Significance of Smoking as a Postoperative Prognostic Factor in Patients with Non-small Cell Lung Cancer

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Introduction: In this study, we investigated the influence of smoking on the postoperative prognosis in patients with non-small cell lung cancer.

Methods: The subjects consisted of 770 patients who underwent a resection of lung cancer in our department between 1994 and 2005. We compared the clinico-pathological findings between the smoking and never-smoking groups. The pack-year index (PYI) was used as a smoking index.

Results: The smoking group consisted of 569 patients (74%), and the never-smoking group consisted of 201 patients (26%). The smokers were composed of 492 men and 77 women. Among the adenocarcinoma patients, there were 293 (61%) smokers and 185 (39%) never-smokers. The patients with squamous cell carcinoma included 204 (95%) smokers and 10 (5%) never-smokers. The proportion of patients with stage IA disease was significantly higher in the never-smokers than that of the smokers. The 5-year survival rate after surgery was 66% in the never-smoking group; however, the rates were 56% in patients with a PYI more than or equal to 20, and 55% in those with PYI more than 20. Seventy-nine (13.9%) patients in the smoking group and seven (3.5%) patients in the never-smoking group died of other diseases, with a significant difference ($p < 0.01$). Of these patients, 44 (56%) and 13 (16%) in the smoking group died of respiratory and cardiovascular disorders, respectively. In our series, excluding those who died of other diseases, there were no significant differences in the postoperative prognosis.

Conclusions: In the smoking group, the prognosis was poorer than that in the never-smoking group. The higher proportion of early stage disease (stage IA) and female gender were major causes of the better prognosis of the never-smokers. Nevertheless, the high pulmonary/cardiovascular complication-related mortality was another cause of the poor prognosis of the smokers with lung cancer.

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Lung cancer is still the leading cause of cancer-related mortality in many industrialized countries.[1,2] It becomes a considerable public health problem, and reducing the death of lung cancer remains an important issue. Smoking is well known to be the main cause of lung cancer and therefore an increase of lung cancer mortality is significantly associated with the increase in the number of smokers.[3] It was estimated that 80 to 90% of lung cancer cases can be attributed to smoking.[4,5] Approximately one third of adults are known to be smokers, and smoking rates are still increasing among the female population. Intensive awareness campaigns to quit smoking have greatly contributed to the prevention of lung cancer as a primary prophylaxis.[5–7] Moreover, smoking is also strongly related to several pulmonary and cardiovascular diseases such as chronic obstructive pulmonary disease, asthma, hypertension, and ischemic heart disease.[8] Because passive smoke is also a well-known risk factor for such respiratory diseases, including lung cancer, efforts to prohibit both public smoking and workplace smoking have been promoted over the past decade in several countries.

The effects of smoke on the respiratory system are understood by two main mechanisms: inducing inflammation and a mutagenic (carcinogenic) effect. Inflammation consists of damage of the ciliated epithelia, increased mucus secretion, and the accumulation of activated inflammatory cells in the respiratory tract. Tobacco smoke contains more than 60 carcinogens, and among them the most harmful substances are the polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines.[9,10] Therefore, tobacco smoke is an established human carcinogen in not only lung cancer but also in several other cancers such as cancer of larynx, oral cavity and esophagus, and bladder, and it is associated with the concept of field cancerization.[11] Thirty percent of all cancers is reported to be caused by smoking.[12] Nevertheless, the influence of smoking on the prognosis of lung cancer remains to be clarified. In the present study, we investigated the influence of smoking on the postoperative prognosis in patients with non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

The subjects consisted of 770 patients who underwent resection of primary NSCLC in our department between 1994 and 2005. We compared the clinico-pathological findings between the smoking and never-smoking groups. The patients' records including the clinical data, preoperative examination results, details of surgical operation, histopathological findings, and tumor, node, metastasis staging were also reviewed. The history of cigarette smoking was thoroughly evaluated according to the description given in the patient's medical records on admission. The pack-year index (PYI) was used as a smoking index. The PYI was defined as the number of cigarette packs (20 cigarettes per pack) consumed a day multiplied by years. The patients were classified to three subgroups according to the PYI as never-smoker, less than 20 (PYI ≤20), and more than 20 (PYI >20). Never-smokers were defined as having less than 20 cigarettes in a lifetime. The calculation of PYI for smokers included both current smoking and former smoking.

