TABLE 6. Odds Ratios of Acute Exacerbation of IIPs for Various Risk Factors in the Patients Combined from Two Studies

Risk Factors	*N*	OR	95% CI	*p*
Gender				
Male	35	2.84	0.30–27.3	0.37
Age (yr)				
>69[a]	35	3.50	0.73–16.9	0.12
PS				
≥1	35	0.58	0.13–2.71	0.49
Type of IIPs				
IPF	35	3.19	0.70–14.6	0.13
LDH (IU/L)				
>254[a]	35	0.62	0.14–2.73	0.52
CRP (mg/dl)				
>1.34[a]	35	0.34	0.07–1.61	0.17
WBC (mm^3)				
>7820[a]	35	1.08	0.25–4.70	0.91
Pao_2 (Torr)				
<80[a]	27	0.18	0.03–1.14	0.07
KL-6 (U/ml)				
>762[a]	32	0.56	0.12–2.54	0.45
Positive		0.88	0.17–4.54	0.87
SP-D (ng/ml)				
>94[a]	29	2.22	0.42–11.83	0.35
Positive		0.98	0.18–5.24	0.87
%VC predicted				
<80[a]	23	0.69	0.12–3.96	0.67
ANA				
Positive	19	0.80	0.11–6.11	0.83

[a] Median.

IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; PS, performance status; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cells; Pao_2, arterial oxygen tension; SP-D, surfactant protein D; ANA, antinuclear antibody; %VC, percent vital capacity; OR, odds ratio; CI, confidence interval.

significantly higher than in those with a non-IPF pattern (OR: 3.19, $p = 0.13$). Neither poor PS nor smoking status increased the risk of AE. We carried out the analysis in various additional settings (data not shown), but no statistically significant risk factor was indentified in any of these cases.

DISCUSSION

Optimal chemotherapy for treatment of advanced LC with IIP still remains controversial, because there have been few reports focusing on AE of IIPs related to chemotherapy for lung cancer. In the case of chemotherapy, the incidence of treatment-related AE previously reported ranged from 8.7 to 21% in Japan.[28–31] Therefore, AE is now increasingly being recognized as a common clinical event for LC with IIP. Nevertheless, there are conflicting views as to whether chemotherapy for NSCLC with IIP can contribute to OS, because its antitumor efficacy for NSCLC is less than that for SCLC. In patients with SCLC with IIPs, we can expect that the benefit of chemotherapy outweighs the risk of AE. On the other hand, because the prognosis of SCLC without active treatment is remarkably poor, SCLC shows considerable sensitivity to chemotherapy. This is the first prospective study to analyze the safety and efficacy of a specific regimen for SCLC with IIP. In this pilot study of carboplatin combined with etoposide for advanced SCLC with IIP, we observed an incidence of treatment-related AE of 5.9%, median PFS of 5.5 months, and MST of 8.7 months.

Currently, platinum agent plus etoposide administered every 3 weeks is one of the most widely used protocols for advanced SCLC as the established standard regimen. Because of the right heart overload, the patients with hypoxemia and/or low pulmonary function often have the high risk of pulmonary congestion. We selected the chemotherapy regimen based on carboplatin not cisplatin. Moreover, CE has been reported to have good safety and efficacy in high-risk patients such as the elderly and those with poor PS.[4,5] We observed an ORR of 88% and median PFS of 5.5 months, which was comparable with the results of the randomized phase III trial (JCOG 9702) in Japanese patients without IIPs (ORR, 73%; median PFS, 5.2 months; MST, 10.6 months; 1-year survival rate, 41%).[4] Nevertheless, the MST (8.7 months) and 1-year survival rate (29%) in this study would be regarded as unsatisfactory for patients without interstitial lung disease (ILD). Because of the difference between comparatively good PFS and unsatisfactory OS, we considered that only 8 of 16 patients, excluding one patient for treatment-related death, received second-line chemotherapy. We considered that the existence of IIPs had a negative influence in performing second-line chemotherapy.

Attention is now being paid to the induction of AE of IIPs by anticancer agents, following Japanese reports of ILD developing after treatment with the epithelial growth factor receptor tyrosine kinase inhibitor gefitinib. In 3166 Japanese patients with advanced/recurrent NSCLC enrolled in a cohort and nested case-control study, gefitinib-induced ILD was manifested in 3.98%. More interestingly, that study demonstrated that a predisposing background of preexisting IIPs was an independent risk factor for developing AE, regardless of gefitinib therapy or other chemotherapies (OR: 4.8–5.6).[32]

It has recently become a well-known phenomenon that patients with IIP without lung cancer develop AE in the normal course of the disease. Kim et al.[33] reported retrospectively that the 1-year frequency was 8.5% after diagnosis. Kubo et al.[34] reported a high incidence of AE (64%) in the control group of a randomized study on the role of anticoagulants. In another prospective randomized study on the role of pirfenidone, Azuma et al.[35] found a 14% incidence in 35 untreated patients during a 9-month follow-up period.

In some cases, it can be difficult in the individual patient to differentiate AE of IIPs from lung cancer progression lymphangitic spread of the disease leading to diffuse interstitial infiltrate. The frequency of AE of IIPs seems to be higher in Japanese than in white. Serum KL-6 and SP-D levels, markers of interstitial pneumonia, are common for differential diagnosis in Japan. Another important differential diagnosis is infectious diseases, such as pneumocystis jiroveci pneumonia with typical ground-glass opacities in a multifocal or diffuse pattern in previously uninvolved area. A

serum β-D glucan is also used for the diagnosis of pneumocystis jiroveci pneumonia.

For differential diagnosis of AE, there are various infectious diseases, congestive heart failure, thromboembolism, and carcinomatous progress. We routinely performed the details of differential diagnosis of AE (i.e., HRCT, lung function test, arterial blood gas, tumor markers, KL-6, SP-D, evaluation of cardiac function by ultrasound cardiography and brain natriuretic peptide, β-D-glucan, D-dimer, and culture of sputum). HRCT is a useful modality in the diagnosis of AE. Nevertheless, the exact incidence of AE from IIPs may be overdiagnosed, because radiological changes cannot specifically identify or diagnose histpathological changes. Therefore, it would be recommended to identify histopathological/microbiological findings.

In this study, AE unrelated to anticancer treatment was observed in two patients, and a further two patients had AE related to second-line chemotherapy. The incidence of total AE, including AE related to second-line chemotherapy and AE unrelated to treatment at MST (8.7 months) and throughout the follow-up period was 18% (3/17 patients) and 29% (5/17 patients), respectively. Regardless of treatment, prolongation of the observation period may increase the numbers of AE manifested. In our previous study of NSCLC with IIP, AE related to first-line treatment with carboplatin plus paclitaxel was observed in one patient (5.6%), and AE was observed in five patients (28%) in total. Although the incidence of first-line chemotherapy-related AE was low in both studies, the incidence of total AE may be high in comparison with its incidence in IPF without lung cancer. The coexistence of lung cancer and IIPs may also be potential risk factors for AE of IIPs.

Localization of active oxygen and a growth factor, inflammatory cytokine, or vascularization factor to lung tissue plays an important role in inducing inflammation.[36] It seems that these factors induced by anticancer treatment may have been one cause of AE. Nevertheless, a useful predictive risk factor for AE or drug-induced ILD has not yet been identified. In our previous report, KL-6, SP-D, Pao_2 and %VC, which are considered to be markers of progression of IIPs, were not predictive of developing AE. There was no statistically significant difference in clinical background or values for pretreatment parameters between those who did and did not experience AE.[22]

We analyzed the predictors of development of AE for patients in this study combined with those in our previous pilot study for NSCLC.[22] Throughout the follow-up period, AE developed in 10 of 35 patients from the combined studies. We conducted univariate analysis for gender, age, PS, smoking status, IIP pattern as clinical factors and LDH, CRP, white blood cells, Pao_2, %VC, KL-6, SP-D, and antinuclear antibody from examination data before initial chemotherapy. Nevertheless, there was no statistically significant risk factor for AE even under a variety of conditions. Nonetheless, in male, elderly patients and in patients with an IPF pattern, a nonsignificant trend toward a high risk of AE was indicated. Moreover, as four of five patients with AE were clinically diagnosed with IPF in this study, IPF may be the anticipated risk factor for AE. On the other hand, using LDH, CRP, KL-6, Pao_2, and %VC as markers to reflect activity and severity of IIPs, the opposite trends to those predicted by us were indicated. It has been reported that the existence of focal usual interstitial pneumonia, which was undetectable by conventional chest CT, but confirmed in a biopsy specimen, was closely related to AE after lung resection for lung cancer.[37] These suggest that disease severity and progression of IIPs are not always correlated with the risk of AE. Large-scale studies are required for clarification.

