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The Role of Cigarette Smoking in the Development of Primary Lung Adenocarcinoma：Concurrent Evaluation of Histological Grade and Prognosis of Each Histological Grade for Tumors Measuring Less than 20 mm in Diameter

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Abstract：Adenocarcinomas of the lung are observed in both cigarette smokers and non－smokers, and no or little association between cigarette smoking and the development of these tumors has previously been found. Recent studies, however, have reported that cigarette smoking increases the risk of adenocarcinoma, particularly that of less differentiated tumors. However, no studies have concurrently investigated the role of smoking in the development of primary lung adenocarcinoma in relation to the histological grade, and the prognosis of each histological grade. This is the first report to concurrently evaluate both of these areas. The study population consisted of 88 patients with small (less than 20－mm diameter) primary lung adenocarcinomas surgically resected at the Second Department of Surgery of Fukuoka University, Fukuoka, Japan. The patients ranged between 29 and 85 years of age, with an average age of 64. They were classified as either cigarette smokers (N＝47) or non–smokers (N＝41). Pathologically, the patients were categorized as having well–, moderately, or poorly differentiated adenocarcinoma (N＝53, 25, and 10, respectively). The smoking status correlated with the pathological differentiation of tumors：cigarette smoking was associated with less differentiated tumors ($p=0.09$). Cigarette smoking was significantly more frequent in men (N＝41) than women (N＝47；$p<0.001$), and a statistical trend was apparent between gender and histological grade less differentiated adenocarcinoma was diagnosed more frequently among men ($p=0.07$). Within the cigarette–smoking group, cumulative smoking was correlated with the development of poorly differentiated adenocarcinoma ($p<0.05$), particularly when the smoking index was≧1,000 ($p=0.004$). Furthermore, among cigarette smokers, poorly differentiated adenocarcinoma was associated with poorer prognosis than well– or moderately differentiated adenocarcinoma ($p=0.001$). Our study indicated a correlation between cigarette smoking and the histological grade of primary adenocarcinomas of the lung as well as a correlation between the histological grade and the prognosis.

Key words：**Cigarette smoking, Lung cancer, Adenocarcinoma, Histological grading, Prognosis**

1. Introduction

Lung cancer is the leading cause of cancer death in many industrialized countries, including Japan.[1)2)] Histologically, lung cancer is classified into small cell and non–small cell categories, the latter including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.[3)] Among the four major histological types of lung tumors (ade-

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nocarcinoma, squamous cell carcinoma, small cell carcinoma and large cell carcinoma), squamous cell carcinoma and small cell carcinoma are closely linked with cigarette smoking.[4)5)] In contrast, adenocarcinoma is observed in both cigarette smokers and non−smokers, and previously little or no association between cigarette smoking and the development of lung adenocarcinoma has been found.[6)7)] Recent studies, however, have reported that cigarette smoking increases the risk of adenocarcinoma, as well as squamous cell and small cell carcinoma of the lung.[8)9)]

According to the World Health Organization (WHO) Classification of Tumors, primary adenocarcinoma of the lung is typically classified into three histological grades ; well−, moderately and poorly differentiated.[10)] Tumors exhibiting a bronchioloalveolar pattern are virtually always well or moderately differentiated, whereas solid adenocarcinomas are poorly differentiated.[10)] Previous reports have suggested a relation between cigarette smoking and histological grade of lung adenocarcinoma ; finding that smoking increases the risk of poorly differentiated tumors.[8)11)] In addition, the above−mentioned WHO histological grading system has prognostic implications in non−T1 peripheral adenocarcinoma ; poorly differentiated adenocarcinoma exhibits worse prognosis than well or moderately differentiated adenocarcinomas.[10)] It has also been strongly suggested that cigarette smoking is related to the histological grade and prognosis, even in peripheral T1 adenocarcinoma.[12)]

In this study, we aimed to more clearly elucidate the role of cigarette smoking in the tumor grade and to determine prognosis associated with each grade. We focused on relatively small primary peripheral adenocarcinomas of the lung (less than 20 mm in diameter) for two reasons. First, we sought to minimize the confounding effect of tumor size as a factor in the data analysis, as large tumor size is a poor prognostic factor in itself. Second, we aimed to minimize the effect of variation in histological grading, since adenocarcinoma of the lung is histologically very heterogeneous (the major individual histologic patterns/subtypes are acinar, papillary, bronchioloalveolar, and solid with mucin production.)− and this tendency is greater among larger tumors.[10)]

To the best of our knowledge, this is the first English−language report to concurrently evaluate the role of cigarette smoking in the histological grade of primary adenocarcinoma of the lung, and prognosis of each histological grade.