The preoperative assessments included chest roentgenography, computed tomography of the chest, and upper abdomen, magnetic resonance imaging of brain, bronchoscopy, and bone scintigraphy. All resected specimens including the primary tumor and the systematically dissected hilar and mediastinal lymph nodes were examined for tumor histology and the extent of lymph node metastases. The histopathological findings were classified according to the World Health Organization criteria and the Union Internationale Contra le Cancer tumor, node, metastasis staging system were employed.[13,14] The reasons for classifying 35 patients as stage IV included pulmonary metastasis in 17, bone metastasis in 7, axillay lymph node metastasis in 4, adrenal metastasis in 3, liver metastasis in 2, brain metastasis in 1, and metastasis of the kidney in 1 patient. The pulmonary metastasis, axillary lymph node metastasis, and adrenal metastasis were also resected either concurrently or sequentially. Bone metastasis was treated using radiotherapy, and brain metastasis was also treated by gamma knife therapy.

Follow-up information was obtained from all patients through office visits or telephone interviews with either the patient, a relative, or their primary physicians. The mean observation time was 3.3 years. The survival curve was calculated by the Kaplan-Meier method, and compared by using the log-rank test for univariate analysis. The prognostic factors were analyzed by a multivariate analysis using Cox's proportional hazard model after adjusting for potential confounding factors. Categorical variables were compared by Fisher's exact test for proportion. The differences were considered to be significant if the p value was less than 0.05. The Statview V software program (Abacus Concept, Berkeley, CA) was used for all statistical analyses.

RESULTS

The smoking group consisted of 569 (73.9%) patients, and the never-smoking group consisted of 201 (26.1%) patients (Table 1). Concerning gender, the 569 patients consisted of 492 (86.5%) men and 77 (13.5%) women. The never-smoking group was composed of 33 (16.4%) men and 168 (83.6%) women. The proportion of women in the never-smokers was significantly higher than that of men. The proportion of adenocarcinoma was significantly higher in the never-smokers than the smokers. In the smokers with PYI more than 20, pathological stage IA disease were less frequent than that in the never-smoking group (Table 1). Among adenocarcinoma patients, there were 293 (61.3%) smokers and 185 (38.7%) never-smokers. The proportion of patients with stage IA adenocarcinoma was significantly higher in never-smokers than that in the smokers with PYI more than 20 ($p < 0.01$). There was no difference in the presence or absence of symptoms between smokers and never-smokers. The patients with squamous cell carcinoma consisted of 204 (95.3%) smokers and 10 (4.7%) never-smokers.

TABLE 1. Characteristics of Non-small Cell Lung Cancer Patients According to Smoking History

Characteristics	Smoker (PYI >20) (n = 492) Number of Patients (%)	Smoker (PYI <20) (n = 77) Number of Patients (%)	Never Smoker (n = 201) Number of Patients (%)
Male	444 (90.2)	48 (62.3)	33 (16.4)[a]
Female	48 (9.8)	29 (37.7)	168 (83.6)
Histology			
Adenocarcinoma	232 (47.2)	59 (76.6)	185 (92.0)[b]
Squamous cell ca.	193 (39.2)	11 (14.3)	10 (5.0)
Large cell ca.	36 (7.3)	1 (1.3)	1 (0.5)
Others	31 (6.3)	6 (7.8)	5 (2.5)
Pathological stage			
IA	138 (28.0)	34 (44.2)	99 (49.3)[c]
IB	102 (20.7)	11 (14.3)	35 (17.4)
II	77 (15.7)	7 (9.1)	14 (7.0)
IIIA	108 (22.0)	9 (11.7)	19 (9.5)
IIIB	45 (9.1)	13 (16.9)	24 (11.9)
IV	22 (4.5)	3 (3.9)	10 (5.0)

[a] The proportion of never smokers was significantly lower in men than in women ($p < 0.01$).
[b] The incidence of adenocarcinoma in the never smoker was significantly higher than that in the other smoker groups (both in PYI ≤20 and PYI >20) ($p < 0.01$).
[c] The proportion of stage IA disease in never smokers was significantly higher than that in the smokers with PYI >20 ($p < 0.01$).

