate that the pathological factors, LY, VI, and PL, are not only prognostic factors but can also act as surrogate markers of tumor malignancy.

Relationship between pathological factors and smoking status

The statistical relationship between clinical and pathological factors among patients with adenocarcinoma and non-adenocarcinoma are presented in *Table 4*. While not only invasive tumor size but also tobacco habit was significantly correlated with pathological factors among adenocarcinoma patients, there was no such relationship in patients with non-adenocarcinomas. These results indicate that smoking may contribute to the progression of adenocarcinoma.

Long-term smoking accelerates tumor progression in pathological stage I adenocarcinoma

In the clinical data, we focused on the smoking history of patients who underwent resection for stage I NSCLC. Smoking status was evaluated using the following four parameters: cigarettes per day, number of years of smoking, pack-years, and number of years since smoking cessation. As summarized in *Table 5*, LY, VI, and PL were significantly associated with accumulative smoking habit in patients with adenocarcinoma. Particularly, long-term cessation of smoking could potentially mitigate local invasion of adenocarcinoma. In contrast, no apparent relationship between the duration of smoking and these factors was identified in non-adenocarcinomas.

Smoking influence on tumor progression according to invasive size in adenocarcinoma

Generally, as the invasive part of a tumor increases, its malignant characteristics accelerate, as is seen in "T" factors of TNM staging (16). We classified stage I adenocarcinomas into three groups according to the invasive size: ≤2, 2–3, and 3–4 cm. Although no strong effects of preoperative smoking on postoperative OS and DSS were confirmed, patients with ≤3 cm adenocarcinoma who had never smoked had favorable RFS (*Figure 2*). In terms of the relationship between smoking status and pathological factors, PL correlated with accumulative smoking in ≤2 cm adenocarcinomas; both VI and PL were related to heavy

Table 2 Univariate analyses of postoperative survival among patients with adenocarcinoma and non-adenocarcinoma according to clinicopathological factors

Factors	Adenocarcinoma							Non adenocarcinoma						
	n	OS HR (95% CI)	P	RFS HR (95% CI)	P	DSS HR (95% CI)	P	n	OS HR (95% CI)	P	RFS HR (95% CI)	P	DSS HR (95% CI)	P
Sex														
Male	136	1.64 (0.94–2.87)	0.08	1.59 (1.00–2.53)	0.05	1.55 (0.72–3.36)	0.26	106	1.69 (0.51–5.59)	0.39	2.12 (0.65–6.90)	0.21	1.10 (0.32–3.83)	0.87
Female	189	1		1		1		22	1		1		1	
Age														
>70	165	1.39 (0.78–2.46)	0.26	1.36 (0.85–2.18)	0.2	1.04 (0.47–2.31)	0.92	80	1.94 (0.89–4.20)	0.1	1.44 (0.72–2.88)	0.31	1.90 (0.68–5.29)	0.22
≤70	160	1		1		1		48	1		1		1	
Smoking														
Ever	169	2.23 (1.22–4.05)	<0.01	2.21 (1.35–3.63)	<0.01	2.07 (0.92–4.66)	0.08	120	1.71 (0.23–12.5)	0.6	2.06 (0.28–15.0)	0.48	1.68 (0.38–7.10)	0.51
Never	156	1		1		1		8	1		1		1	
COPD														
Present	56	1.83 (0.98–3.40)	0.06	1.48 (0.86–2.56)	0.16	1.64 (0.63–4.12)	0.32	47	2.33 (0.68–3.55)	0.3	1.72 (0.91–3.25)	0.1	1.84 (0.75–4.52)	0.19
Absent	269	1		1		1		81	1		1		1	
Invasive size														
>3 cm	42	3.39 (1.81–6.33)	<0.01	4.22 (2.51–7.07)	<0.01	5.60 (2.52–12.5)	<0.01	46	1.62 (0.82–3.22)	0.17	1.48 (0.77–2.83)	0.24	2.65 (1.07–6.54)	0.04
≤3 cm	283	1		1		1		82	1		1		1	
LY														
Present	48	2.08 (1.10–3.93)	0.03	2.96 (1.78–4.93)	<0.01	3.53 (1.59–7.82)	<0.01	17	1.58 (0.68–3.65)	0.29	1.66 (0.75–3.64)	0.21	2.32 (0.84–6.46)	0.11
Absent	277	1		1		1		111	1		1		1	
VI														
Present	86	3.74 (2.11–6.61)	<0.01	4.55 (2.85–7.27)	<0.01	6.15 (2.66–14.3)	<0.01	68	1.90 (0.92–3.90)	0.08	1.81 (0.92–3.55)	0.08	2.64 (0.95–7.35)	0.06
Absent	239	1		1		1		60	1		1		1	
PL														
Present	74	2.33 (1.32–4.11)	<0.01	3.57 (2.25–5.67)	<0.01	2.74 (1.26–5.96)	0.01	37	2.28 (1.16–4.48)	0.2	2.13 (1.12–4.03)	0.02	2.37 (0.96–5.82)	0.06
Absent	251	1		1		1		91	1		1		1	
Operation														
Segmentectomy	40	2.20 (0.68–7.09)	0.19	3.78 (1.19–12.0)	0.02	1.67 (0.39–7.08)	0.49	17	1.15 (0.44–2.99)	0.78	1.07 (0.42–2.76)	0.89	0.85 (0.25–2.93)	0.8
Lobectomy	285	1		1		1		111	1		1		1	

