Risk Factors for Recurrence and Unfavorable Prognosis in Patients with Stage I Non-small Cell Lung Cancer and a Tumor Diameter of 20 mm or Less

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Background: The purpose of this study was to identify risk factors for disease recurrence and unfavorable prognosis after surgical resection for stage I non-small cell lung cancer in patients with tumor diameters of ≤20 mm.

Methods: One hundred sixty-three patients who had pathologic stage I non-small cell lung cancer with tumor diameters ≤20 mm and who had undergone a lobectomy with mediastinal lymph node dissection were retrospectively reviewed. The relationships between clinicopathologic factors and clinical outcomes, including recurrence and survival, were then examined. The clinicopathologic factors examined in this study were age, sex, smoking status, preoperative serum carcinoembryonic antigen level, pathologic tumor size, histologic subtype, histologic grade, and visceral pleural invasion.

Results: Among the clinicopathologic factors that were examined, the histologic grade of the carcinoma status was significantly related to a high risk of recurrence when analyzed using univariate ($p = 0.01$) and multivariate analyses ($p = 0.049$). Regarding survival, patients with poorly differentiated carcinomas showed a significantly unfavorable overall survival ($p < 0.001$), disease-specific survival ($p = 0.003$), and disease-free survival ($p = 0.002$) compared with patients with well-/moderately differentiated carcinomas according to univariate analyses. A Cox proportional hazards model indicated that a poorly differentiated carcinoma status was the only independent factor for an unfavorable overall survival ($p = 0.02$), disease-specific survival ($p = 0.046$), and disease-free survival ($p = 0.04$).

Conclusions: Poor differentiation of tumor was the only risk factor for recurrence and an unfavorable prognosis for stage I non-small cell lung cancer patients with tumor diameters of ≤20 mm.

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/07/0209-0808

Key Words: Non-small cell lung cancer, Stage I, Tumor diameter of ≤20 mm, Prognostic factor, Histologic grade.

(*J Thorac Oncol.* 2007;2: 808–812)

Lung cancer is the leading cause of cancer death in Japan and many countries around the world.[1,2] Survival among patients with non-small cell lung cancer (NSCLC) remains unsatisfactory because many locally advanced or metastatic cases are unresectable.[3] Even patients with early stages of the disease who undergo complete resections often experience recurrences, resulting in an unfavorable prognosis.

Recently, the detection rate of small peripheral lung cancer has been increasing as a result of advances in diagnostic technology, including high-resolution computed tomography.[4] Unfortunately, approximately 30% of patients with stage IA NSCLC die within 5 years of surgery.[5,6] Recent studies have demonstrated the usefulness of postoperative adjuvant chemotherapy among patients with stage IB to IIIA NSCLC who have undergone complete resections.[7–9] These facts suggest that adjuvant chemotherapy for high-risk patients with stage IA NSCLC may be useful for improving survival in this population. Kato et al.[10] reported that adjuvant chemotherapy with uracil-tegafur prolonged survival among patients with stage I adenocarcinoma and a tumor diameter of ≥20 mm. They concluded that patients with tumor diameters of <20 mm should be excluded from adjuvant therapy unless a subgroup with a poor prognosis was identified. This consideration encouraged us to identify factors associated with recurrence and a poor prognosis as indicators for adjuvant chemotherapy among patients with tumor diameters ≤20 mm.

In this study, we retrospectively analyzed the relationship between clinicopathologic factors and the clinical courses of patients with stage I NSCLC and tumor diameters ≤20 mm to identify risk factors for recurrence and unfavorable prognosis after surgery.

