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Pleural Lavage Cytology Immediately After Thoracotomy in Patients With Completely Resected Non–Small Cell Lung Cancer

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This study evaluated 325 patients who had undergone pleural lavage cytology (PLC) immediately after thoracotomy following a complete resection for non–small cell lung cancer (NSCLC) between 2004 and 2008. The number of patients with negative and positive findings in PLC was 309 and 13, respectively. The proportion of T1 in the PLC-positive group was significantly smaller than that of the PLC-negative group. The pathologic examinations revealed that the parietal pleural invasion was significantly more severe in the PLC-positive group than in the PLC-negative group. Pathologic lymphovascular invasion was also significantly more prominent in the PLC-positive group than in the PLC-negative group. The 5-year survival rate after surgery in the PLC-positive group and PLC-negative group was 54.7% and 79.0%, respectively. The positive finding in PLC showed a tendency of an unfavorable prognosis for NSCLC patents following complete resection. Further clinical studies will be necessary to evaluate the efficacy of adjuvant therapy for PLC-positive patients.

Key words: Pleural lavage cytology – Surgical resection – Non–small cell lung cancer – Postoperative prognosis

Lung cancer is among the most prevalent and lethal cancers worldwide, and non–small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases.[1,2] Lung cancer is a highly treatment-refractory cancer. Early detection and surgical resection remains the mainstay for improving the survival of lung cancer patients.[3] However, the survival of early stage NSCLC is reported to be

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50% to 80% in stages I and II.[4,5] This wide range of survival rates suggests that patients who undergo surgery are a heterogeneous population with a spectrum of disease progression. The process of lymphovascular invasion and metastasis might be the cause of treatment failure and mortality in NSCLC.

NSCLC patients with pleural dissemination have a very poor prognosis and are not considered suitable candidates for surgery.[6] However, malignant cells are observed on pleural lavage cytology (PLC), even in cases with no apparent pleural effusion and dissemination at the time of thoracotomy for NSCLC, and most of these cases are considered to be the intrathoracic dispersion of cancer cells due to the visceral pleural invasion of lung cancer. Tumor metastasis occurs by a series of steps including angiogenesis, cell migration, intravasation, cell attachment, extravasation, proliferation, and invasion.[7,8] The status of PLC has not been considered to be a determining factor in the TNM staging system.[9] Adjuvant treatment, including the use of local and systemic chemotherapy, might be necessary for PLC-positive patients if positive findings of PLC imply establishment of micrometastasis and unfavorable prognosis. This study retrospectively investigated the clinical significance of PLC at thoracotomy following a complete resection for NSCLC.

Patients and Methods

The hospital records of 433 consecutive patients who underwent a resection of NSCLC between 2004 and 2008 were reviewed. The other preoperative assessments included chest roentgenography and computed tomography (CT) of the chest, upper abdomen, and brain. Clinical N2 status was defined by the presence of a lymph node more than 1 cm in a short axis diameter. Bone scintigraphy was performed to detect any bone metastasis. Magnetic resonance imaging (MRI) of the brain was routinely employed for assessment of distant metastasis. Bronchoscopy was routinely performed to obtain a pathologic diagnosis by a transbronchial lung biopsy, and to evaluate endobronchial staging. The patients' records, including their clinical data, preoperative examination results, details of any surgeries, histopathologic findings, and TNM stages were also reviewed.

One hundred milliliters of normal saline solution was poured into the thorax immediately after thoracotomy without being shot directly at the tumor. Patients with severe adhesion, definite pleural effusion, or pleural dissemination were excluded. Approximately 80 mL of lavage solution was collected after agitation for 20 seconds without manipulation of any pulmonary parenchyma. Staining was performed using the Papanicolaou method after centrifugal separation.

All resected specimens, including the primary tumor and resected hilar and mediastinal lymph nodes, were examined to determine both the tumor histology and the extent of lymph node metastases. Intraoperative frozen sections were examined if invasion of the tumor was suspected at the surgical margins. The histopathologic findings were classified according to the World Health Organization criteria, and the International Union Against Cancer (UICC) TNM staging system (7th edition) was employed.[9,10]

Follow-up information was obtained from all patients through office visits or telephone interviews either with the patient, with a relative, or with their primary physicians. The patients were evaluated every 3 months by chest roentgenography, and chest CT scans and bone scintigraphy were performed every 6 months for the first 2 years after surgery and annually thereafter. The mean duration of observation was 3.0 years.