No recommended regimen for LC with IIP has previously existed. To reduce the levels of toxicity and complications, especially various infectious diseases due to severe neutropenia, and overhydration causing lung congestion, we selected chemotherapy regimens based on carboplatin. The incidence of myelosuppression in this study was not thereby increased compared with that previously reported,[1–5] and nonhematological toxicities were mostly mild to moderate and manageable. Although a high incidence of leukocytopenia and neutropenia was evident, the acceptability of this treatment was good.

In conclusion, the combination chemotherapy of carboplatin plus etoposide used in this study during each 3-week schedule was effective and safe for patients with advanced SCLC with IIP. This is the first report indicating that chemotherapy for SCLC with IIP may be beneficial. To further confirm the feasibility of carboplatin plus etoposide for advanced SCLC with IIP, we are now carrying out a more large-scale clinical trial with detailed evaluation including proteomic analysis, to detect a risk factor for AE.

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Long-term prognosis of patients with lung cancer detected on low-dose chest computed tomography screening

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ABSTRACT

The effectiveness of lung cancer screening using low-dose chest computed tomography (CT) remains elusive. The present study examined the prognosis of patients with lung cancer detected on CT screening in Japanese men and women. Subjects were 210 patients with primary lung cancer identified on CT screening at two medical facilities in Hitachi, Japan, where a total of 61,914 CT screenings were performed among 25,385 screenees between 1998 and 2006. Prognostic status of these patients was sought by examining medical records at local hospitals, supplemented by vital status information from local government. The 5-year survival rate was estimated according to the characteristics of patients and lung nodule. A total of 203 (97%) patients underwent surgery. During a 5.7-year mean follow-up period, 19 patients died from lung cancer and 6 died from other causes. The estimated 5-year survival rate for all patients and for those on stage IA was 90% and 97%, respectively. Besides cancer stage, smoking and nodule appearance were independent predictors of a poor survival; multivariable-adjusted hazard ratio (95% confidence interval) was 4.7 (1.3, 16.5) for current and past smokers versus nonsmokers and 4.6 (1.6, 13.9) for solid nodule versus others. Even patients with solid shadow had a 5-year survival of 82% if the lesion was 20 mm or less in size. Results suggest that lung cancers detected on CT screening are mostly curative. The impact of CT screening on mortality at community level needs to be clarified by monitoring lung cancer deaths.

1. Introduction

Much attention has been paid to the effectiveness of low-dose chest computed tomography (CT) screening for lung cancer [1,2], which has poor prognosis. Screening with chest CT has been shown to have higher detection rate of lung cancer and, of cases identified, have higher curative resection rate than does screening with conventional chest X-ray [1–3]. However, data for the prognosis of lung cancer cases identified on CT screening are limited [4–6] and the effect of this screening procedure on mortality remains inconclusive. While several randomized controlled trials are ongoing [7–10], results of previous analyses [11–13] have not supported an effect of CT-based screening in lowering lung cancer mortality. Recently, however, the National Lung Screening Trial (NLST), a randomized trial targeted for current and former heavy smokers, found a 20% reduction in lung cancer death among participants screened with low-dose helical CT compared to participants screened with chest X-ray [14]. So far, screening lung cancer using CT has not been recommended in any set of guidelines except for research purpose [15,16].

In Hitachi Medical Area, a large-scale chest CT screening program for lung cancer has been introduced in two medical facilities since 1998 and 2001, respectively. We previously reported the characteristics of cancers detected on the CT screening [3,17]. In the present study, we followed 210 patients with lung cancer detected on the CT screening in collaboration with local hospitals and administrative office. The objectives of the present study were: (1) to estimate survival of prognosis of patients with lung cancer detected on CT screening and (2) to examine the prognosis of lung cancer patients according to a history of CT screening, patient characteristics, and the size and density of lung shadow on CT.

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2. Materials and methods

2.1. Study design and patients

In Hitachi Health Care Center (Hitachi Ltd, Hitachi), chest CT screening for lung cancer has been conducted for ages 50–69 years for employees, retired persons, and their spouse since in 1998. In Hitachi Medical Center (Hitachi) also initiated chest CT screening for lung cancer for community dwellers aged 50 years or older in 2001. Informed consent was obtained from each participant in both facilities prior to the examination. The protocol of the follow-up survey of patients whose cancer was detected on the CT screening has been approved by the ethics committee of Hitachi Health Care Center (1998–2001).

Detail of the screening procedure, the numbers of participants and patients with lung cancer, and clinical features of screen-detected cases in each facility has been described elsewhere [3,17]. In short, two readers independently interpreted the CT images. If they could not reach a consensus, the final decision was made at a reading conference. When we detected noncalcified solitary pulmonary nodules (SPNs) ≥8 mm (Hitachi Health Care Center) or those ≥5 mm (Hitachi Medical Center), a detailed CT scan was carried out 1 month later. For SPNs ≥11 mm in size, we recommended biopsy, thoracoscopy, thoracotomy, fine-needle aspiration, or a combination of these methods according to the standards of care at that time. For SPNs of 8–10 mm (Hitachi Health Care Center) or 5–10 mm (Hitachi Medical Center), detailed CT scans were performed at 3 months and 6 months. Further follow-up of SPNs was performed at referred hospitals according to the "Low-dose CT lung cancer screening guidelines for pulmonary nodules management" [18]. If there was a sign of growth in either scan, patients were recommended to receive confirmatory diagnostic tests as noted above. Among participants who underwent invasive diagnostic test, the number of false-positive cases was 14 and 5 for Hitachi Health Care Center and Hitachi Medical Center, respectively. Participants were given an advice on quitting smoking orally or using a leaflet at the time of screening if they were current smokers.

As of March 2006, a total of 61,914 CT screenings were performed among 25,385 screenees (Table 1). The characteristics of screening participants were different between the two facilities. For instance, screenees at Hitachi Health Care Center were on average younger than those at Hitachi Medical Center (57 years old versus 64 years old). Moreover, the proportion of those with a history of smoking was much higher in Hitachi Health Care Center than that in Hitachi Medical Center, reflecting a higher male-to-female ratio in Hitachi Health Care Center than in Hitachi Medical Center. Of all the screening participants, 169 cases of lung cancer were identified at the initial screening and 41 cases at repeat screenings. Mean (SD) diameter of the tumors identified was 17.5 mm (9.3 mm) and 178 (85%) were on stage IA. The observed difference in detection rate between the two facilities is probably ascribed to the differences of characteristics, especially age distribution, of screening participants as mentioned above. Of all the 210 lung cancer patients, 159 (76%) were residents of Hitachi city and 202 (96%) were referred to either Hitachi General Hospital (Hitachi Co Ltd) or Ibarakihigashi National Hospital.

Table 2 shows epidemiologic and clinical features of lung cancer cases detected on chest CT screening. Compared with patients whose cancer was detected at repeat screening, those whose cancer was detected at initial screening were more likely to be female and a nonsmoker, and tended to have a larger lesion in size. As regards histology, 195 (93%) were adenocarcinoma. Of all patients, 178 (85%) had stage IA cancer, 145 (81%) of which had a nodule of 20 mm or less in diameter. A total of 203 patients (97%) underwent surgery, 6 had unresectable lesion, and one refused any medical treatment. Mean time period between CT screening and initiation of medical therapy was 161 days.

2.2. Follow-up

We made a follow-up survey to determine prognostic status of the 210 patients with primary lung cancer detected on chest CT screening by examining medical records and log of screening participation, supplemented by vital status information from local government. We used two definitions of outcome: one for death from all causes and another for death from lung cancer. Censoring was made at either the date of death from causes other than lung cancer (if the outcome is death from lung cancer), the date of last contact, or 28 February 2010 (end of follow-up period), whichever came first. Follow-up period was calculated for each patient as time period from the date of initiation of medical therapy and the date of the occurrence of either outcome or censoring. We estimated

Table 1
Summary and results of thoracic CT screening in Hitachi Medical Area as of March 2006.

	Hitachi Medical Center	Hitachi Health Care Center
CT scanner	Multi detector row CT (mobile, 4 rows)	Single slice spiral CT
Screening participants	Local residents, 50 years or older	Employees, retired persons, and their spouses, 50–69 years old
Start of screening program	April 2001	April 1998
Baseline screening		
Participants	11,204	14,181
Lung cancer cases	109	60
Detection rate (%)	0.97	0.42
Mean diameter, mm	18.5	17.9
Stage IA (%)	83	83
Repeat screening		
Examinations	4387	32,142
Lung cancer cases	20	21
Detection rate (%)	0.46	0.07
Mean diameter, mm	13.1	15.1
Stage IA (%)	90	86

Table 2
Characteristics and outcome of lung cancer cases detected on CT screening according to the type of screening.