OS, overall survival; RFS, recurrence free survival; DSS, disease specific survival; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LY, lymphatic permeation; VI, vascular invasion; PL, pleural invasion.

Table 3 Multivariate analyses of postoperative survival among patients with adenocarcinoma and non-adenocarcinoma according to clinicopathological factors

Factors		Adenocarcinoma						Non-adenocarcinoma						
		OS		RFS		DSS			OS		RFS		DSS	
	n	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	n	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Invasive size														
>3 cm	42	–		2.80 (1.64–4.77)	<0.01	3.40 (1.48–7.78)	<0.01	–	–		–		–	
≤3 cm	283	–		1		1		–	–		–		–	
VI														
Present	86	–		2.98 (1.74–5.13)	<0.01	4.68 (1.95–11.3)	<0.01	68	1.90 (0.92–3.90)	0.08	–		–	
Absent	239			1		1		60	1		–		–	
PL														
Present	74	2.33 (1.32–4.11)	<0.01	1.75 (1.02–3.00)	0.04	–		37	–		2.13 (1.12–4.03)	0.02	2.37 (0.96–5.82)	0.06
Absent	251	1		1		1		91			1		1	

OS, overall survival; RFS, recurrence free survival; DSS, disease specific survival; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LY, lymphatic permeation; VI, vascular invasion; PL, pleural invasion.

and current smoking in adenocarcinomas of 2–3 cm; and no apparent relationship was identified between them in adenocarcinomas >3 cm (*Table 6*).

Histological subtypes of adenocarcinoma and smoking habit

Histological predominant subtype of adenocarcinoma should be described in the pathological report (17). The cases in this study included 127 lepidic, 115 papillary, 62 acinar, 17 solid, and 4 mucinous adenocarcinomas. There were no cases of micropapillary predominant adenocarcinoma. Adenocarcinomas with micropapillary components are reported to have poorer prognosis than the others and have a higher frequency of recurrence (18); therefore, we evaluated the effects of smoking according to the presence/absence of micropapillary components as well as based on the main subtype of adenocarcinoma. Although postoperative survival was not affected by smoking history in each subtype (*Table 7*), PL correlated with heavy smoking status in lepidic and papillary adenocarcinomas and VI correlated with smoking in acinar and solid adenocarcinomas. Mucinous invasive adenocarcinomas were not analyzed owing to the small number of cases (*Table 8*).

Smoking cessation for at least 10 years may result in similar prognosis as that in non-smokers in adenocarcinomas ≤3 cm

According to our results, smoking accelerates tumor progression in adenocarcinomas ≤3 cm. Early smoking cessation is believed to contribute to reducing the perioperative complications and also to prolonging postoperative survival following NSCLC treatment (19). However, the duration of smoking cessation that would provide any survival benefit following surgical resection of lung adenocarcinoma is unclear. When former smokers with ≥5 years of smoking cessation (y.c.) were combined with non-smokers (never + 5 y.c.), no apparent correlation with the pathological factors was observed in each of the adenocarcinoma size group. Statistical differences in postoperative survival were also not detected between ever-smokers (current or former smokers with <5 years of smoking cessation) and never +5 y.c. both in adenocarcinomas ≤2 and 2–3 cm. However, cases of never +10 y.c., +15 y.c., and +20 y.c. were related to pathological factors (particularly in adenocarcinomas of 2–3 cm), and these patients had significantly better prognosis than ever-