METHODS

Between January 1995 and December 2002, 734 consecutive patients with NSCLC underwent pulmonary resec-

TABLE 1. Relationship Between Recurrence and Clinicopathologic Factors in Patients With Stage I NSCLC Tumors ≤20 mm in Diameter

Variables and Subsets	Recurrences, *n* (%)	*p*
Age, yr (*n*)		
≥65 (94)	10 (10.6)	0.40
<65 (69)	4 (5.8)	
Sex (*n*)		
Male (89)	9 (10.1)	0.58
Female (74)	5 (6.8)	
Smoking history (*n*)		
Ever smoker (85)	10 (11.8)	0.26
Never smoker (78)	4 (5.1)	
Serum CEA level, ng/ml[a] (*n*)		
≥5.0 (20)	4 (20.0)	0.11
<5.0 (140)	10 (7.1)	
Pathologic tumor size, mm (*n*)		
>15 (71)	6 (8.5)	1.00
≤15 (92)	8 (8.7)	
Histologic grade[b] (*n*)		
Well/moderately (156)	9 (5.8)	0.01
Poorly (16)	5 (31.3)	
Histologic subtype (*n*)		
Adeno (136)	13 (9.6)	0.70
Nonadeno (27)	1 (3.7)	
Visceral pleural invasion (*n*)		
p0 (160)	13 (8.1)	0.28
p1[c] (3)	1 (33.3)	

Adeno, adenocarcinoma; CEA, carcinoembryonic antigen; Nonadeno, nonadenocarcinoma; NSCLC, non-small cell lung cancer.

[a] The serum CEA level was not evaluated in three patients.

[b] Histologic grade was not determined in one adenosquamous carcinoma.

[c] Visceral pleural involvement was classified according to the rules of the Japan Lung Cancer Society: p1, tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface.

tions at the Department of Cancer and Thoracic Surgery, Okayama University Hospital. Among them, 163 patients who had pathologic stage I disease with a tumor diameter of ≤20 mm and who had undergone a lobectomy with mediastinal lymph node dissection as a part of complete resection were included in the current study. The primary treatment in this group was pulmonary resection without chemotherapy or radiotherapy before surgery. The following clinicopathologic factors were evaluated: age, sex, smoking status, preoperative serum carcinoembryonic antigen (CEA) level, pathologic tumor size, histologic subtype, histologic grade, and visceral pleural invasion. The cutoff CEA level was set at 5.0 ng/ml between the normal and elevated groups. The histologic grade was categorized into well-differentiated, moderately differentiated, and poorly differentiated carcinoma according to the degree of structural and cytologic atypia. Differentiation in squamous cell carcinoma was determined based on degree of keratinization, intercellular bridges, and squamous pearl formation. Poor differentiation in squamous cell carcinoma was defined as a solid pattern tumor with little degree of these features (<5%). Adenocarcinoma basically composed of malignant glandular epithelium was evaluated by replacing alveolar walls and tubular and papillary structure. Poor differentiation in adenocarcinoma was defined as a solid pattern tumor without any clear gland formation. Clinicopathologic staging was determined according to the International Union Against Cancer's tumor-node-metastasis classification of malignant tumors.[11] Pleural involvement was classified according to the rules of the Japan Lung Cancer Society[12]: (1) a tumor of any size that was exposed on the visceral pleural surface was categorized as p2 and was classified as a pathologic T2 tumor and (2) a tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface was categorized as p1 and was classified as T1. Thus, although we had three patients with p1 disease, all patients in this study were classified as stage IA based on rules of Japan Lung Cancer Society.