	Initial screening (n=169)	Repeat screening (n=41)	Total (n=210)
Age, years (mean ± SD)	62.2 ± 7.8	62.2 ± 7.5	62.4 ± 7.6
Sex (male/female)	76/93	25/16	101/109
Smoking history (%)	63 (37.3)	21 (51.2)	84 (40)
Nodule size, mm (mean ± SD)	18.3 ± 9.7	14.1 ± 7.0	17.5 ± 9.3
Nodule appearance in thin-section CT			
Nonsolid	61	14	75
Part-solid	69	11	80
Solid	39	16	55
Pathology			
Adenocarcinoma	159	36	195
Others	5	0	5
Stage[a]			
IA	142	36	178
IB	12	1	13
IIA to IV	6	2	8
Treatment			
Surgical resection	164	39	203
Other than surgery	4	2	6
No treatment	1	0	1
Time from screening to treatment, days (mean ± SD)	160 ± 147	164 ± 159	161 ± 149

[a] Disease stage was defined according to the UICC 5th edition of TNM staging system.

Table 3
Kaplan–Meier 5-year survival rate and hazard ratio of all cause death among patients with lung cancer detected on CT screening.

	n	Survival rate (95% CI)	*P*[a]	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)[b]
All patients					
Total	210	90 (84, 93)			
Initial	169	91 (85, 94)	0.39	1 (reference)	
Repeat	41	84 (68, 93)		1.1 (0.4, 2.9)	
Women	109	97 (92, 99)	<0.001	1 (reference)	1 (reference)
Men	101	81 (72, 88)		5.9 (2.1, 17.3)	1.0 (0.3, 3.9)
Nonsmoker	126	98 (93, 99)	<0.001	1 (reference)	1 (reference)
Smoker[c]	84	77 (66, 85)		2.4 (0.7, 8.3)	4.7 (1.3, 16.5)
Nodule size, mm					
<11	52	98 (87, 100)	0.001	1 (reference)[d]	1 (reference)[d]
11 to <21	102	93 (85, 96)			
21+	56	76 (63, 86)		3.3 (1.5, 7.2)	1.9 (0.7, 5.1)
Nodule appearance					
Nonsolid	75	100	<0.001	1 (reference)[e]	1 (reference)[e]
Part-solid	80	96 (89, 99)			
Solid	55	66 (51, 77)		10.3 (3.7, 28.2)	4.6 (1.6, 13.9)
Stage IA					
Total	178	97 (92, 98)			
Initial	142	97 (92, 99)	0.69	1 (reference)	
Repeat	36	94 (79, 99)		1.2 (0.2, 6.1)	
Women	100	98 (92, 100)	0.35	1 (reference)	
Men	78	95 (86, 98)		2.0 (0.5, 8.5)	
Nonsmoker	112	99 (94, 100)	0.03	1 (reference)	1 (reference)
Smoker	66	92 (82, 97)		12.8 (1.4, 115.3)	3.4 (0.6, 18.8)
Nodule size, mm					
<11	52	98 (87, 100)	0.46	1 (reference)[d]	
11 to <21	93	96 (89, 98)			
21+	33	97 (79, 100)		0.6 (0.1, 4.7)	
Nodule appearance					
Nonsolid	74	100	0.03	1 (reference)[e]	1 (reference)[e]
Part-solid	72	97 (89, 99)			
Solid	32	87 (69, 95)		4.5 (1.0, 19.9)	3.2 (0.7, 14.1)

[a] Log-rank test.
[b] Variables adjusted for the multivariate model were sex, smoking, diameter of lesion, nodule appearance (which showed $P \leq 0.1$ in age- and sex-adjusted model), and cancer stage for all patients; smoking and nodule appearance (which showed $P \leq 0.1$ in age- and sex-adjusted model) for patients on stage IA.
[c] Including former and current smokers.
[d] Including nodules of <11 mm and 11 to <21 mm in size.
[e] Including nonsolid and part-solid nodules.

a 5-year survival rate for the 210 cases detected and according to the size of nodule (<11 mm, 11–<21 mm, or 21+ mm), features of nodule (solid, part-solid, or nonsolid), or the timing of detection (initial or repeat screening). Further, we examined clinical features of cases died from lung cancer detected on repeat screening.

2.3. Statistical analysis

Statistical analysis was done by using Stata version 10.0. Difference in continuous variable among groups was tested by *t* test or Mann–Whitney *U* test. Survival rate was estimated by using Kaplan–Meier method and its difference among groups was tested by using Log-rank test. Cox proportional hazard model was used to estimate hazard ratio and its 95 confidence interval. We calculated two types of hazard ratio: one using a model with adjustment of age and sex only and another using a model with adjustment of variables showing $P \leq 0.1$ in the age- and sex-adjusted model plus clinical stage of cancer. A two-sided *P* value of <0.05 was considered as statistically significant.

3. Results

The mean of follow-up period for all patients was 2076 days (5.7 years), with more than 70% of surviving patients being observed for at least 5 years. During the follow-up period, 25 (12%) died; 19 died from lung cancer and 6 died from other causes. Among 169 patients with lung cancer detected on initial screening, 19 (11%) died during follow-up period; of these, 14 died from the lung cancer detected. Causes of death other than lung cancer were colorectal cancer, esophageal cancer, ischemic heart disease (myocardial infarction), cerebrovascular infarction, and myeloid-fibrosis. Among 41 patients with lung cancer identified on repeat screening, 6 (15%) died; of these, 5 died from lung cancer and 1 from stomach cancer.

The estimated 5-year survival rate for death from all causes and hazard ratio and its 95% confidence interval were presented according to the characteristics of patients and nodule detected on screening (Table 3). Among all patients, the 5-year survival rate for death from all causes was 90%. The survival rate did not significantly differ between initial and repeat screenings (initial, 91%; repeat, 84%; $P = 0.39$). Male gender and smoking were each associated with a significantly poorer prognosis ($P < 0.001$ versus female gender and nonsmoking, respectively). Larger nodule and solid nodule on thin-section CT were significant predictors of lower survival. Patients with a lesion of 20 mm or smaller, compared with those with a lesion of 21 mm or larger in diameter, had a better prognosis (overall $P = 0.001$; Fig. 1). In age- and sex-adjusted model, a statistically significant increase in hazard of death was observed in association with male gender, smoking, larger nodule, and solid nodule. However, only smoking and solid nodule were associated with a statistically significantly increased hazard ratio after multivariate adjustment.

Patients with lung cancer on stage IA had a 5-year survival rate of 97% for death from all causes. Both solid nodule and smoking remained significant predictors of poor survival in this subgroup, whereas nodule size did not. Fig. 2 shows survival curves according to nodule density among patients with a lesion of 20 mm or smaller in diameter. Patients with a lesion of solid nodule had a 5-year

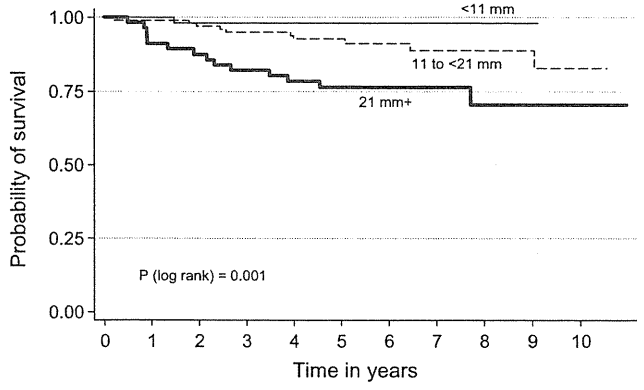

Fig. 1. Kaplan–Meier survival estimates for death from all causes by size of lung nodule.

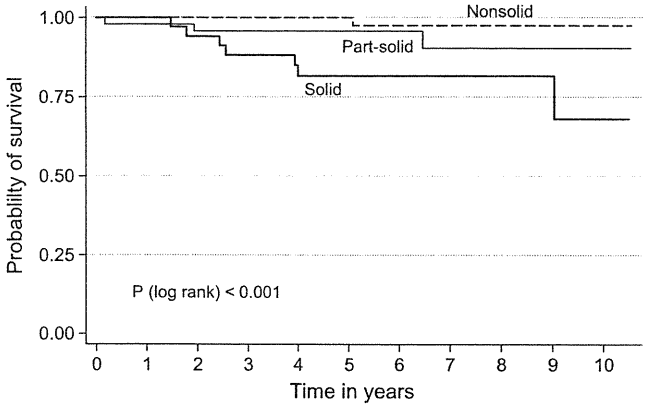

Fig. 2. Kaplan–Meier survival estimates for death from all causes in patients with small lung nodule (<21 mm in diameter).

survival of 82%, a value significantly lower than that among those with a lesion of combined nonsolid and part-solid shadow (98%; $P = 0.001$). In age- and sex-adjusted model, hazard ratio of death was statistically significantly increased in association with smoking and solid nodule. After multivariate adjustment, none of these variables remained statistically significant.