Table 4 Relationship between clinical factors and pathological factors among patients with adenocarcinoma (A) and non-adenocarcinoma (B)
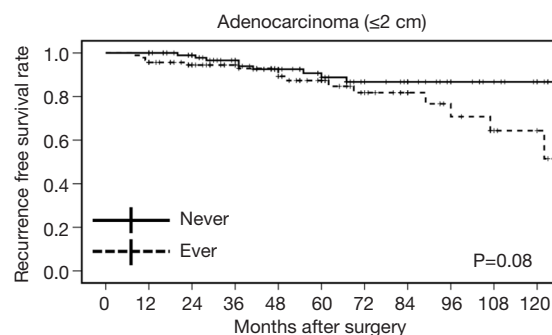
| | Adenocarcinoma | | | | | | | | | Non-adenocarcinoma | | | | | | | | |
| | LY | | | VI | | | PL | | | LY | | | VI | | | PL | | |
Factors	Present	Absent	P	Present	Absent	P	Present	Absent	P	Present	Absent	P	Present	Absent	P	Present	Absent	P
Sex																		
Male	25	111	0.12	46	90	0.01	33	103	0.59	13	93	0.46	57	49	0.75	30	76	0.74
Female	23	166		40	149		41	148		4	18		11	11		7	15	
Age																		
>70	24	141	0.91	42	123	0.68	34	131	0.35	7	73	0.06	44	36	0.58	23	57	0.96
≤70	24	136		44	116		40	120		10	38		24	24		14	34	
Smoking																		
Ever	31	138	0.06	57	112	<0.01	50	119	<0.01	15	105	0.29	64	56	0.86	34	86	0.58
Never	17	139		29	127		24	132		2	6		4	4		3	5	
COPD																		
Present	7	49	0.6	16	40	0.69	15	41	0.43	3	44	0.08	26	21	0.71	16	31	0.33
Absent	41	228		70	199		59	210		14	67		42	39		21	60	
Invasive size																		
>3 cm	11	31	0.03	22	20	<0.01	21	21	<0.01	7	39	0.63	31	15	0.02	19	27	0.02
≤3 cm	37	246		64	219		53	230		10	72		37	45		18	64	

LY, lymphatic permeation; VI, vascular invasion; PL, pleural invasion; COPD, chronic obstructive pulmonary disease.

Table 5 Correlation of pathological factors and smoking status according to histological type
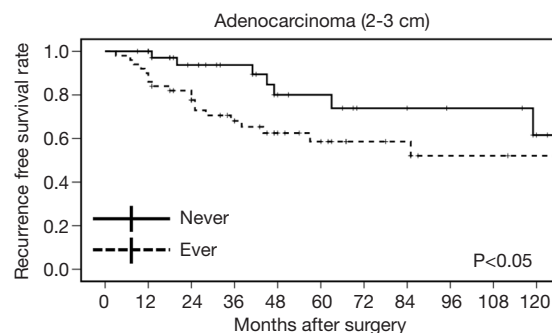
Factors	Adenocarcinoma									Non-adenocarcinoma								
	n	Cigarettes per day Median [range]	P	Years of smoking (year) Median [range]	P	Pack-years Median [range]	P	Quit years (year) Median [range]	P	n	Cigarettes per day Median [range]	P	Years of smoking (year) Median [range]	P	Pack-years Median [range]	P	Quit years (year) Median [range]	P
LY																		
Present	48	15 [0–40]	0.04	31 [0–62]	0.02	52 [0–80]	0.02	15 [0–81]	0.04	17	20 [0–100]	0.48	42 [0–52]	0.15	56 [0–104]	0.86	0 [0–85]	0.61
Absent	277	2 [0–80]		0 [0–68]		0 [0–232]		48 [0–87]		111	40 [0–40]		46 [0–67]		45 [0–260]		0 [0–77]	
VI																		
Present	86	15 [0–60]	<0.01	32 [0–61]	<0.01	30 [0–105]	<0.01	13 [0–83]	<0.01	68	20 [0–60]	0.81	46 [0–65]	0.64	53 [0–112]	0.78	0 [0–85]	0.09
Absent	239	0 [0–80]		0 [0–68]		0 [0–232]		50 [0–87]		60	20 [0–100]		45 [0–67]		52 [0–260]		3 [0–77]	
PL																		
Present	74	20 [0–60]	<0.01	30 [0–68]	<0.01	30 [0–108]	<0.01	13 [0–87]	<0.01	37	20 [0–60]	0.66	46 [0–64]	0.93	51 [0–105]	0.65	0 [0–85]	0.65
Absent	251	0 [0–80]		0 [0–67]		0 [0–232]		50 [0–84]		91	20 [0–100]		45 [0–67]		53 [0–260]		0 [0–77]	