TABLE 2. Summary of Recurrent Cases

No.	Age (yr)	Sex	Smoking Status	CEA (ng/ml)	T Size (mm)	Histologic Subtype	Histologic Grade	Pleural Invasion	Recurrent Sites
1	59	Male	Current	4.46	13	Ad	Poor	p1	Liver
2	68	Male	Current	5.88	9	Ad	Poor	p0	Lung, meningitis
3	71	Female	Former	15.23	18	Ad	Poor	p0	Neck LN
4	72	Male	Current	3.98	20	Sq	Poor	p0	Liver
5	76	Male	Former	18.22	14	Ad	Poor	p0	Mediastinal LN, pericardium
6	47	Female	Never	1.22	14	Ad	Moderate	p0	Malignant pleural effusion
7	56	Male	Former	1.68	20	Ad	Moderate	p0	Lung, bone, mediastinal LN
8	69	Male	Current	6.10	16	Ad	Moderate	p0	Lung
9	70	Male	Former	1.36	15	Ad	Moderate	p0	Lung
10	71	Male	Former	2.12	20	Ad	Moderate	p0	Brain, small intestine, neck LN
11	57	Female	Never	0.79	20	Ad	Well	p0	Lung, malignant pleural effusion
12	65	Female	Never	1.14	15	Ad	Well	p0	Lung, brain
13	73	Female	Never	1.70	15	Ad	Well	p0	Brain
14	75	Male	Former	2.87	13	Ad	Well	p0	Lung

Ad, adenocarcinoma; LN, lymph node; Sq, squamous cell carcinoma.

TABLE 3. Multivariate Analysis for Recurrence

Variable	Odds Ratio	95% CI	*p*
Age	1.93	0.13–2.03	0.35
Sex	2.33	0.053–3.49	0.43
Smoking status	4.02	0.45–36.31	0.22
Serum CEA level	1.23	0.22–6.77	0.82
Pathologic tumor size	0.90	0.26–3.08	0.87
Histologic subtype	0.26	0.028–2.34	0.23
Histologic grade	4.94	1.01–24.21	0.049
Visceral pleural invasion	4.89	0.28–84.57	0.28

CEA, carcinoembryonic antigen; CI, confidence interval.

Patients were followed at the outpatient clinic at least every 6 months for 2 years after surgery and annually thereafter. All patients underwent a complete blood count, blood chemistry analysis, plain chest radiograph, measurement of serum CEA level, and a computed tomography scan of the chest and abdomen to screen for recurrent disease when appropriate. Biopsies of new lesions suspected to be recurrences were performed, if possible, and the attending physician made the final diagnosis regarding relapse. The overall survival (OS) and the disease-free survival (DFS) periods were calculated from the date of surgery until the date of death or the last follow-up for OS and the date of recurrence or the last follow-up for DFS. The disease-specific survival period was also calculated from the date of surgery until the date of original disease-related death or the last follow-up; patients who died from other causes were considered censored cases.

Differences in significance among categorized groups were compared using Fisher's exact or χ^2 tests, as appropriate. Univariate analyses of survival were performed using the Kaplan-Meier method and a log-rank test. Multivariate analyses for recurrence were performed using a multilogistic regression model. Multivariate analyses for survival were performed using a Cox proportional hazards model. All data were analyzed using StatView 5.0 Program for Windows (SAS Institute Inc., Cary, NC). All statistical tests were two sided, and probability values <0.05 were regarded as statistically significant.

RESULTS

Details of the patient characteristics are shown in Table 1. The median age was 64 years (range, 30–84 years); 89 male and 74 female patients were examined retrospectively. One hundred thirty-six patients (83.4%) had adenocarcinoma histology, 26 (16.0%) had squamous cell carcinoma histology, and one (0.6%) had adenosquamous carcinoma histology. The histologic grade was determined as well differentiated in 86 (52.8%) cases, moderately differentiated in 60 (36.8%) cases, and poorly differentiated in 16 (9.8%) cases. The histologic grade was not determined in one adenosquamous carcinoma. Because the Kaplan-Meier survival curves for patients with well-differentiated and moderately differentiated carcinomas were similar, we considered well-differentiated and moderately differentiated carcinomas as one group (supplemental material).