2. Materials and Methods

2.1. Patients

The surgical pathology files of the Fukuoka University Hospital, Fukuoka, Japan, were searched for all cases of resected primary adenocarcinoma of the lung in which tumors measured less than 20 mm in diameter. Between January 1993 and December 2002, a surgical resection was performed in 128 patients with a pathological diagnosis of adenocarcinoma, including 106 who underwent a complete surgical resection. For the accuracy of survival analysis, we excluded cases with any other malignancies that occurred before or after the primary lung cancer ; therefore, the population for this study consisted of the remaining 88 subjects. None of the patients had distant metastases, as was confirmed by head and chest/abdominal computed tomography and radionuclide bone scanning before resection.

In this study, ex−smokers were included in the smoking group and informed consent was obtained from all subjects at the time of surgery.

2.2. Histological diagnosis and staging

Surgically resected specimens were routinely fixed in 15% buffered formalin, cut serially into 5−7 mm thick slices, and macroscopically examined for metastases. For the histological diagnosis, tumor tissue as well as surrounding lung tissue was taken from the section that contained the largest tumor diameter, and embedded in paraffin. Hematoxylin/eosin staining was performed using 4 μm sections. If the tumor exhibited a mostly solid growth pattern (Fig. 1(c) lower), then periodic acid Schiff reaction and alcian blue staining were performed to distinguish between poorly differentiated adenocarcinoma and poorly differentiated squamous carcinoma or large cell carcinoma.

The histological diagnosis was based on the WHO classification.[10)] In addition, all cases were categorized into three histological grades, largely

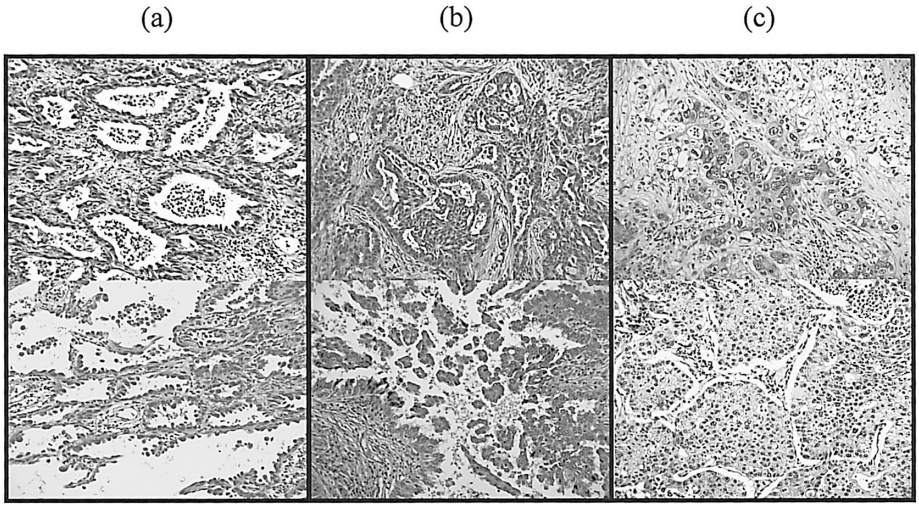

Fig. 1. (a)Histological appearance of well-differentiated adenocarcinomas. Tumors were composed mainly of glands lined by one-layered tumor cells, the bronchioloalveolar carcinoma belongs to this category (lower). (b)Moderately differentiated lesions contains glands in a cribiform pattern which were fused with one another (upper), or glands lined by tumor cells which were obviously layered, with or without a micropapillary pattern (lower). (c)Poorly differentiated carcinomas show mainly solid growth and only occasionally exhibit glandular/papillary patterns and/or mucus production.