The 5-year survival rate after surgery was 66.8% in the never-smokers. The rates were 56.2% in the smokers with PYI less than or equal to 20 and 55.1% in those with PYI more than 20 (Figure 1*A*). The prognosis was significantly poorer in the smokers with PYI more than 20 than that of the never-smokers ($p = 0.001$). The 5-year survival rates in patients at stage I were 83.2%, 77.8%, and 69.9% in the never-smokers, smokers with PYI of 20 or less, and those with PYI more than 20, respectively (Figure 1*B*). In patients at stage I, the prognosis was also significantly poorer in the smokers with PYI more than 20 than that of the never-smokers ($p = 0.007$). In patients at stage II and III, no significant differences were observed among the three groups (Figures 1*C*, *D*). In the patients with adenocarcinoma, the overall survival was significantly lower in the smoking group (smokers with PYI ≤20; 59.1%, PYI >20; 59.7%) than that of the never-smokers (70.3%) ($p = 0.022$) (Figure 2). In a

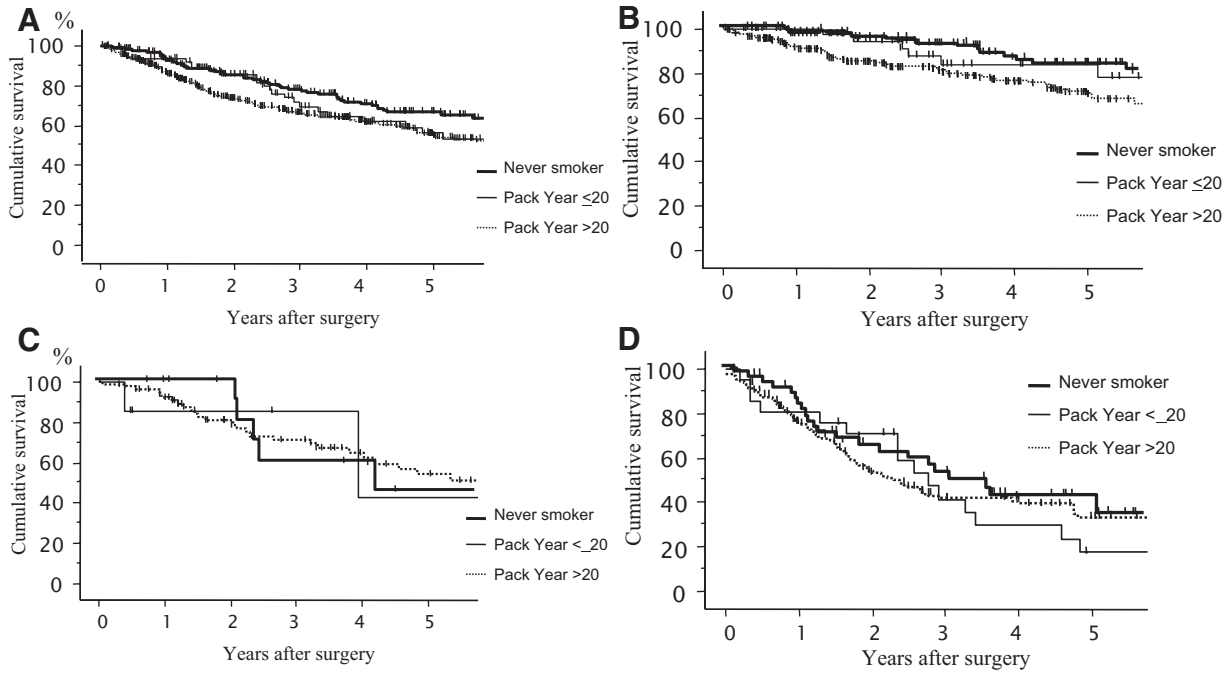

FIGURE 1. Overall survival curves of patients according to smoking history. *A*, Overall survival curves of all patients according to smoking history. The 5-year survival rates were 66.8%, 56.2%, and 55.1% in never-smokers, smokers with PYI >20, and smokes with PYI ≤20, respectively. The prognosis was significantly poorer in the smokers with PYI >20 than that of the never-smokers ($p = 0.001$). *B*, The 5-year survival rates in patients at stage I were 83.2%, 77.8%, and 69.9% in the never-smokers, smokers with PYI ≤20, and smokers with PYI >20, respectively. In patients at stage I, the prognosis was also significantly poorer in the smokers with PYI >20 than that of the never-smokers ($p = 0.007$). C, The overall survival in the patients at stage II. There was no significant difference among the three groups (never-smoker; 45.0%, smokers with PYI ≤20; 42.9%, smokers with PYI >20; 53.9%). *D*, The overall survival in the patients at stage III. The 5-year survival rates were 42.0% in the never-smokers, 17.8% in smokers with PYI ≤20, and 35.5% in smokers with PYI >20.

multivariate analysis using variables such as smoking, sex, age, pathological stage, T factor, and N factor as significant prognostic factors, smoking was not a significant prognostic factor independent of the other factors ($p = 0.871$) (Table 2). Because the smoking status was suggested to be a prognostic factor for stage I, a multivariate analysis was therefore also performed. Because smoking was more popular for men than women, and squamous cell carcinoma was more frequently observed than adenocarcinoma, both the sex and histological type were thus included in the analysis. Although being a never-smoker was found to be a significantly better prognostic factor based on a univariate analysis ($p = 0.007$), the hazard ratio of never-smokers in a multivariate analysis was 0.893 ($p = 0.758$), and therefore smoking was not determined