LY, lymphatic permeation; VI, vascular invasion; PL, pleural invasion.

Figure 2 Recurrence-free survival curves of patients with adenocarcinomas for various invasive tumor sizes (≤2, 2–3, 3–4 cm) and smoking status (ever *vs*. never).

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Table 6 Correlation of pathological factors and smoking status according to invasive size of adenocarcinoma

Factors	n	Cigarettes per day		Years of smoking (year)		Pack-years		Quit years (year)	
		Median [range]	P	Median [range]	P	Median [range]	P	Median [range]	P
Adenocarcinoma [≤2 cm]									
LY									
Present	15	10 [0–40]	0.45	23 [0–62]	0.38	23 [0–64]	0.33	22 [0–81]	0.50
Absent	180	0 [0–80]		0 [0–67]		0 [0–232]		50 [0–87]	
VI									
Present	21	5 [0–50]	0.44	3 [0–60]	0.50	1.5 [0–105]	0.28	33 [0–80]	0.27
Absent	174	0 [0–80]		0 [0–67]		0 [0–232]		52 [0–87]	
PL									
Present	23	15 [0–50]	0.02	17 [0–62]	0.12	4.3 [0–105]	0.04	17 [0–87]	0.09
Absent	172	0 [0–80]		0 [0–67]		0 [0–232]		54 [0–83]	
Adenocarcinoma [2–3 cm]									
LY									
Present	22	20 [0–30]	0.50	36 [0–61]	0.12	36 [0–705]	0.35	17 [0–80]	0.13
Absent	66	8 [0–60]		13 [0–67]		4.8 [0–103]		42 [0–84]	
VI									
Present	43	20 [0–60]	0.02	40 [0–61]	< 0.01	40 [0–100]	< 0.01	9 [0–81]	0.01
Absent	45	0 [0–50]		0 [0–67]		0 [0–103]		63 [0–84]	
PL									
Present	30	20 [0–60]	0.01	40 [0–61]	0.02	42 [0–100]	0.01	7 [0–81]	0.02
Absent	58	0 [0–50]		0 [0–67]		0 [0–103]		51 [0–84]	
Adenocarcinoma [3–4 cm]									
LY									
Present	11	10 [0–40]	0.41	32 [0–53]	0.80	8.8 [0–80]	0.46	11 [0–77]	1.00
Absent	31	4 [0–40]		20 [0–68]		9 [0–108]		15 [0–83]	
VI									
Present	22	9 [0–40]	0.76	29 [0–60]	0.93	8.4 [0–77]	0.79	13 [0–83]	0.90
Absent	20	7 [0–40]		22 [0–68]		8.4 [0–108]		19 [0–81]	
PL									
Present	21	12 [0–40]	0.83	32 [0–68]	0.97	8 [0–108]	0.78	13 [0–83]	0.61
Absent	21	4 [0–40]		34 [0–60]		10 [0–80]		5 [0–81]	

LY, lymphatic permeation; VI, vascular invasion; PL, pleural invasion

Table 7 Univariate analysis of postoperative survival according to smoking history among adenocarcinoma patients