according to the Japanese Lung Cancer Society criteria.[13] Briefly, well-differentiated tumors are mainly composed of glands lined by one-layered tumor cells ; bronchioloalveolar carcinoma belongs to this category (Fig. 1(a)). Moderately differentiated lesions are composed of glands in a cribriform pattern which are fused with one another, or glands lined by tumor cells showing obvious piling-up, with or without micropapillary patterns (Fig. 1(b)). Poorly differentiated carcinomas show mainly solid growth and only occasionally exhibit glandular/papillary patterns or mucus production (Fig. 1(c)). In cases where two or more patterns were observed, the tumor was classified as the dominant pattern.[11][12]

To stage tumors pathologically, the classification of the Union Internationale Contre le Cancer (UICC) was employed.[14]

2.3. Clinicopathological factors examined and statistical methods

The following clinicopathological factors were considered in this study : age ($\leq$60 years old or $>$ 60 years old) ; gender (male or female) ; lymph node metastasis status (negative or positive) ; invasion of the visceral pleura (negative or positive) ; and micropapillary pattern[15][16] (negative or positive). Associations between smoking and all the above clinicopathological factors were evaluated using the chi-square for independence test (2×2 or $m\times n$ contingency table) or, where appropriate, Fisher's exact test (without the Yates correction). Correlations among cumulativesmoking and histological grade were evaluated by the one-factor ANOVA and post-hoc tests. Cumulative smoking was represented by a smoking index, defined as the product of the number of cigarettes smoked per day and duration of smoking (years). The survival curves were plotted using the Kaplan-Meier method, and p-values were calculated using Wilcoxon's test.[17] All tests were one-tailed with $P<0.05$ considered statistically significant and $P<0.1$ considered a borderline significant. We successfully collected the survival data from 87 of the 88 cases.

3. Results

3.1. General outcomes

The study population consisted of 88 patients ; 41 were male and 47 were female. Age ranged from 29 to 85 years, with an average of 64. Patients

were classified into a smoking group (47 patients) and a non-smoking group (41 patients). Pathologically, well-, moderately and poorly differentiated adenocarcinomas were diagnosed in 53, 25 and 10 patients, respectively. The smoking status was associated to histological grade : smoking was associated with a greater incidence of poorly differentiated adenocarcinoma (Fig. 2.). The number of patients with pathological stage (p-stage) Ⅰ, Ⅱ, Ⅲ, and Ⅳ disease were 73(83%),4(5%),11(12%) and 0(0%), respectively. No association was found between the smoking status and histological grade within each pathological stage, as shown in Table 1.

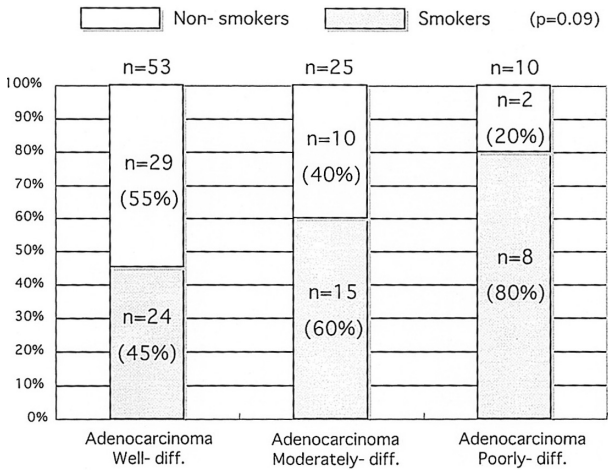

Fig. 2. Smoking status and histological grade. Note that cigarette smoking was associated with a decreased adenocarcinoma differentiation.

3.2. Assosiation of smoking with clinicopathological factors

A variety of clinicopathological factors were compared between the smoking and non-smoking groups (Table 2). Cigarette smoking was significantly more frequent in men than women : most

Table 1. Smoking status and histological grading of lung adenocarcinoma at each pathological stage (p-stage, n=88)

p-stage		Well-diff.	Mod. diff.	Poorly diff.	Total	(p-value)
stage Ⅰ	smokers	21	11	6	38	N.S.
	non-smokers	26	7	2	35	(p=0.19)
stage Ⅱ	smokers	1	2	0	3	N.S.
	non-smokers	1	0	0	1	(p=0.50)
stage Ⅲ	smokers	2	2	2	6	N.S.
	non-smokers	2	3	0	5	(p=0.34)
Total		53	25	10	88	

(Well-diff : well-differentiated adenocarcinoma ; Mod. diff : moderately differentiated adenocarcinoma ; Poorly diff : Poorly differentiated adenocarcinoma)