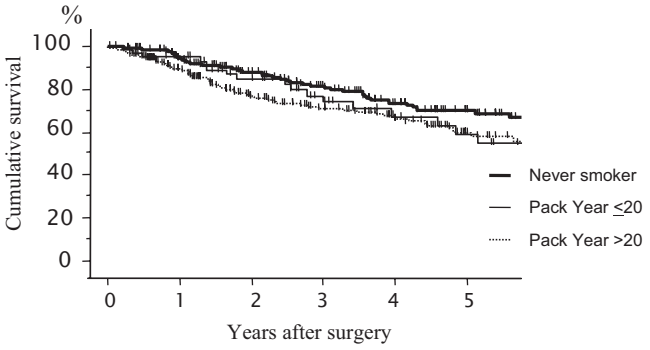

FIGURE 2. Overall survival curves of patients with adenocarcinoma according to smoking history. In the patients with adenocarcinoma, the 5-year survival rates were 70.3%, 59.1%, and 59.7% in never-smokers, smokers with PYI >20, and smokers with PYI ≤20, respectively. The never-smoker had a significantly more favorable prognosis than smokers with PYI >20 ($p < 0.01$).

TABLE 2. Multivariate Cox Proportional Hazard Analysis of the Overall Survival in All Patients

Factors	Relative Risk	95% Confidence Interval	*p*
Women vs. men	0.706	0.483–1.032	0.070
Tumor size (T1 vs. T2–4)	0.412	0.301–0.563	<0.001
Nodal status (N0 vs. N1–3)	0.478	0.369–0.620	<0.001
Histology (adenocarcinoma vs. others)	0.956	0.722–1.266	0.752
Age (<75 vs. >75)	0.716	0.537–0.954	0.022
Smoking status (never smoker vs. former and current smoker)	0.967	0.688–1.322	0.871

to be a significant independent prognostic factor in patients at stage I (Table 3).

Seventy-nine (13.9%) patients in the smoking group (smokers with PYI >20 and PYI ≤20) and seven (3.5%) patients in the never-smoking group died of other than lung cancer, thus indicating a significant difference in mortality rate caused by other diseases ($p < 0.01$) (Table 4). Of these patients, 41 (8.3%) of the smokers with a PYI more than 20 and two (1.0%) in the never-smoking group died of respiratory disease, thus indicating a significant difference ($p < 0.01$). Eleven (3.8%) patients in the smoking group and 1 (0.5%) in the never-smoking group died because of cardiovascular disorders. Fourteen patients in the smoking group died of other cancers (second primary lung cancer in five, esophageal cancer in two, laryngeal cancer in two, hepatoma in two, gastric cancer in one, colon cancer in one, and pancreatic cancer in one). On the other hand, three patients among 201 never-smokers died of two gastric cancers and one colon cancer, respectively. The death from primary cancer other than lung cancer tended to be more frequent (2.6%) in the smokers with PYI more than 20 than that (1.5%) of the never-smoker. Of our series, excluding those who died of other than lung cancer, the 5-year survival rates were 70.2% in the never-smoking group, 67.3% in the smokers with a PYI less than or equal to 20, and 66.5% in those with a PYI more than 20. Nevertheless, no significant differences were observed among cancer-specific survival (Figure 3).