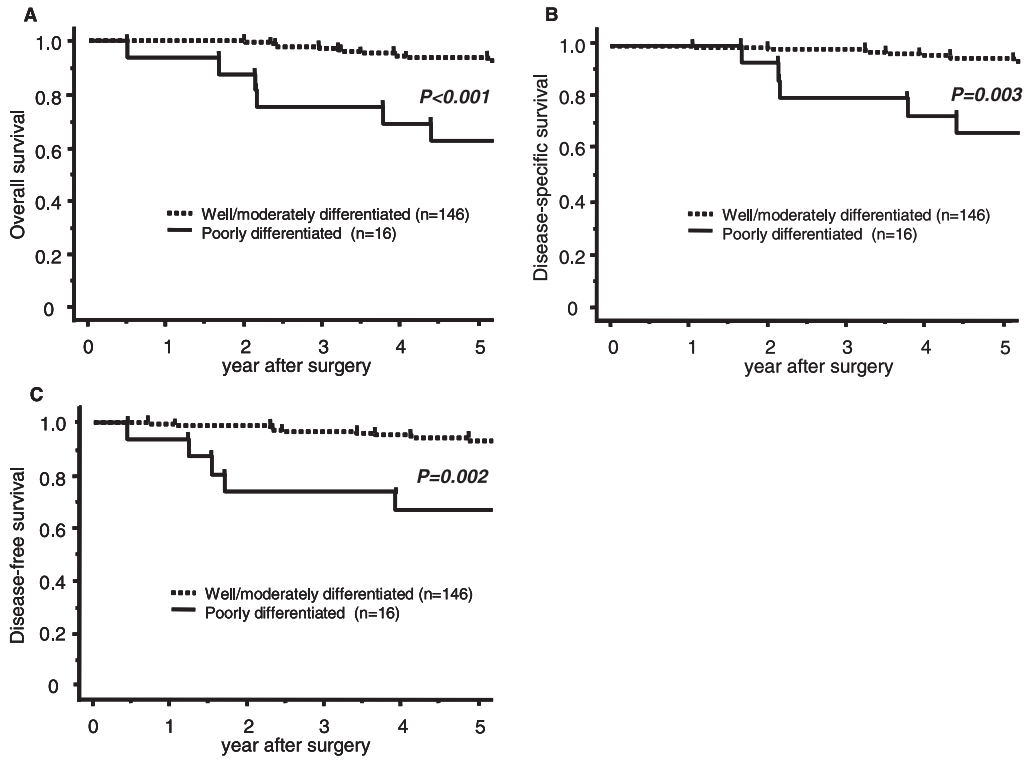

FIGURE 1. Crude survival curves stratified according to histologic grade. (A) Overall survival. (B) Disease-specific survival. (C) Disease-free survival.

Of the total study population, the 5-year OS, disease-specific survival, and DFS rates were 91.4%, 93.3%, and 91.4%, respectively. Fourteen patients (8.4%) developed recurrences after surgical resection. Detailed data regarding the recurrences are shown in Table 2. No local recurrences at the bronchial stump were reported. According to univariate analyses, a poorly differentiated carcinoma status was the only risk factor significantly associated with recurrence ($p = 0.01$). No significant differences in disease recurrence according to age, sex, smoking status, serum CEA level, pathologic tumor size, histologic subtype, or visceral pleural invasion were observed (Table 1). A multivariate analysis indicated that histologic grade was the only independent factor associated with disease recurrence (odds ratio = 4.94, 95% confidence interval [CI]: 1.01–24.21, $p = 0.049$) (Table 3). With regard to survival, univariate analyses indicated that advanced age (65 years and older) ($p = 0.005$), male sex ($p = 0.01$), ever smoking status ($p = 0.005$), high CEA level (≥ 5) ($p = 0.005$), and poor differentiation of the tumor ($p < 0.001$) were significantly related to the poor OS. In addition, patients with poorly differentiated carcinomas also showed a significantly poor disease-specific survival ($p = 0.003$) and DFS ($p = 0.002$), compared with those with well-/moderately differentiated carcinomas (Figure 1). A Cox proportional hazards analysis indicated that poorly differentiated carcinoma was the only independent factor associated with an unfavorable OS (hazard ratio = 3.61, 95% CI: 1.24–10.51, $p = 0.02$), disease-specific survival (hazard ratio = 4.20, 95% CI: 1.03–17.12, $p = 0.046$), and DFS (hazard ratio = 4.45, 95% CI: 1.09–18.19, $p = 0.04$) (Table 4).