Table 2. Clinical and pathological characteristics of small (less than 20 mm diameter) lung adenocarcinomas in the smoking group and the non-smoking group (n=88)

Characteristics	No. of cases	smoking group	Non-Smoking Group	(p-value)
Age (years)				
≤60	34	18(53%)	16(47%)	N.S.
>60	54	29(54%)	25(46%)	(p=0.94)
Gender				
Male	41	38(93%)	3(7%)	
Female	47	9(19%)	38(81%)	(p<0.001)
Lymph node metastasis				
Negative	76	40(53%)	36(47%)	N.S.
Positive	12	7(58%)	5(42%)	(p=0.95)
Visceral pleural invasion				
Negative	53	31(58%)	22(42%)	N.S.
Positive	34	16(47%)	18(53%)	(p=0.29)
Micropapillarypattern				
Negative	65	32(49%)	33(51%)	N.S.
Positive	23	15(65%)	8(35%)	(p=0.18)

N.S. : not significant

women were non-smokers. The analysis failed to reveal any association of smoking with age, lymph node metastasis, visceral pleural invasion or presence of micropapillary pattern (Table 2).

Because a significant gender difference was apparent between the smoking and non-smoking groups, the association between gender and the histological grade of lung adenocarcinoma was investigated. A statistical trend was shown between gender and histological grade: more men were diagnosed to have less differentiated adenocarcinoma (Table 3).

3.3. Cumulative smoking (smoking index) and histological grade of lung adenocarcinoma

To further investigate the effect of smoking on the development of small lung adenocarcinoma, the association between cumulative smoking and histological grade was examined in the smoking group (n=47). The average smoking index for patients with well-, moderately, and poorly differentiated adenocarcinoma was 758, 884, and 1408, respectively. Cumulative smoking was well associated with histological grade: poorly differentiated adenocarcinoma occurred significantly more frequently than well- and moderately differentiated adenocarcinoma with increased smoking index (Fig. 3). No significant difference was found between the well- and moderately differentiated adenocarcinoma in terms of the smoking index. In the smoking group, poorly differentiated adenocarcinoma developed significantly more frequently than well- and moderately differentiated adenocarcinoma combined, particularly when the smoking index was ≧1,000 (Table 4).

3.4. Survival

The mean follow-up of the 88 patients was 48 months (range: 2-129 months). At final follow-up, 68(77%) remained alive and 19(23%) had died. Of the deaths, 16 were attributed to documented progressive lung cancer, one to heart failure, one

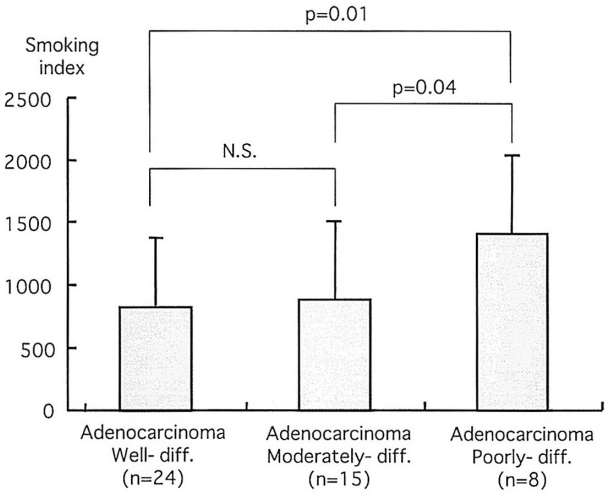

Fig. 3. Smoking index (cumulative smoking, see text) and histological grade of lung adenocarcinoma. Note that cumulative smoking closely correlated with the histological grade; the proportion of poorly differentiated adenocarcinoma was significantly greater with the increasing cumulative smoking dose.