As smoking was a strong predictor of increased mortality among patients whose lung cancer was detected on CT screening, we presented background factors according to smoking status (Table 4). Smokers including past smokers were more likely to be male, had a larger nodule and a higher proportion of solid nodule, and tended to be on advanced clinical stage than nonsmokers.

Table 4
Clinical features of lung cancer detected on CT screening by smoking status.

	Smoker[b] ($n = 84$)	Nonsmoker ($n = 126$)	P[a]
Women	7 (8)	102 (81)	<0.001
Cancer stage			
IA	66 (79)	112 (89)	0.06
IB	9 (11)	4 (3)	
II to VI	9 (11)	10 (8)	
Mean (SD) nodule size, mm	19.4 (10.5)	16.2 (8.3)	0.01
Nodule appearance			
Nonsolid	19 (23)	56 (44)	<0.001
Part-solid	29 (35)	51 (40)	
Solid	36 (43)	19 (15)	

Figures in the table are number and percentage (in parenthesis) unless stated otherwise.

[a] Chi-square test for categorical variable and t-test for continuous variable.

[b] Including former and current smokers.

Among 14 deceased patients with lung cancer detected on baseline screening, the mean diameter of nodule was 32.1 mm and the proportion of advanced cancer showing solid shadow was high. Of these, 12 (86%) were male and 9 (64%) had a smoking history; 12 underwent surgical operation, 1 received chemotherapy, and 1 refused receiving medical therapy. Mean period from initiation of medical therapy to death was 3.0 years. Included in the 14 patients who subsequently died from lung cancer were one patient who chose alternative medicine and another patient who was under the care of physician due to interstitial pneumonia at the time of diagnosis. All five patients who died from the lung cancer detected on repeat screening were male, had a history of smoking, and showed a solid nodule. Of these, 4 had a lesion of 20 mm or smaller in diameter and only one had a nodule (4 mm in diameter and solitary) detectable at the time of initial screening.

4. Discussion

We investigated the prognosis of 210 patients with lung cancer detected on low-dose chest CT screening in two medical facilities in Hitachi City, Japan, with a 5.7-year mean follow-up period. Our study showed that lung cancer cases detected on CT screening had a fairly good prognosis, with a 5-year survival rate of 90%. A total of 19 patients, including 3 who refused or delayed medical therapy, died from lung cancer detected on the screening. No premature death was documented associated with therapeutic intervention. Patients with a lesion of solid shadow, indicative of invasive cancer, had a 5-year survival of 82% if the lesion detected was 20 mm or less in diameter.

The high survival rate among patients with lung cancer detected on CT screening observed in the present study is consistent with those in Japanese studies [4,6] as well as multi-country study [5]. However, lower survival rate have been reported in some Western studies [11,12], in which the proportion of stage I cancer of all cases detected was less than those in Japanese studies [2–4]. This may be attributed in part to the different characteristics of target population; Western studies have recruited persons with a history of smoking only, whereas Japanese studies also included persons without smoking experience. Moreover, there is ethnic difference in histological types of lung cancer; the proportion of adenocarcinoma among lung cancer patients in Japanese CT screening studies [2–4] is much higher than that observed in Western CT screening study [19]. Therefore, an extrapolation of findings obtained in Western populations to Japanese or vice versa requires caution. The analysis of data from an on-going Japanese cohort [20] using a simulation approach [21,22] may reveal the effectiveness of CT screening for lung cancer for Japanese populations.

We observed no measurable difference in survival rate between lung cancers detected on initial screening and those detected on repeat screening, similar to findings in previous studies [4–6]. Clinical characteristics of lung cancer cases differ according to whether the cancer was detected on initial or repeat examination [19]. At initial screening, not only cases showing small, vaguely delineated nodule but also those on advanced stage will be identified, leading to a wide variation in the nature of cancers ranging from non-invasive, slow-growing type to advanced one. High survival rate of patients with screening-detected cancer has been ascribed to well known bias; namely, lead time bias, length bias, and over-diagnose bias [23]. The effects of these types of bias are serious if cancers detected are mainly non-invasive and slow-glowing. However, given that 64% of patients with lung cancer detected at initial screening in the present study showed solid or part-solid nodule, which are likely invasive cancer [24], we believe that the observed high survival rate cannot fully be explained by these types of bias only. We should note that there was no death observed among patients with lung cancer with nonsolid nodule of 20 mm or less

in diameter at initial screening. More research is required to examine whether in-depth work-up for such a small, nonsolid nodule can be suspended until the next CT screening.

As regards repeat screening, lung cancers are detected due mainly to the emergence of new nodule or enlargement and change in concentration of CT image of the nodule detected on the previous screening. Although cancers detected on repeat screening are on average smaller than those detected on initial screening, they probably progress rapidly and thus are life-threatening if left untreated. In other words, the aforementioned bias inherent to the evaluation of screening may exert to a lesser extent in the survival of cases detected on repeat CT screening. Therefore, the present finding showing a good prognosis of these cases adds to evidence that repeat chest CT screening can prevent early death from lung cancer.

In the present study, smokers had a significantly poorer survival than nonsmokers even among stage IA patients, and all the three patients with small lung cancer (20 mm or less in diameter) detected on repeat screening who subsequently died from the lung cancer were current smokers. Poorer survival of smokers compared with nonsmokers is compatible with results of previous studies, including one among Japanese patients with CT-screen detected lung cancer [6]. These findings suggest that smoking-related lung cancers are likely aggressive and incurable even if detected on early stage, and thus underscore the importance of providing smoking cessation program at all settings including CT screening to decrease overall mortality [25].

Our study has several strengths including larger number of lung cancer patients who were detected on low-dose chest CT screening and longer follow-up period (mean 5.7 years) relative to most previous studies. In addition, the present study provided data not only for high-risk group (ever-smokers) but also for low risk group (lifetime nonsmokers), which makes it possible to compare survival of patients with lung cancer detected on CT screening between smokers and nonsmokers. The present study is limited due to bias inherent to screening studies of one arm design, as discussed above. Besides, we acknowledge two other limitations. First, our study was done only among patients whose cancer was detected at the time of CT screening and did not obtain any information about lung cancer diagnosed between the screenings. However, such interim cancers are probably few, and the inclusion of such cases may not greatly distort the result. Another limitation is that, as Hitachi CT screening program covered both ever-smokers and lifetime nonsmokers, overall result may not be applied to high-risk populations with a history of smoking.

CT screening for lung cancer has been performed at community and occupational settings in Hitachi City. If we assume 76% of screening participants (the proportion of residents in Hitachi City among lung cancer patients detected on CT screening) reside in Hitachi City, it is estimated that 18,115 residents (nearly 30% of residents aged 50–69 years [26]) of Hitachi City had participated into the CT screening program as of May 2006. The number of screening participants is increasing constantly, with some 700 individuals and another 2000 individuals receiving the screening at Hitachi Health Care Center and Hitachi Medical Center, respectively, each year. Given this wide-spread practice of CT screening in this community, it would be of interest whether lung cancer mortality among residents of Hitachi City will decrease more rapidly than that in other areas. Such time-trend analysis may provide valuable data for assessing the effectiveness of CT screening at population level.

5. Conclusion

Patients with lung cancer detected on low-dose CT screening had a fairly good prognosis, with the estimated 5-year survival rate for all patients and for those on stage IA being 90% and 97%, respectively. Besides cancer stage, smoking and nodule appearance were independent predictors of a poor survival. It is anticipated that chest CT screening program combined with anti-smoking campaign could effectively decrease risk of deaths from lung cancer. The impact of CT screening on mortality at community level needs to be clarified by monitoring lung cancer deaths.

6. Conflicts of interest

There are no conflicts of interest to disclose.

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Cytological Characteristics of Pulmonary Pleomorphic and Giant Cell Carcinomas

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Key Words
Cytology · Giant cell carcinoma · Lung neoplasms · Pleomorphic carcinoma · Sarcomatoid carcinoma

Abstract
Objective: To establish cytological features of pulmonary pleomorphic carcinoma (PC) or giant cell carcinoma (GC), we evaluated the cytological characteristics of these tumors using a multidisciplinary approach. ***Study Design:*** Samples from 13 surgically resected and histologically confirmed PC or GC patients were collected from our institutes. Eight cases without prior chemotherapy before surgery were selected, and cytological features were analyzed. ***Results:*** The background contained numerous lymphocytes and neutrophils. The tumor cells were arranged in flat loose clusters, but some were in fascicles. The shape of the tumor cell was spindle or pleomorphic, and the sizes of the tumor cells varied by more than 5-fold. The tumor cells had an abundant, thick and well-demarcated cytoplasm. The location of the nucleus was centrifugal, and the nucleus was oval or irregularly shaped. Multinucleated giant cells were frequently observed. The size of the nucleus was more than 5 times that of normal lymphocytes, and its size also varied by more than 5-fold. The nuclear membrane was thin, and nuclear chromatin was coarsely granular, while the nucleolus was single and round. ***Conclusion:*** PC or GC has characteristic cytological features, however, spindle cells tended to be hardly observed in cytological specimens in some cases.