Factors	n	OS		RFS		DSS	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Lepidic adenocarcinoma							
Smoking							
Ever	54	1.64 (0.47–5.71)	0.44	1.58 (0.51–4.94)	0.43	1.72 (0.11–27.6)	0.70
Never	73	1		1		1	
Papillary adenocarcinoma							
Smoking							
Ever	63	1.59 (0.64–3.93)	0.31	1.50 (0.71–3.15)	0.29	1.28 (0.43–3.86)	0.66
Never	52	1		1		1	
Acinar adenocarcinoma							
Smoking							
Ever	36	2.11 (0.56–7.99)	0.27	2.29 (0.87–6.03)	0.09	1.60 (0.29–8.77)	0.59
Never	26	1		1		1	
Solid adenocarcinoma							
Smoking							
Ever	16	22.8 (0.00–4,752)	0.67	23.2 (0.00–1,427)	0.58	22.9 (0.00–2,840)	0.74
Never	1	1		1		1	
Adenocarcinoma with micropapillary component							
Smoking							
Ever	19	1.17 (0.28–4.95)	0.83	1.75 (0.43–7.01)	0.43	1.74 (0.41–5.81)	0.45
Never	15	1		1		1	

OS, overall survival; RFS, recurrence free survival; DSS, diseases specific survival; HR, hazard ratio; CI, confidence interval.

Table 8 Univariate analysis of postoperative survival according to smoking history among adenocarcinoma patients

Factors	n	Cigarettes per day		Years of smoking (year)		Pack-years		Quit years (year)	
		Median [range]	P	Median [range]	P	Median [range]	P	Median [range]	P
Lepidic adenocarcinoma									
LY									
Present	7	0 [0–20]	0.71	0 [0–30]	0.78	0 [0–30]	0.94	68 [0–81]	0.59
Absent	120	0 [0–60]		0 [0–68]		0 [0–147]		62 [0–84]	
VI									
Present	6	10 [0–20]	0.46	8 [0–41]	0.83	7.5 [0–41]	0.69	58 [6–80]	0.62
Absent	121	0 [0–60]		0 [0–68]		0 [0–147]		61 [0–84]	

Table 8 (*continued*)

Table 8 (*continued*)

Factors	n	Cigarettes per day		Years of smoking (year)		Pack-years		Quit years (year)	
		Median [range]	P	Median [range]	P	Median [range]	P	Median [range]	P
PL									
Present	12	18 [0–40]	0.01	23 [0–68]	0.04	12.5 [0–100]	0.05	27 [0–80]	0.25
Absent	115	0 [0–60]		0 [0–61]		0 [0–147]		65 [0–84]	
Papillary adenocarcinoma									
LY									
Present	22	9 [0–40]	0.88	27 [0–62]	0.36	8.4 [0–69]	0.63	14 [0–80]	0.19
Absent	93	5 [0–60]		3 [0–67]		1.5 [0–90]		40 [0–82]	
VI									
Present	40	10 [0–60]	0.27	24 [0–57]	0.13	8.4 [0–90]	0.09	14 [0–81]	0.02
Absent	75	0 [0–50]		0 [0–67]		0 [0–74]		48 [0–82]	
PL									
Present	32	18 [0–60]	0.08	36 [0–62]	0.02	41 [0–90]	0.02	2 [0–81]	<0.01
Absent	83	2 [0–50]		0 [0–67]		0.3 [0–90]		42 [0–82]	
Acinar adenocarcinoma									
LY									
Present	12	15 [0–40]	0.62	38 [0–61]	0.23	30 [0–80]	0.37	13 [0–77]	0.52
Absent	50	10 [0–80]		10 [0–61]		6.5 [0–232]		24 [0–87]	
VI									
Present	29	15 [0–50]	0.35	38 [0–61]	0.05	31.5 [0–105]	0.06	12 [0–83]	0.13
Absent	33	2 [0–80]		2 [0–58]		0.8 [0–232]		38 [0–87]	
PL									
Present	22	5 [0–50]	0.90	0 [0–61]	0.47	13 [0–105]	0.98	40 [0–87]	0.44
Absent	40	10 [0–80]		23 [0–61]		25 [0–232]		21 [0–84]	
Solid adenocarcinoma									
LY									
Present	7	30 [20–30]	0.60	47 [5–53]	0.81	53 [5–77]	0.67	3 [0–53]	0.54
Absent	10	20 [0–50]		39 [0–60]		36 [0–108]		0 [0–78]	
VI									
Present	11	30 [0–40]	0.96	37 [0–51]	0.05	52.5 [0–76.6]	0.59	0 [0–0]	< 0.01
Absent	6	23 [3–50]		52 [37–60]		49.6 [9–108]		5 [0–78]	
PL									
Present	7	30 [6–40]	0.19	37 [5–54]	0.48	64.5 [4.5–108]	0.54	4 [0–53]	0.16
Absent	10	20 [0–50]		49 [0–60]		48.6 [0–103]		0 [0–0]	