Table 3. Gender and histological grade of lung adenocarcinoma (n=88)

Gender	Well-diff.	Mod. diff.	Poorly diff.	Total	(p-value)
Male	22	11	8	41	
Female	31	14	2	47	(p=0.07)
Total	53	25	10	88	

(Well-diff: well-differentiated adenocarcinoma; Mod. diff: moderately differentiated adenocarcinoma; Poorly diff: Poorly differentiated adenocarcinoma)

Table 4. Histological grade of lung adenocarcinoma in cigarette smokers (n=47) and cumulative smoking

Cumulative smoking	Well- and moderately diff. adenocarcinoma combined	Poorly diff. adenocarcinoma	Total	(p-value)
S.I.<1,000	27	1	28	
S.I.≥1,000	12	7	19	(p= 0.004)
Total	39	8	47	

(S.I.: Smoking Index, see text)

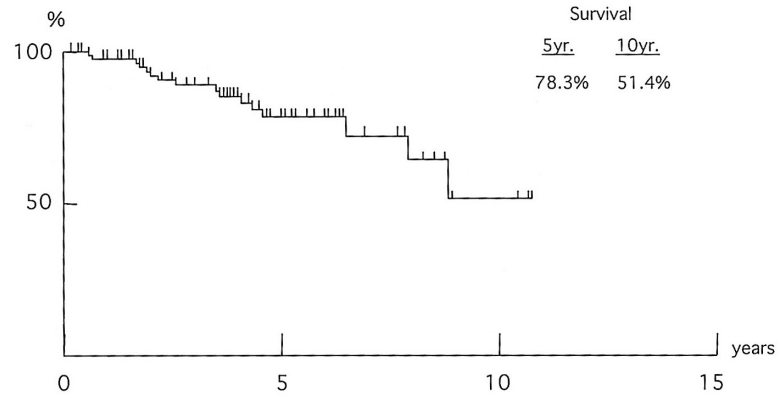

Fig. 4. Overall survival of adenocarcinoma of the lung, less than 20 mm diameter in size (n=88).

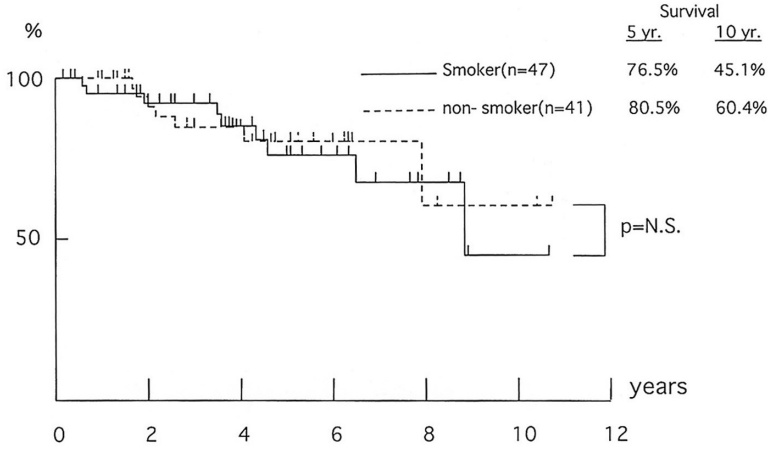

Fig. 5. Prognosis of smokers and non－smokers. No significant difference was found between the two groups.

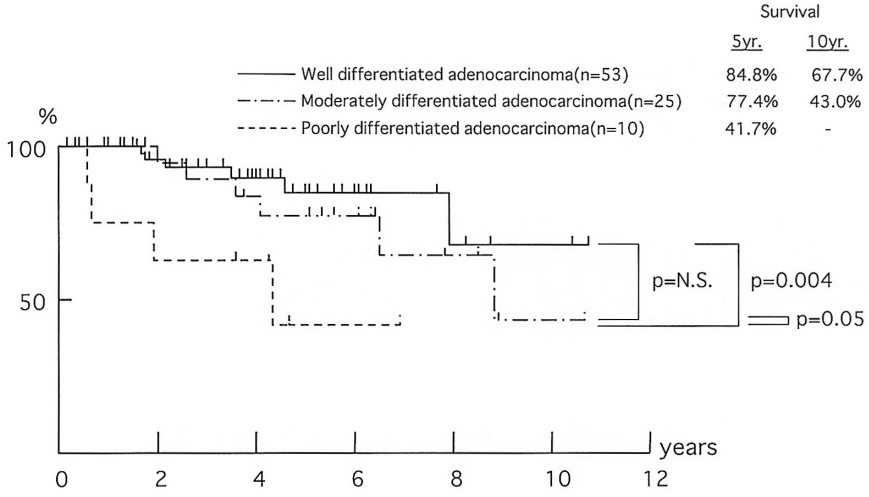

Fig. 6. Prognosis and histological grade in all cases. Note that well- and moderately differentiated adenocarcinomas were associated with significantly better survival than poorly differentiated adenocarcinomas.