Pleomorphic carcinoma (PC) is defined as a poorly differentiated non-small cell lung carcinoma (NSCLC), namely squamous cell carcinoma, adenocarcinoma or large cell carcinoma containing spindle cells and/or giant cells, or a carcinoma containing only spindle cells and giant cells [1]. The spindle or giant cell component should comprise at least 10% of the tumor. Giant cell carcinoma (GC) is NSCLC composed of highly pleomorphic mono- and/or multinucleated tumor giant cells. This tumor is composed entirely of giant cells and does not have specific patterns of adenocarcinoma, squamous cell or large-cell carcinoma. The tumor cells are discohesive and tend to dissociate from each other [1].

The prognosis for PC patients is worse than that for patients with other NSCLC in surgically operated cases [2–4]. However, there have been some contradictory reports that PC has similar clinical behavior and prognosis as other NSCLC [5–7]. Histologic diagnosis is usually

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Table 1. Clinical summary of cases with pleomorphic carcinoma or giant cell carcinoma

Case	Age/ sex	Location	Smoking pack-years	Size mm	Stage	Adjuvant therapy	Follow up		Component
							months	prognosis	
1	69/F	LU/P	49	17		none	14	alive	S/G/A/L
2	76/M	LU/P	122	55	IIIA	chemo. + rad.	7	alive	S/G/A/L
4	62/M	RU/P	126	80	IV	none	3.5	dead	S/A
7	68/M	LL/P	18	16	IA	none	32	recurrence	S/G/A
8	68/M	LL/P	50	32	IIB	none	21	recurrence	S/A
9	82/M	RM/P	60	60	IIB	none	60	alive	S/G
10	39/F	LL/C	8	50	IIIA	rad. + chemo.	40	alive	S/G/A
12	78/M	RU/P	55	25	IV	UFT	23	alive	G

LU = Left upper lobe; RU = right upper lobe; LL = left lower lobe; RM = right middle lobe; P = peripheral; C = central; S = spindle cells; G = giant cells; A = adenocarcinoma; L = large cell carcinoma; Chemo. = chemotherapy; Rad. = radiotherapy; UFT = 5-fluorouracil derivative.

made with surgically removed tumors; however, diagnosis has to be made based on small biopsies or cytological specimens for patients with an advanced-stage tumor. Because of the difficulty in making a definite diagnosis of PC or GC, it is not clear whether the prognosis of patients with those tumors in the advanced stage is worse than that for patients with other NSCLCs. Although cytological findings of PC or GC have been documented in a few reports [8–13], there have been no multi-institutional studies carried out by pulmonary cytopathologists. The aim of this study was to elucidate the cytological characteristics of PC or GC with specimens obtained from the touch imprints of surgically removed tumors or pre-operative transbronchial cytology specimens in patients whose tumor was surgically removed and confirmed histologically to be PC or GC, and to extend application of those findings to specimens obtained from brushing or curettage of advanced-stage tumors.

Materials and Methods

We collected 16 resected tumors that were identified as PC or GC from our own institutes or from consultation cases. Pathological findings were reviewed by 3 pulmonary pathologists (K.H., T.K., and Y.M.), after which 13 of the tumors were diagnosed as PC or GC. Members of the Committee on Pulmonary Cytology of the Japan Lung Cancer Society evaluated the findings of their own original cytological and pathological specimens using a microscope and made digital images of representative microscopic findings for the 13 selected tumors. The digital images were copied to a CD and distributed to each member of the committee. Autopsy cases and patients who received chemotherapy before surgery were eliminated from this study, and 8 cases were selected for analyses of cytological features. All of the authors are experienced pulmonary cytopathologists with Board Certification from the Japanese Society of Clinical Cytology, and all are members of the Committee on Pulmonary Cytology of the Japan Lung Cancer Society.

Each member of the Committee on Pulmonary Cytology evaluated the cytological findings of the samples independently. We defined sarcomatoid component of PC as malignant giant and/or spindle cells. We defined epithelial component of PC as malignant tumor cells with glandular or squamous differentiation. Component of large-cell carcinoma is also included in epithelial component of PC. We defined large-cell carcinoma component as tumor cells which have a tendency to form loosely structured clusters composed of cells of unequal sizes without glandular or squamous differentiation. We evaluated cytological features of sarcomatoid component in each of the cases using the following parameters of the tumor cells by light microscopy: component of tumor cells, background, number, sizes of clusters, nuclear overlapping, arrangement, shape, size, variability in size, pleomorphism, surface, adhesion, color of the cytoplasm, nature of the cytoplasm, nuclear to cytoplasmic ratio, localization of the nucleus (centrifugal or peripheral), shape of the nucleus, size of the nucleus, pleomorphism of the nucleus, nuclear membrane, amount of chromatin, chromatin texture, distribution of chromatin, size and shape of the nucleolus, and number of nucleoli in the nucleus.

The age of the patients ranged from 39 to 82 years old (mean 67.8 years). Six were men and 2 were women. The tumor existed at the periphery of the lung in 7 cases and at the central part of the lung in 1 case. All of the patients were smokers. They smoked from 8 to 126 pack-years (average 61 pack-years). The size of the tumor was from 16 to 80 mm in diameter (average 42 mm). Lobectomy with lymph node dissection was performed in 7 cases, and partial resection of the lung without lymph node dissection was done in 1 case because of poor pulmonary function (case 1). The tumor stages were IA in 1 case, IIB in 2 cases, IIIA in 2 cases, and IV in 2 cases. The TNM classification of case 1 is T1NXMX (table 1).

Results

The cytological specimens were obtained with touch imprint in 4 cases, and with transbronchial brushing in 3 cases; 2 of these were also evaluated with a touch imprint sample, and 1 with transbronchial curettage. The histological diagnosis was PC in 7 cases and GC in 1. The NSCLC component of tumor cells in PC was adenocarcinoma in 6 cases, while in 1 case the tumor was composed of only spindle cells and giant cells.

Clinical Findings and Clinical Courses

The white blood cell counts were elevated to 9,400/μl in 1 case but were within normal range in the other 7 cases. Tumor markers were elevated in 5 cases. CEA was high in 4 cases (cases 1, 7, 8, and 9), and the CA19-9 level was also high in 1 (case 8). The CYFRA level was high in 1 case (case 4). One patient had metastasis to the brain (case 4), and another had metastasis to the right adrenal gland at the time of surgical removal of the lung tumor (case 12). Removal of the metastatic adrenal gland was performed after resection of the lung tumor. Chemoradiotherapy was performed in 2 patients after surgery. Recurrence was observed in 2 cases: 1 had a recurrent tumor in the lung (case 7) and another in the brain (case 8). Radiotherapy to the recurrent tumor in the lung was performed. The observation period from the time of the surgery was 3.5–60 months (average 29.7 months); 1 patient is dead, 2 are alive with recurrence, and 5 are alive without recurrence (table 1).

Cytological Findings

There was no difference in cytological findings depending on how the cytological specimens were obtained. However, the amount of tumor cells was small in transbronchial curettage samples, and large in transbronchial brushing samples and in touch imprint of the surgically resected tumor.

The background contained numerous lymphocytes and neutrophils with or without necrotic debris (fig. 1). There were a large number of tumor cells on the slides in some cases, but not in others. The size of the clusters seen on the slides was small, and the number of tumor cells forming the clusters was less than 20 in half of the cases. The shape of the tumor cell was spindle, or pleomorphic, and variable (fig. 2, 3). The tumor cells were large and the pleomorphism was marked. The tumor cell sizes varied by more than 5-fold in half of the cases. The pleomorphic cells varied in diameter from 40 to 80 μm, and occasionally reached up to 120 μm. The tumor cells had an abundant, thick and well-demarcated green cytoplasm that

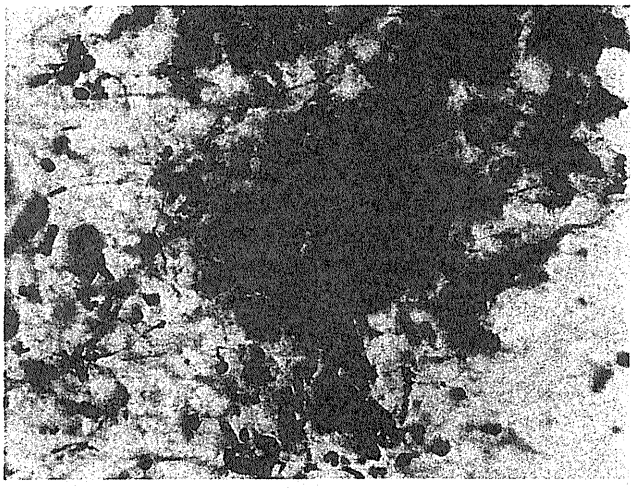

Fig. 1. Touch imprint cytology of the resected tumor from case 10. Pleomorphic spindle cells were observed in a necrotic background. Papanicolaou stain, ×40.

was green and vacuolated in some of the cells. The nuclear to cytoplasmic ratio was high. The location of the nucleus was centrifugal, and the nucleus was oval or irregularly shaped. Multinucleated giant cells were observed frequently. The nucleus was more than 5 times the size of normal lymphocytes in half of the cases and its size varied by more than 5-fold in half of the cases, ranging from 15 to 30 μm. The nuclear membrane was thin, and the nuclear chromatin was coarsely granular with an increased amount of chromatin, compared to non-tumor cells. The distribution of chromatin was uneven in most cases. The nucleolus was single, medium-sized, and round. The tumor cells were arranged in flat loose clusters (fig. 2, 3), but some were in fascicles (fig. 4). Cohesive clusters of atypical epithelial cells were also observed (fig. 5).