TABLE 4. Multivariate Analysis for Survival

Variables	Hazard Ratio	95% CI	*p*
A. Overall survival			
Age	3.57	0.078–1.01	0.051
Sex	1.27	0.14–11.60	0.83
Smoking status	2.18	0.23–20.64	0.50
Serum CEA level	1.03	0.34–3.08	0.97
Pathologic tumor size	1.67	0.68–4.12	0.26
Histologic subtype	1.06	0.39–2.91	0.90
Histologic grade	3.61	1.24–10.51	0.02
Visceral pleural invasion	4.15	0.49–35.35	0.19
B. Disease-specific survival			
Age	1.71	0.17–2.06	0.40
Sex	2.65	0.063–2.27	0.29
Smoking status	4.20	0.59–30.01	0.15
Serum CEA level	1.23	0.27–5.55	0.79
Pathologic tumor size	1.12	0.35–3.54	0.85
Histologic subtype	0.33	0.040–2.75	0.31
Histologic grade	4.20	1.03–17.12	0.046
Visceral pleural invasion	3.91	0.44–34.83	0.22
C. Disease-free survival			
Age	1.74	0.16–2.02	0.39
Sex	2.51	0.067–2.37	0.31
Smoking status	4.12	0.58–29.31	0.16
Serum CEA level	1.15	0.25–5.25	0.85
Pathologic tumor size	0.98	0.32–3.04	0.98
Histologic subtype	0.36	0.043–2.94	0.34
Histologic grade	4.45	1.09–18.19	0.04
Visceral pleural invasion	5.20	0.58–46.49	0.14

CEA, carcinoembryonic antigen; CI, confidence interval.

DISCUSSION

Recent randomized phase III trials have shown that patients with stage IB–IIIA NSCLCs are candidates for adjuvant chemotherapy after complete surgical resection.[7–9] The indications for adjuvant chemotherapy among patients with stage IA NSCLC, conversely, are still under debate, despite the performance of subset analyses in randomized trials. One reason for the debate is the small NSCLCs, especially adenocarcinomas with a dominant bronchoalveolar carcinomatous component, are unlikely to recur after surgery.[13] Thus, the natural prognosis of this population may already be good enough that any additional benefits from adjuvant chemotherapy would prove to be minimal, without further selection to identify a subpopulation with a poor natural prognosis.

Previous studies have reported several factors associated with a poor prognosis in patients with small NSCLCs: tumor size, preoperative serum CEA level, visceral pleural invasion, vascular vessel invasion, and histologic grade.[14–18] We focused on the risk factor for recurrence as well as unfavorable survival time in this study to identify candidates for adjuvant chemotherapy. A recent large-scale study also indicated that patients with less differentiated carcinomas after resection had a higher risk of recurrence and death, according to a multivariate analysis. Ichinose et al.[14] also reported that histologic grade was a significant predictor of a poor prognosis for patients with resected stage I tumors.

In this study, the subjects were limited to patients with stage I NSCLC tumors with diameters ≤ 20 mm. Our main result was that poor tumor differentiation was the only independent risk factor for recurrence and an unfavorable prognosis. Histologic grade classifications are assumed to lack objectivity because no specific criteria have been developed for standardizing lung cancer histology. Although a four-tiered system of grading (well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated carcinomas) for lung cancer is mentioned in the World Health Organization's Histological Typing of Lung and Pleural Tumors,[19] histologic grade was removed from the current criteria of the Japan Lung Cancer Society.[12] However, our result indicates that poor tumor differentiation has a crucial contribution to poor clinical outcome, suggesting that this factor may be a useful indicator of a need for postoperative adjuvant chemotherapy in patients with small NSCLC. Thus, an objective grading system should be developed, not only for enabling reproducible assessments, but also for determining treatment strategies in patients with NSCLC.