TABLE 4. Causes of Death Unrelated to Lung Cancer

Cause of Death	Smoker (PYI >20) (n = 492)	Smoker (PYI <20) (n = 77) Number of Patients (%)	Never Smoker (n = 201) Number of Patients (%)
Pulmonary disease	41 (8.3)[a]	3 (3.9)	2 (1.0)
Cardiac and cerebrovascular disease	8 (1.6)	3 (3.9)	1 (0.5)
Other cancer	13 (2.6)	1 (1.3)	3 (1.5)
Others	9 (1.9)	1 (1.3)	1 (0.5)
Total	71 (14.4)	8 (10.4)	7 (3.5)

[a] The incidence of death due to pulmonary disease was significantly higher in the smokers with PI >20 than those in never smokers ($p < 0.01$).

DISCUSSION

Smoking is an apparent risk factor for the development of lung cancer.[15,16] Compared with never-smokers, heavy smokers are 10 to 20 times more likely to develop lung cancer.[17] Smoking is also responsible not only for lung cancer but also for such aero-digestive tract tumors as the larynx, oral cavity, and esophagus.[9–11] Slaughter et al.[11] first proposed the concept of "field cancerization" based on observations of the occurrence of multiple primary tumors. Tobacco smoking induces somatic mutations with various DNA damage such as mutation of p53, and the normal epithelium can be "preconditioned" by carcinogen exposure contained in smoke.[18] Cigarette smoke contains about 4000 chemical agents, including over 60 carcinogens such as polycyclic aromatic hydrocarbons, *N*-nitrosamines, aromatic amines, heterocyclic aromatic amines, and aldehydes.[10] Smoking is well known to have a strong association with the incidence of squamous cell carcinoma and small cell carcinoma as compared with adenocarcinoma.[19] Nevertheless, smoking also reported to contribute to the development of multiple primary lung adenocarcinomas, especially in patients with preexisting atypical adenomatous hyperplasia.[20]

Smoking not only causes lung cancer but it also might negatively affect the prognosis of patients with lung cancer. It is known that smoking affects the systemic immune response and reduces the proliferative activity of the helper T cells and B cells.[21] Smoking contributes to an increase in the white blood cell count and a decline in the circulating natural killer (NK) cell count.[22] The host immune defense mechanisms might play an important role in eliminating cancer cells and controlling tumor growth and metastases formation. Several investigators also reported that smokers had lower levels of NK-cell activity than non-smokers and smoking impaired the systemic NK cell-dependent tumor immune surveillance.[23,24] Moreover, smoking has been reported to reduce local airway immunity and that the alveolar macrophages of smokers

TABLE 3. Multivariate Cox Proportional Hazard Analysis of the Overall Survival in Patients at Stage I

Factors	Relative Risk	95% Confidence Interval	p
Women vs. men	0.589	0.255–0.638	0.122
Tumor size (T1 vs. T2)	0.403	0.301–0.563	<0.001
Histology (adenocarcinoma vs. others)	0.997	0.610–1.630	0.990
Age (<75 vs. >75)	0.574	0.364–0.907	0.017
Smoking status (never smoker vs. former and current smoker)	0.893	0.434–1.837	0.758