The components of tumor cells in pathological and cytological specimens are listed in table 2. The spindle cell component was observed in cytological specimens from 4 cases, and in pathological specimens from 7 cases. The giant cell component was observed in cytological specimens from all cases with a giant cell component in the pathological specimens. The adenocarcinoma component was observed in cytological specimens from 4 cases, and in pathological specimens from 6 cases. The large-cell carcinoma component was observed in cytological specimens obtained from all cases with a large cell carcinoma component. Summary of cytological features of sarcomatoid component of pleomorphic carcinoma and giant cell carcinoma is listed in table 3.

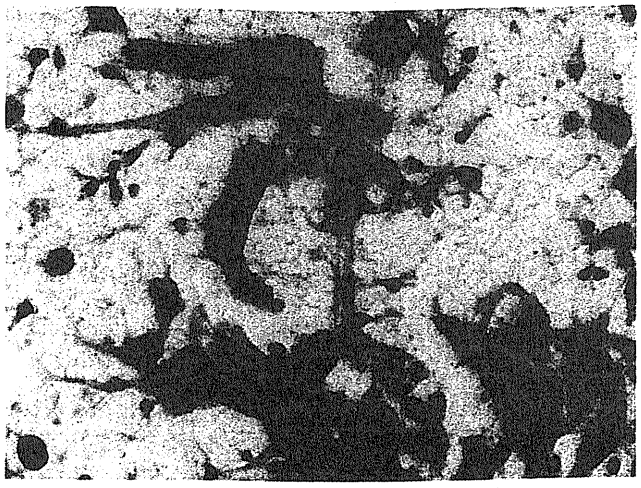

Fig. 2. Transbronchial brushing cytology of case 9. Pleomorphic spindle cells were arranged in loose clusters. Papanicolaou stain, ×40.

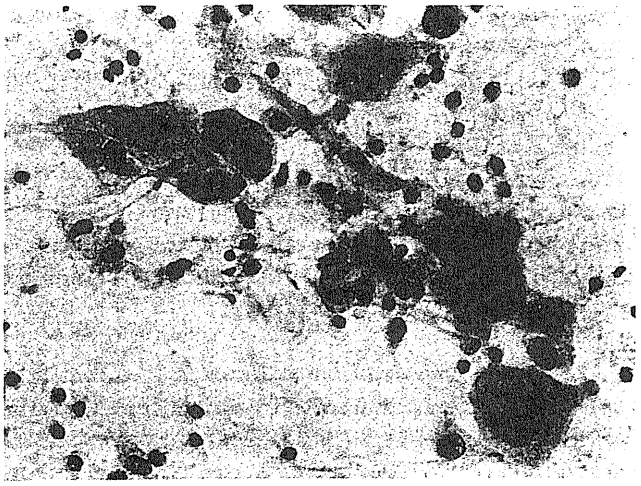

Fig. 3. Multinucleated cells were arranged in loose clusters in a background of lymphocytes (case 1). Papanicolaou stain, ×40.

Fig. 4. Transbronchial brushing cytology of case 9. Pleomorphic spindle cells were arranged in fascicles. Papanicolaou stain, ×40.

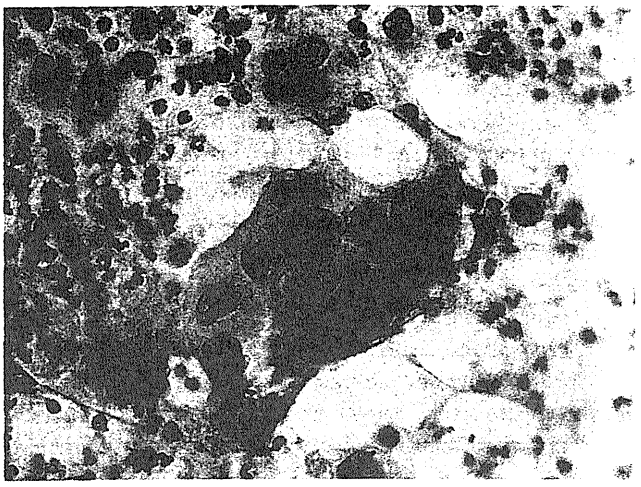

Fig. 5. Cohesive clusters of atypical epithelial cells were observed in a background of neutrophils (case 2). Papanicolaou stain, ×40.

Discussion

Hummel et al. reported that cytological findings of PC include a conspicuous population of pleomorphic spindle cells arranged singly, in loose clusters, and in fascicles, and as microtissue fragments in a necrotic background [8]. Myxoid stromal fragments are also present. In addition, cohesive clusters of typical epithelial cells have been noted. There have been reports that pre-operative transbronchial brushing cytology of the PC revealed adenocarcinoma or atypical cells [10, 11]. Cytological study of the tumor in cases 1, 2, and 4 in our study revealed adenocarcinoma and giant cells, but not spindle cells, although spindle cells were components of the tumor. The results of our study and others suggest that spindle cells have poor adhesiveness to each other, and that they detach eas-

Table 2. Components of tumor cells observed in pathological and cytological specimens

Case	Methods	Component of tumor cells in pathological specimens				Component of tumor cells in cytological specimens			
		spindle cells	giant cells	AD	LA	spindle cells	giant cells	AD	LA
1	TI	present	present	present	present	X	present	present	present
2	TI	present	present	present	present	X	present	present	present
4	Cr	present		present		X		present	
7	TI	present	present	present		present	present	X	
8	TI	present		present		present		present	
9	Br	present	present			present	present		
10	Br	present	present	present		present	present	X	
12	Br		present				present		

AD = Adenocarcinoma; Br = brushing; Cr = curettage; LA = large-cell carcinoma; TI = touch imprint; X = absent.

Table 3. Summary of cytological features of sarcomatoid component of pleomorphic carcinoma and giant cell carcinoma

Background	necrosis	present	2/8 (25%)
	type of cells	lymphocytes, neutrophils	7/8 (88%)
Amount of tumor cells		large	5/8 (63%)
Clusters	size	small	4/8 (50%)
	nuclear overlapping	not obvious	8/8 (100%)
	arrangement	2-dimensional	6/8 (75%)
Cells	shape	spindle, pleomorphic, variable	8/8 (100%)
	size	large	7/8 (88%)
	variability in size	5 times or more	4/8 (50%)
	pleomorphism	marked	7/8 (88%)
	margin	demarcated	5/8 (63%)
	cell adhesion	poor	7/8 (88%)
Cytoplasm	color	green/blue	8/8 (100%)
	nature	translucent or vacuole, thick	8/8 (100%)
Nucleocytoplasmic ratio		increased	7/8 (88%)
Nucleus	location	centrifugal	5/8 (63%)
	shape	irregular, oval	8/8 (100%)
	size	5 times of lymphocyte or more	4/8 (50%)
	variability in size	5 times or more	4/8 (50%)
	nuclear membrane	thin, slightly thick	8/8 (100%)
	hyperchromatism	present	8/8 (100%)
	chromatin texture	coarsely granular	7/8 (88%)
	distribution of chromatin	uneven	5/8 (63%)
Nucleolus	shape	round	7/8 (88%)
	size	medium	4/8 (50%)
	number	single	7/8 (88%)

ily from the glass slide during the staining process. On the other hand, the adenocarcinoma component was not observed in cytological specimens from cases 7 and 10. Pathological specimens from case 7 revealed that the adenocarcinoma component was a solid adenocarcinoma with mucin that had bizarre nuclei. Giant cells and spindle cells were marked in this case, and mucin in the cytoplasm was difficult to discern in cytological specimens. Pathological specimens in case 10 revealed that the adenocarcioma component comprised a small percentage of the tumor. This may be the reason why the adenocarcinoma component did not appear in cytological specimens from case 10.