Table 8 (*continued*)

Table 8 (*continued*)

Factors	n	Cigarettes per day		Years of smoking (year)		Pack-years		Quit years (year)	
		Median [range]	P	Median [range]	P	Median [range]	P	Median [range]	P
Adenocarcinoma with micropapillary component									
LY									
Present	8	13 [0–40]	0.74	24 [0–57]	0.44	25.4 [0–64]	0.54	15 [0–77]	0.80
Absent	26	3 [0–50]		3 [0–61]		0.4 [0–94]		51 [0–81]	
VI									
Present	15	10 [0–40]	0.97	2 [0–57]	0.89	0.4 [0–94]	0.81	16 [0–81]	0.81
Absent	19	10 [0–50]		10 [0–61]		0.3 [0–61]		48 [0–77]	
PL									
Present	10	20 [0–40]	0.07	36 [0–57]	0.17	46.9 [0–94]	0.06	10 [0–81]	0.18
Absent	24	1 [0–50]		1 [0–61]		3 [0–61]		51 [0–77]	

LY, lymphatic permeation; VI, vascular invasion; PL, pleural invasion.

smokers (*Table 9* and *Figure 3*). This indicates that at least 10 years of smoking cessation may be needed to achieve similar postoperative prognosis as that of non-smokers in cases of adenocarcinomas ≤3 cm. In contrast, adenocarcinomas >3 cm may grow and invade independent of the preoperative smoking status.

Discussion

Pathological factors including LY, VI, and PL were significantly related to the degree of preoperative smoking in adenocarcinomas, particularly those with invasive diameters of 2–3 cm, whereas such a relationship was not identified in non-adenocarcinomas. As multiple studies have stated, our findings agree that some clinicopathological factors, including VI and PL, were unfavorable prognostic factors in surgically resected early-stage NSCLC (*Tables 2,3*) (4-6). Obviously, these pathological findings represent the process of metastasis of the tumor cells. As summarized in *Tables 4-6*, smoking would promote this process, particularly in adenocarcinomas ≤3 cm, which indicates that the malignant extent of adenocarcinoma in heavy smokers is relatively high and could lead to poor prognosis, despite the small size. Indeed, some clinical trials have demonstrated that chest screening tests, including screening CT, are recommended for high-risk patients with 30 or more pack-years of smoking (20). Needless to say, in addition to regular examinations of the chest, early

interventions such as surgery are essential for current/ex-smokers with NSCLC to improve their survival.

Ideally, all smokers should quit smoking for the prevention of NSCLC. Although there is a reduction in the numbers of smokers worldwide, several still love smoking (21). There is inadequate information regarding the duration of smoking cessation prior to the diagnosis of stage I NSCLC that may result in outcomes and prognosis in smokers similar to that in non-smokers. Such information, if available, may be useful in encouraging smokers to quit. In this study, we also evaluated the number of years of smoking cessation that would provide postoperative survival benefits to former smokers with small lung adenocarcinomas. Our findings suggest that ≥10 years of smoking cessation would improve RFS following resection. Zhou *et al.* reported that the benefit of smoking cessation is obtained after ≥9 years of smoking cessation in patients with NSCLC when compared with current smokers (19). Although that study included advanced NSCLC including squamous cell carcinomas, they reported similar findings as observed in our study. These data suggest that prolonged smoking cessation could inhibit the progression of lung cancer. This merit of smoking cessation should be conveyed to current smokers as it may result in significant survival benefits.