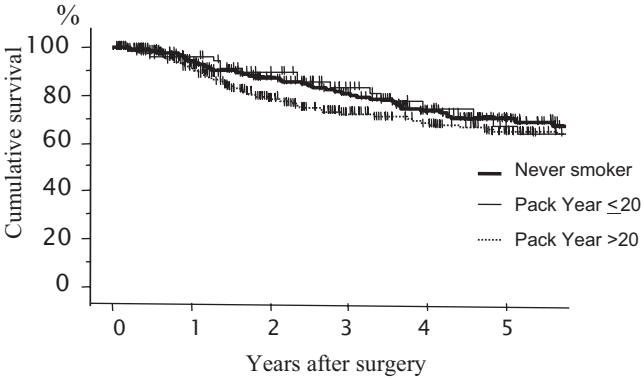

FIGURE 3. Cancer-specific survival curves of the patients according to smoking history. With the exception of death caused by unrelated disease, the 5-year survival rates were 70.2%, 67.3%, and 69.6% in never-smokers, smokers with PYI >20, and smokers with PYI ≤20, respectively. There was no significant difference.

suppressed NK cell activity by producing prostaglandins and oxygen radicals.[25] Smoking may induce damages of numerous alveolar macrophage functions, and it inhibited macrophage accumulation and markedly reduced phagocytic and microbicidal activity of the alveolar macrophage.[25]

It is considered that smoking may induce resistance to chemotherapeutic agents of lung cancer by altering metabolism for such drugs by induction of cytochrome P450 (CYP).[4] The nicotinic acetylcholine receptors in bronchial and vascular endothelial cells respond to acetylcholine, nicotine, or some nitrosoamines and modulate cell proliferation through the calcium-dependent pathways.[26] Smoking induces mutations through the formation of DNA-adducts in the bronchial and alveolar epithelium and contributes to the development of lung cancer. The expression of CYP and arylhydrocarbon receptor in the bronchial epithelium was increased in heavy smokers with NSCLC, and CYP positivity showed a close correlation with a poor survival of lung cancer patients.[27] Tsao et al.[28] reported that never-smokers were found to have a better outcome over smokers when treated with chemotherapy, although continued smoking during the chemotherapy did not affect on survival. Another retrospective report demonstrated that former and never-smokers had also better survival rates than current smokers.[29] Regarding the smoking status on radiation therapy for NSCLC, it was reported that current smokers with stage I and II disease may have a poorer prognosis than the non-smoker after radiation therapy.[30]

Bryant et al.[31] reported that never-smokers who develop NSCLC are more likely to be young and women, and that never-smokers show a significantly better survival than smokers. In the present study, the proportion of patients with stage IA was also significantly higher in never-smokers than that in smokers. Moreover, proportion of women in the never-smokers (83.5%) was significantly higher than in the smokers (13.5%). These might be major causes for the favorable prognosis of the never-smokers. Nevertheless, when death from other than lung cancer was excluded, smoking was not found to be a prognostic factor. Smoking is also responsible for several pulmonary and cardiovascular diseases such as chronic obstructive pulmonary disease, asthma, hypertension, atherosclerosis, and ischemic heart disease, all of which have a significant systemic impact for the patient's condition.[8] The prevalence of pulmonary/cardiovascular complication-related mortality after surgery was significantly higher in the smokers than the never-smokers (Table 4).

Baliunas et al.[32] reported that cigarette smoking is one of the most important risk factors for the burden of various diseases and is a major contributor to mortality including malignant neoplasms, cardiovascular diseases, and respiratory diseases. These findings suggest that the unfavorable prognosis of smokers might not be because of the biological behavior of lung cancer. The studies about influences of smoking on genetic alteration and damage of lung tissue, and suppression of immune surveillance should be necessary for further understanding of the biological behavior of lung cancer in smokers.

We concluded that the prognosis of postoperative patients with lung cancer was poorer in the smoking group than that in the never-smoking group. It was thus considered that higher proportions of early stage disease (stage IA) and female gender were a major cause of the better prognosis of the never-smoker. Nevertheless, the high pulmonary/cardiovascular complication-related mortality was another cause of the poor prognosis of the smokers with lung cancer. Therefore, the harmful effects of smoking against complicating benign diseases, and carcinogenesis of other aero-digestive tract tumors were thus found to have a substantial influence on the postoperative prognosis of primary NSCLC. Further prospective studies and better documentation of smoking history and passive smoking are therefore required to better characterize the effect of smoking on the prognosis of surgical treatment.

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