There have been only a few cytological studies of GC [12, 13]. GC cytology specimens have exhibited numerous mono- or multinucleate giant cells with significant pleomorphism in size and shape. The cytoplasm of the giant cells is abundant, eosinophilic, microvesicular, and well demarcated. Most of the tumor cells have round, oval or irregularly shaped macronuclei with coarse, granular chromatin and large, prominent nucleoli. Their cytoplasm is occasionally infiltrated with neutrophils. The tumor cells usually occurred singly, and the background contains tumor diathesis with numerous polymorphonuclear leukocytes [12, 13].

Giant cells are one component of PC or GC [1]. However, there is no clear definition of how large these giant cells are. Fishback et al. reported that the single large pleomorphic nucleus of GC measured greater than the diameter of four small resting lymphocytes [14]. Guillan and Zelman reported that the giant cells varied in size from 50 to 120 μm in diameter [15], and Hellstrom and Fisher reported that the giant cells measured from 80 to 100 μm [16]. This vague definition of giant cells causes confusion among pathologists. In our study, the mononucleated giant tumor cells had large nuclei, the size of which was greater than the diameter of 5 resting lymphocytes in half of the cases. There was variability in the size of the nuclei, and the size of the largest nucleus was 5 times greater than that of the smallest nucleus of the tumor cells in half of the cases.

It has been reported that the prognosis for PC patients is worse than that for patients with other NSCLC in surgically resected cases [2–4]. In contrast, Nakajima et al. reported similar clinical behaviors and prognosis between PC and other NSCLC [7]. Pelosi et al. reported that stage I PC behaves more aggressively than ordinary NSCLC; however, the differences were not statistically significant for both overall and disease-free survival curves [6]. Yamamoto et al. reported that the overall 5-year survival rate of surgically resected PC was 80.0% and the disease-free survival rate was 63.3%, which were both far better than rates reported elsewhere [5].

PCs have been reported to be highly metastatic. In our study, some patients had a recurrence even though the tumor was stage I or II; the patient with a stage IA tumor had a recurrence in the lung 31 months after surgery (case 7), and 1 patient with a stage IIB tumor had a brain metastasis 21 months after the surgery (case 8). In contrast, some patients had a favorable prognosis. One patient with a stage IIB tumor is alive 5 years after surgery without any adjuvant therapy (case 9). One patient with a stage IIIA tumor underwent thoracic radiotherapy and chemotherapy (CDDP + GEM) and is alive without recurrence 40 months after the surgery (case 10). One patient (case 12) had an enlarged right adrenal gland the size of which was 15 mm, and its size had become 53 mm six months later. It was surgically removed and confirmed to be metastasis from a pulmonary PC. The patient is alive 23 months after the surgery of the lung tumor.

The contradictory prognoses of PC in different studies may be due to the different criteria of PC used among pathologists. Because ours is a multidisciplinary study, we selected cases that underwent pathological review by pathologists specialized for lung cancers. We did not include patients treated with chemotherapy or radiotherapy before the surgery, because these therapies may modify the tumor cells and enlarge them even further. The present study, by analyzing carefully selected PC or GC cases, suggests that some patients with PC or GC can expect long survival after resection of the tumor with adjuvant therapy. We could not address the pathological or molecular differences between long-survivors and short-survivors suffering from PC or GC. Further studies are needed to clarify the mechanisms of different biological behaviors among this type of lung carcinoma.

Acknowledgments

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the endocardial linear lesion with the roofline resulted in conversion to sinus rhythm (Figure 1, *B* and *C*).

Bilateral video-assisted thoracoscopic PV isolation is a safe, beating-heart approach for curative surgical treatment of AF.[1] Linear lesions are known to improve the outcome of catheter ablation in patients with persistent atrial fibrillation.[2] The left fibrous trigone line was introduced by Edgerton and colleagues.[3] This linear lesion serves as an alternative to the endocardial mitral isthmus line extending from the left inferior PV to the mitral valve annulus. The creation of a completely transmural left fibrous trigone line can be hampered by the presence of epicardial fat. Not completely transmural lesions exhibit zones of low voltages and conduction slowing and can become pro-arrhythmic.[4] In our patient, an incomplete left fibrous trigone line resulted in left atrial flutter. Most of these iatrogenic arrhythmias are very symptomatic. To prevent, as much as possible, such reentry circuits from occurring, it is of paramount importance to prove complete transmurality of each deployed linear lesion. This can effectively be done using an epicardial approach or a combined simultaneous thoracoscopic surgical and transvenous catheter procedure.[5]

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Extremely rare but potential complication of diffuse brain edema due to air embolism during lung segmentectomy with selected segmental inflation technique by syringe needle during video-assisted thoracoscopic surgery

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A 65-year-old man was diagnosed with right lung cancer in the upper lobe and S8 segment.

To avoid right pneumonectomy, he underwent right upper lobectomy and S8 segmentectomy by video-assisted thoracoscopic surgery. During segmentectomy, the A8 was ligated first, and then B8 was resected using an automatic stapler. An 18-gauge needle was inserted in the distal B8 bronchus without any blood regurgitation. After removing the inner needle, an air tube of a Bolheal Spray Set (The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) with a filter attached was connected to the outer

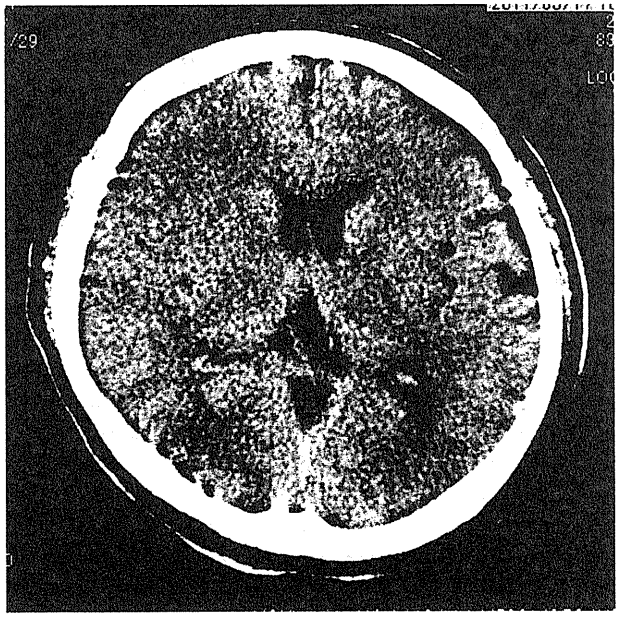

FIGURE 1. Computed tomography scan after hyperbaric oxygen therapy revealing diffuse brain edema.

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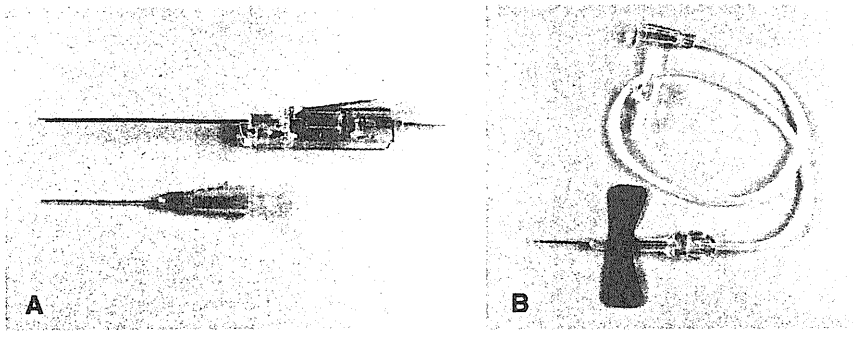

FIGURE 2. Needles used during lung segmentectomy with selected segmental inflation technique: A, inner needle *(Upper)* and outer sheath *(Lower)*; B, other type of needle (butterfly needle) used during lung segmentectomy with selected segmental inflation technique.

dwelling sheath, and air was blown into the tube. Because the air was not confirmed in the target area, which usually inflates, we stopped blowing air and removed the punctured in-dwelling needle. Immediately after this, a sudden elevation in blood pressure (220 mm Hg/150 mm Hg) and a decline in end-tidal carbon dioxide pressure were observed, and ST-segment elevation on the electrocardiogram followed. On the transthoracic echocardiogram, air in the right atrium was observed and was diagnosed as an air embolism. Because the bronchus and pulmonary artery of the right S8 were already resected at this point, we decided to continue with the segmentectomy. The bronchial lumen was confirmed, and the sheath without the needle was inserted to blow air into the lumen. Segmentectomy using the automatic stapler was then completed. Immediately after the operation, hyperbaric oxygen therapy was performed. However, computed tomography images showed diffuse brain edema, and cerebral infarction was diagnosed (Figure 1). After 1 week of hypothermic therapy at 35°C, the body temperature was restored, and the respirator was removed 2 weeks after the operation. Although symptoms of left hemiplegia and left spatial neglect were observed immediately after the first hyperbaric oxygen therapy, they were almost completely absent by 4 weeks after the operation.