We also found a strong relationship between the histological subtypes of adenocarcinoma and smoking. PL correlated with smoking in lepidic and papillary adenocarcinomas, and VI was related to smoking in acinar

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Table 9 Correlation of pathological factors and smoking cessation years according to invasive size of adenocarcinoma

Factors	Never + 5 y.c.			Never + 10 y.c.			Never + 15 y.c.			Never + 20 y.c.			Never		
	Ever	nv.+5	P	Ever	nv.+10	P	Ever	nv.+15	P	Ever	nv.+20	P	Ever	Never	P
Adenocarcinoma (≤2 cm)															
LY															
Present	4	11	0.50	6	9	0.20	7	8	0.14	7	8	0.25	8	7	0.79
Absent	34	146		41	139		49	131		56	124		84	96	
VI															
Present	5	16	0.57	8	13	0.17	9	12	0.13	10	11	0.14	11	10	0.65
Absent	33	141		39	135		47	127		53	121		81	93	
PL															
Present	6	17	0.41	10	13	0.04	10	13	0.14	11	12	0.10	15	8	0.08
Absent	32	140		37	135		46	126		52	120		77	95	
Adenocarcinoma (2–3 cm)															
LY															
Present	8	14	0.28	10	12	0.21	10	12	0.62	12	10	0.23	15	7	0.32
Absent	16	50		20	46		25	41		26	40		35	31	
VI															
Present	13	30	0.64	22	21	0.01	24	19	0.01	25	18	0.01	31	12	0.01
Absent	11	34		8	37		11	34		13	32		19	26	
PL															
Present	11	19	0.21	16	14	0.01	18	12	0.01	19	11	0.01	22	8	0.04
Absent	13	45		14	44		17	41		19	39		28	30	
Adenocarcinoma (3–4 cm)															
LY															
Present	4	7	1.00	5	6	1.00	7	4	0.49	7	4	0.73	8	3	0.72
Absent	13	18		13	18		15	16		17	14		19	12	
VI															
Present	9	13	1.00	9	13	1.00	13	9	0.54	13	9	1.00	15	7	0.75
Absent	8	12		9	11		9	11		11	9		12	8	
PL															
Present	8	13	1.00	8	13	0.76	11	10	1.00	11	10	0.76	13	8	1.00
Absent	9	12		10	11		11	10		13	8		14	7	

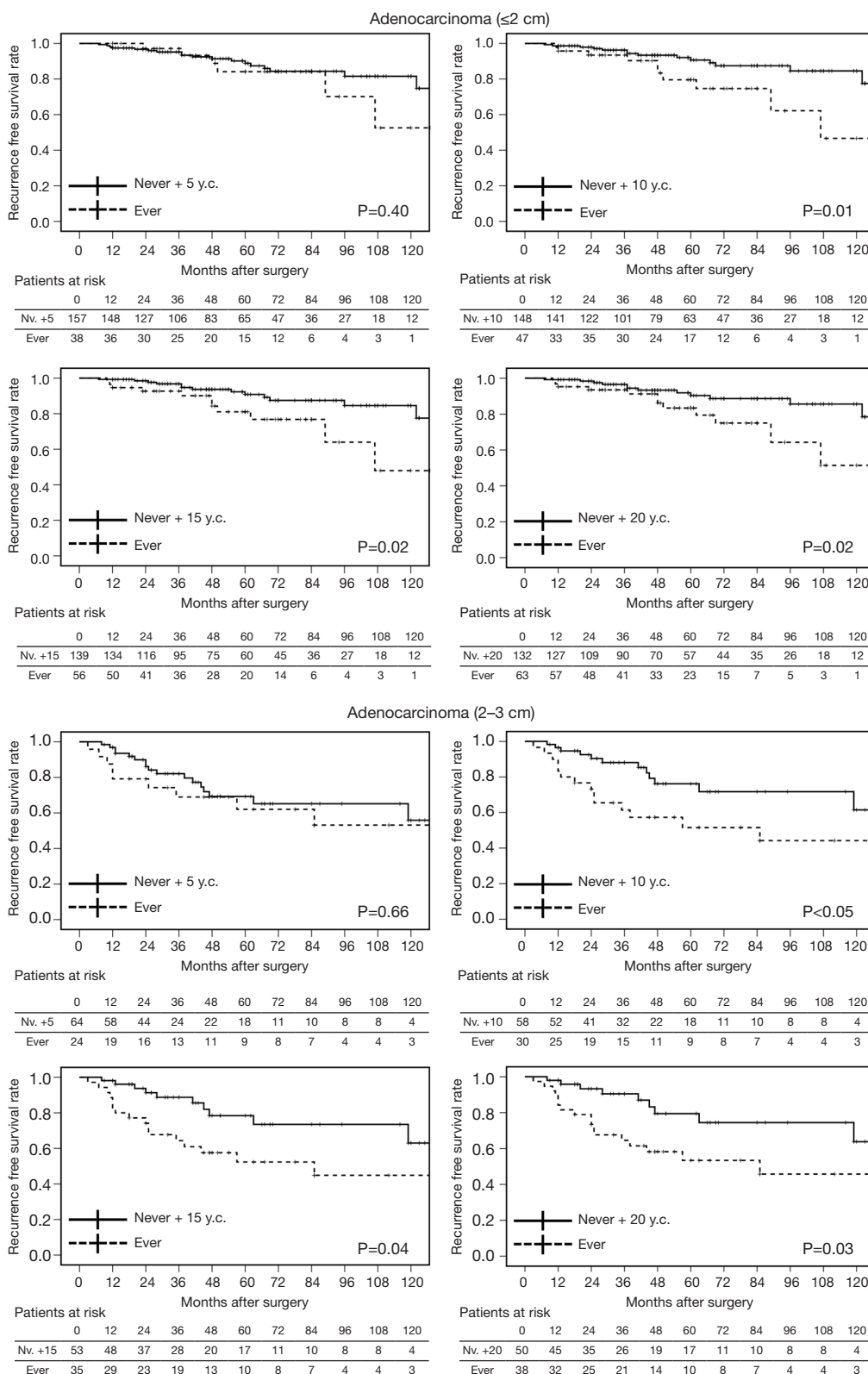LY, lymphatic permeation; VI, vascular invasion; PL, pleural invasion; y.c., year cessation; nv., never.