to pulmonary dysfunction, and one to unknown causes. Overall survival was 78.3% at five years and 51.4% at 10 years (Fig. 4.).

a) Prognosis of smokers and non-smokers

Survival in the smoking group (n=47) was 76.5% at five years, and 45.1% at 10 years. Survival for the non-smoking group (n=41) was 80.5% and 60.4%, respectively. No statistically significant survival difference was found (p=0.97 ; Fig. 5).

b) Prognosis and histological grade

The patients were classified as having well-, moderately or poorly differentiated adenocarcinomas (53, 25, and 10 patients, respectively). The survival of the well-differentiated adenocarcinoma group was 84.8% at five years whereas that of the moderately and poorly differentiated groups was 77.4% and 41.7%, respectively. The well- and moderately differentiated adenocarcinoma groups showed a significantly better survival than the poorly differentiated group (Fig. 6).

c) Prognosis and histological grade in the non-smoking group

Among the non-smoking group (N=41), six patients died from documented progressive lung cancer, and one died from heart failure. Among the non-smoking patients, the tumors were classified as well differentiated in 29, as moderately differentiated in 12, and as poorly differentiated in 2 patients. The five-year survival was 87.6% in the well-differentiated adenocarcinoma group and 47.6% in the moderately differentiated group. Four-year survival was 100% in the poorly differentiated group. No statistically significant differences in survival were found between the histological grades in the non-smoking group (Fig. 7).

d) Prognosis and histological grade in the cigarette smoking group

Among the smoking group (n=47), nine patients died of documented progressive lung cancer, one of heart failure, one of pulmonary dysfunction and one of unknown causes. Tumors were classified as well differentiated in 24 patients, moderately differentiated in 15, and poorly differentiated in 8. Five-year survival was 75.0% in the well-differentiated adenocarcinoma group, 91.7% in the moderately differentiated group, and 25.0% in the poorly differentiated group. The well- and moderately differentiated adenocarcinoma groups exhibited a significantly better survival than the poorly differentiated group (Fig. 8).

4. Discussion

We examined the role of cigarette smoking in the development of primary adenocarcinoma of the lung by focusing on small tumors (less than 20 mm in diameter)so as to minimize the effect of two con-

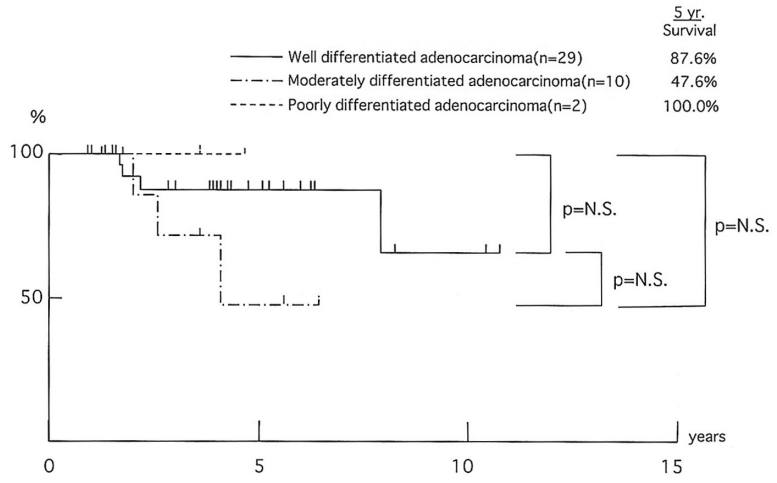

Fig. 7. Histological grade and prognosis in the non - smoking group. No statistically significant differences in the prognosis were found between the three groups.