With progress and the wide use of computed tomography, the number of smaller lesions being detected has been increasing,[1] and segmentectomy with video-assisted thoracoscopic surgery has been one of the common methods. Because of the poor working spaces with video-assisted thoracoscopic surgery, several procedures for detecting the demarcation lines have been reported. Among them, the selected segmental inflation technique is frequently used in Japan.[2,3] Some thoracic surgeons use a needle for this method in the operation field after the segmental bronchus has been resected (Figure 2),[2] and some anesthesiologists blow out the air through the targeted bronchus with a thin bronchoscope before the segmental bronchus is resected.[3]

In our department, we had been using the selected segmental inflation technique with needles to avoid bacterial contamination in the operative field and to reduce the anesthesiologist's burden. We had no problems with this method before the present case. However, although no blood reflux was confirmed, the tip of the needle might have moved during inflation at this time with air blown into the vessels, which resulted in ST-segment elevation and diffuse brain edema. After the present case, we started using an "open-cut" method, in which the segmental bronchus is resected and opened, followed by insertion of the outer sheath without the needle, with air then blown into the lumen.

Before this experience, we had never seen such a complication. From the published data, only 1 case with the same complication was reported in 2010 in Japan,[4] which suggests it is extremely rare, but possible, when a needle is used in the selected segmental inflation technique. Thus, we recommend an "open-cut" selected segmental inflation technique without the use of a needle or the use of the selected segmental inflation technique through a thin bronchoscope.

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Case Report

Primary Ependymoma in the Posterior Mediastinum

Sumiko Maeda, MD, PhD, Satomi Takahashi, MD, PhD, Kaoru Koike, MD, PhD and Masami Sato, MD, PhD

A 46-year-old woman was referred to our hospital because of back pain and an abnormality on chest imaging. Chest computed tomography showed a well-delineated tumor in the left paravertebral space. Histological analysis of the resected tumor revealed perivascular pseudorosettes, and immunoreactivity for glial fibrillary acidic protein established the diagnosis of ependymoma. A few cases have been reported in the ovary, broad ligament, sacrococcygeal region, lungs, and mediastinum, but the pathogenesis has not yet been clarified. Female predominance in these tumors and organogenesis of the sites may suggest a key to the pathogenesis.

Keywords: mediastinal tumor, ependymoma, female, embryology

Introduction

Ependymomas generally arise from ependymal cells of the central nervous system (CNS): the ventricular system, choroid plexus, and central canal of the spinal cord,[1] and less often in the brain parenchyma as a result of migration of ependymal cells from periventricular areas during embryogenesis.[1] They rarely arise in the extra-axial region, outside the CNS. A few cases have been reported in the ovary, broad ligament, sacrococcygeal region, lungs, and mediastinum[2–11]; however, the exact origin of such extra-axial ependymomas has not been clarified.

We treated a patient with an ependymoma in the posterior mediastinum that had no association with the spine. Immunohistochemical analysis of the resected lesion revealed the unique characteristics of this tumor, particularly reactivity for female hormone receptors, which is reportedly common in extra-axial ependymomas.[5]

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Case Presentation

A 46-year-old female smoker was referred to our hospital because of back pain and an abnormality on chest imaging. She had been well until 6 months earlier, when she developed back pain and was seen by a family doctor without any improvement. Five months later, she had an annual chest screening test, in which an abnormal shadow in the left lung field was noticed on chest X-ray. She also reported weight loss of 3 kg in the previous 3 months.

On examination, vital signs and neurologic examination were unremarkable. Laboratory tests were within the reference range. Chest X-ray revealed a mass in the left middle lung field (**Fig. 1**), and chest computed tomography showed a well-delineated tumor with smooth contours in the left paravertebral space at the T7 to T9 level (**Fig. 2A**). The tumor contained calcification and was heterogeneously and weakly enhanced with intravenous contrast media (**Fig. 2B**). There was no evidence of invasion of the adjacent aortic wall, thoracic vertebrae, or ribs. Magnetic resonance imaging of the chest showed that, compared with the spinal cord, the tumor was iso-intense on T1-weighted images (**Fig. 3A**), and moderately intense with foci of signal heterogeneity on T2-weighted images (**Fig. 3B**). Gadolinium enhancement was moderate and inhomogeneous on T1-weighted images (**Fig. 3C**). Additional CT imaging with myelography indicated no

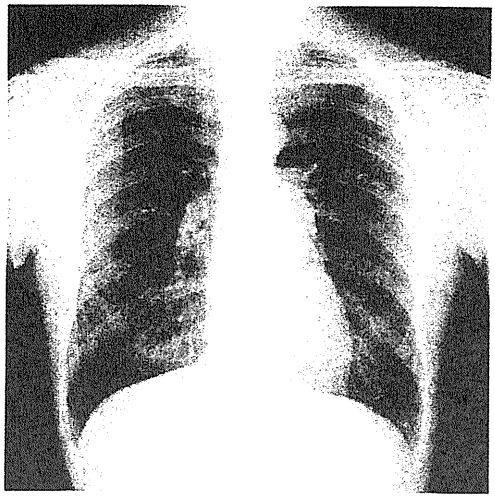

Fig. 1 Chest X-ray revealing a mass in the left middle lung field.

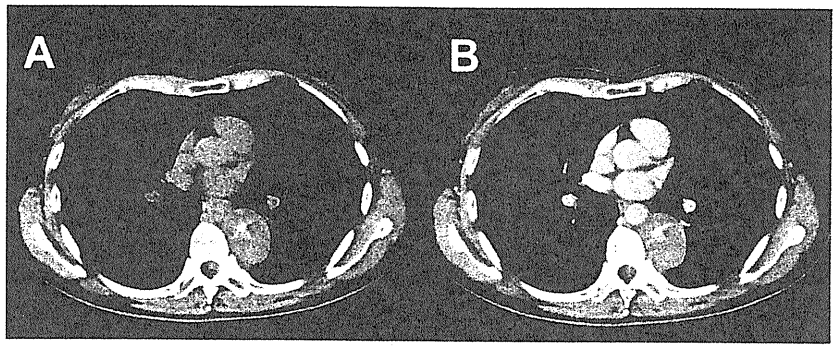

Fig. 2 **A**: Chest CT showing a well-delineated tumor in the left parasvertebral space. **B**: The tumor contained calcification with heterogeneous and weak enhancement.

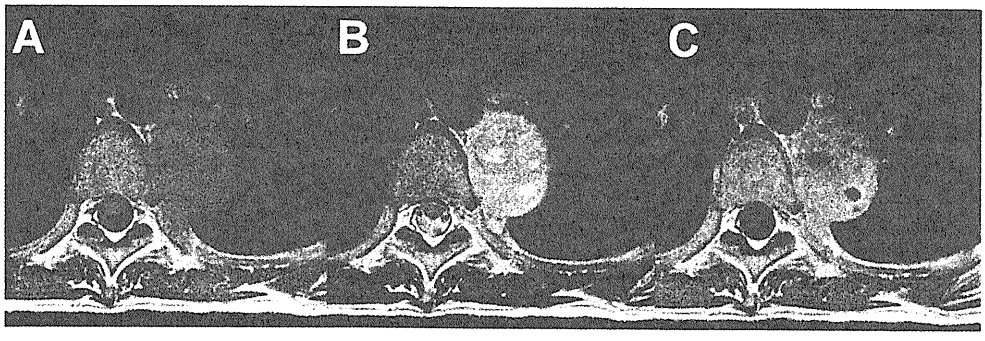

Fig. 3 **A**) MRI of the chest showing that, compared with the spinal cord, the tumor was iso-intense on T1-weighted images, and **B**) moderately intense with foci of signal heterogeneity on T2-weighted images. **C**) Gadolinium enhancement was moderate and inhomogeneous on T1-weighted images.

involvement of the intervertebral foramens or spine. Via thoracotomy, the tumor was resected en-bloc with the 7th and 8th intercostal muscles and the thoracic sympathetic trunk passing over the tumor.

The resected tumor measured 57 × 47 × 33 mm and weighed 50 g with a lobulated pale yellow cut surface and was encapsulated. Microscopically, the tumor demonstrated solid, trabecular, and cystic architecture and consisted of columnar tumor cells with apically located oval nuclei and elongated fibrillary cytoplasmic processes with moderate nuclear pleomorphism (**Fig. 4A**). Perivascular pseudorosettes and true rosettes were frequently