Figure 3 Comparison of recurrence-free survival for adenocarcinoma of various sizes (≤2 and 2–3 cm) of former smokers with ≥ X years of cessation (y.c.) combined with nonsmokers (never + X y.c.).

and solid adenocarcinomas. Few studies have investigated the differences in the invasion pattern of the various histological subtypes. However, it is certain and quite interesting that smoking accelerates the malignant potential of adenocarcinomas in accordance with the invasive features of the respective predominant patterns.

Smoking is usually evaluated in "pack-years". We also examined the number of cigarettes per day, smoking years, and smoking cessation years. Similar tendencies regarding the relationships with pathological factors were observed (*Tables 5,6,8*). Although we cannot comment on the evaluation method best suitable to predict postoperative survival in these patients, smoking is certainly associated with local invasion and progression of lung adenocarcinomas.

This study has some limitations. First, this was a retrospective study at single Institute; therefore, patient selection bias and time trend bias are inevitable. Second, we did not include the postoperative treatments such as adjuvant therapy and post-recurrence treatment in our analyses. Genetic differences may influence these treatment modalities, which could prolong survival after surgery and relapse. Third, we did not focus on postoperative smoking status because we did not ask patients if they had resumed smoking following surgery in every follow-up clinic. We also did not collect information regarding second-hand smoking. Fourth, our analyses regarding smoking history were based on medical records. Objective measurements such as carboxyhemoglobin and cotinine may have been more reliable biomarkers to evaluate tobacco smoking exposure. Fifth, in the analyses of non-adenocarcinomas, it is possible that true probability may not have been obtained owing to the small sample size. Additionally, postoperative survival for each segment of smoking cessation period should be compared to confirm the number of years after cessation that can improve the postoperative survival (e.g., never *vs.* 5 y.c. *vs.* 10 y.c. *vs.* 15 y.c. *vs.* 20 y.c.). Further investigations with a larger number of patients are required to substantiate our findings.

Conclusions

Smoking promotes tumor progression, which is represented by VI and PL, particularly in pathological stage I adenocarcinomas measuring 2–3 cm. Larger adenocarcinomas and non-adenocarcinomas of any size may grow and become invasive independent of the preoperative smoking status. Ten or more years of smoking cessation may

have associated postoperative survival benefits. Outcomes appear to be proportionally related to the duration of smoking cessation. Therefore, current smokers should quit smoking to ensure longer survival even though they suffer from small-sized lung adenocarcinomas in the future.

Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by our institutional review board in March 2020 (approved number #2483). The requirement of informed consent was waived due to the retrospective design of the study and because no personally identifiable information was collected. Clinical data including smoking history were recorded by medical staff (nurses and/or doctors) and used for statistical analysis. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013).

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