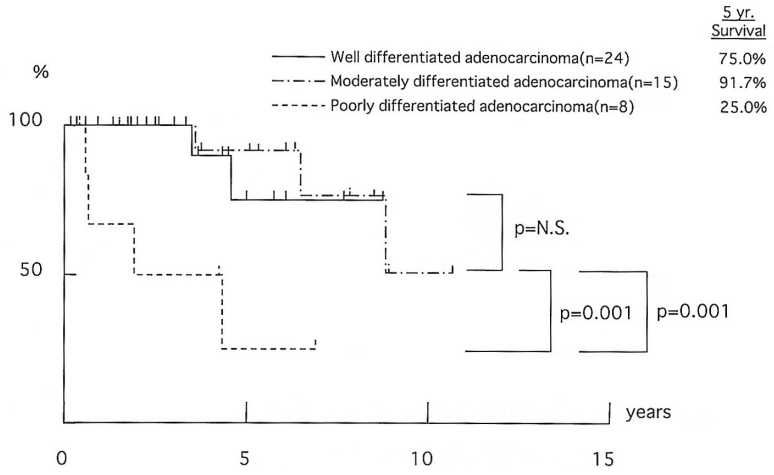

Fig. 8. Histological grade and prognosis in the smoking group. Note that well- and moderately differentiated adenocarcinoma exhibited a significantly better survival than poorly differentiated adenocarcinoma.

founding factors in data analysis ; tumor size and histological variety. A significant gender difference was apparent between the smoking and non-smoking groups, and a statistical trend was shown between gender and histological grade, which may be a consequence of cigarette smoking. Furthermore, our findings indicate an association between cigarette smoking and histological grade of adenocarcinoma of the lung as well as correlation between the histological grade and the prognosis. When the study population was classified into three categories ; diagnosis of well-, moderately or poorly differentiated adenocarcinoma, cigarette smoking was associated with less differentiated adenocarcinoma. Moreover, a dose-response relationship was observed within the smoking group : the cumulative smoking dose was strongly associated with poorly differentiated adenocarcinoma, particularly when the smoking index was $\geq$1,000. Finally, the prognosis for patients with poorly differentiated adenocarcinoma was worse than that for patients with well- or moderately differentiated adenocarcinoma.

Suzuki et al.[8] reported cigarette smoking to be associated with development of adenocarcinoma of the lung, as well as squamous cell and small cell carcinoma, and that increased smoking correlates with the occurrence of less differentiated adenocarcinoma. On the basis of autopsies, Morita et al.[9] reported that the proportion of poorly differentiated adenocarcinoma was higher in cigarette smokers and men. These findings appear to be consistent with those of the present study, despite that fact that our study focused on patients with tumors measuring less than 20 cm in diameter and sample size was therefore limited.

However, some of our findings require further explanation. First, we did not find any proportional difference in tumor differentiation between cigarette smokers and non-smokers for each pathological stage. Because an increase in cigarette smoking was associated with a decrease in tumor differentiation, a proportional difference between cigarette smokers and non-smokers for each pathological stage was anticipated.

Second, no correlation between cigarette smoking and the development of a micropapillary pattern was found in the current study. Recent reports have suggested that the micropapillary pattern, defined as the lack of fibrovascular cores in the papillary structures, is a feature indicating moderate differentiation in adenocarcinoma of the lung.[15][16] In the present study, we also considered adenocarcinomas showing the micropapillary pattern to be moderately differentiated. Miyoshi et al.[16] reported that the micropapillary pattern is found more frequently in non-smokers than in smokers. They hypothesized that the micropapillary pattern reflects a stage of tumor progression in the development of well-differentiated adenocar-

cinoma which is unrelated to smoking. However, our results did not indicate any anticipated correlation between non-smoking status and the presence of micropapillary pattern.

Finally, no statistically significant survival difference was found between cigarette smokers and non-smokers. Because the occurrence of less differentiated adenocarcinoma is related to smoking[8)9)11)] and it is associated with a poor prognosis, a difference in survival between the two groups was expected.

The unanticipated results described above may largely result from the limited sample size. Recent advances in imaging diagnostic technology (such as computed tomography) now enable smaller lung adenocarcinomas to be detected than previously.[18)] However, tumors measuring less than 20 mm account for only around 20% of all resected primary adenocarcinomas of the lung at our institute. In this limited sample, poorly differentiated adenocarcinoma of this size was very rare among the non-smoking group; only two such cases occurred among non-smokers in this study. Furthermore, the relatively short follow-up period (mean follow-up in this study was 48 months) may have affected the survival analysis. These factors might explain the poor statistical power of this study. Accordingly, a database consisting of a larger patient population and longer period of follow-up might have a greater statistical power and may also more clearly demonstrate meaningful findings.

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