It should be noted that our cohort mainly consisted of adenocarcinoma accounting for 83.4%. Thus, our results mainly reflected the feature of adenocarcinomas despite histologic subtype was adjusted by multivariate analysis. Further

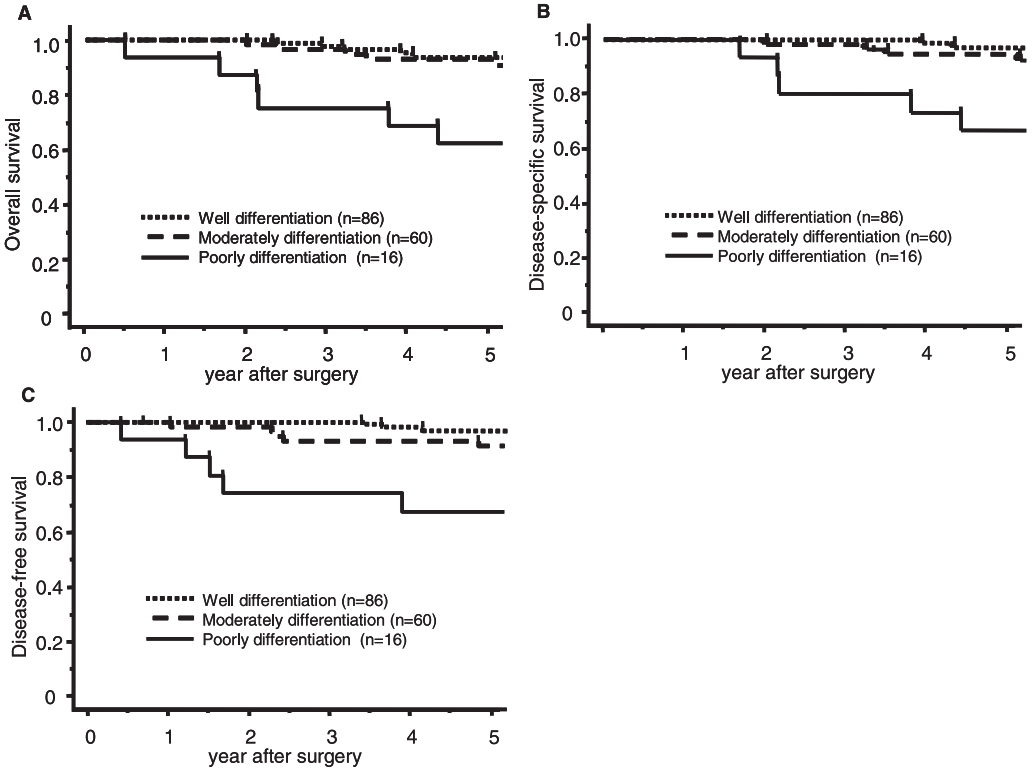

FIGURE 2. Crude survival curves stratified according to well, moderately, and poorly differentiated histologic grade. (A) Overall survival. (B) Disease-specific survival. (C) Disease-free survival.

study was warranted to identify factors for poor clinical outcome focusing on nonadenocarcinoma histology.

In conclusion, we showed that a poor differentiation of tumor was the only risk factor for recurrence and an unfavorable prognosis in patients with stage I NSCLC and a tumor diameter of ≤20 mm. A histologic grade may be an indicator of a need for postoperative adjuvant chemotherapy to improve the clinical outcome of patients with stage I NSCLC and a tumor size ≤20 mm. Randomized trials of adjuvant chemotherapy targeting poorly differentiated small NSCLC are warranted to confirm our retrospective findings and to establish an appropriate therapeutic strategy for NSCLC patients with small tumors.

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