The survival curve was calculated by the Kaplan-Meier method and compared using the log-rank test for a univariate analysis. Categorical variables were compared by Fisher exact test. The differences were considered to be significant if the P value was less than 0.05. The Statview V software package (Abacus Concept, Berkeley, California) was used for all statistical analyses.

Results

There were 433 patients who underwent a resection for non–small cell lung cancer between 1999 and 2008 in the Second Department of Surgery of the University of Occupational and Environmental Health. The subjects of this study were 325 patients who had undergone PLC immediately after thoracotomy following a complete resection. Patients with severe adhesion, definite pleural effusion, or pleural dissemination were excluded.

The number of patients with negative, suspicious, and positive findings in PLC was 309, 3, and 13, respectively (Table 1). The proportion of T1 in the PLC-positive group was significantly smaller than that in the PLC-negative group. The histologic types included 11 adenocarcinomas (85%) and 2 squa-

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Table 1 Patients characteristics of PLC positive group and PLC negative group

	PLC negative group[a] (n = 309)	PLC positive group[a] (n = 13)
Average age	68.9	69.1
Male	182 (59)	8 (62)
Female	127 (41)	5 (38)
T factor		
T1	206 (67)	5 (38)[b]
T2	81 (26)	7 (54)
T3	16 (5)	0
T4	6 (2)	1 (8)
Histology		
Adenocarcinoma	223 (72)	11 (85)
Squamous cell carcinoma	69 (22)	2 (15)
Large cell carcinoma	13 (4)	0
Others	4 (1)	0
Operative procedure		
Pneumonectomy	14 (5)	0
Lobectomy bilobectomy	242 (78)	12 (92)
Segmentectomy	34 (11)	0
partial resection	19 (6)	1 (8)
Pathological stage		
IA	174 (56)	4 (31)[c]
IB	49 (16)	3 (23)
II	34 (11)	3 (23)
IIIA	38 (12)	2 (15)
IIIB	9 (3)	0
IV	5 (2)	1 (8)

[a]Figures in parentheses are percentages.

[b]$P = 0.048$.

[c]$P = 0.068$.

mous cell carcinomas (15%) in the PLC-positive group. Bilobectomy or lobectomy was performed in 12 patients (92%) and partial resection of the lung in one patient (8%) in the PLC-positive group. The proportion of pathologic stage IA (31%) in the PLC-positive group tended to be lower than that of the PLC-negative group (56%; $P = 0.068$).

Pathologic examination revealed that there was parietal pleural invasion in the PLC-positive group, including 3 patients (23%) in p0, 3 (23%) in p1, 4 (31%) in p2, and 3 (23%) in p3 (Table 2). The 3 tumors with p3 invasion were located in the intralobar area (interlobar p3). However, parietal pleural invasion in PLC-negative group was diagnosed in 225 patients (73%) in p0, 57 (18%) in p1, 6 (2%) in p2, and 21 (7%) in p3, respectively. The parietal pleural invasion was significantly more severe in the PLC-positive group compared with

Table 2 Pathological findings of parietal pleural invasion and lymphovascular invasion

	PLC negative group n (%)	PLC positive group n (%)
Parietal pleural invasion		
p 0	225 (73)	3 (23)[a]
p 1	57 (18)	3 (23)
p 2	6 (2)	4 (31)
p 3	21 (7)	3 (23)
Lymphatic invasion		
Negative	169 (59)	3 (23)[a]
Positive	119 (41)	10 (77)
Blood vessel invasion		
Negative	211 (71)	4 (31)[a]
Positive	85 (29)	9 (79)

[a]$P < 0.05$.

the PLC-negative group. Lymphatic invasion around the tumor was pathologically observed in 10 (77%) patients in the PLC-positive group, whereas only 41% had lymphatic invasion in the PLC-negative group. Pathologic blood vessel invasion was positive in 79% of the PLC-positive group, and 29% of the PLC-negative group. Pathologic lymphovascular invasion was significantly more prominent in the PLC-positive group than in the PLC-negative group.

Eleven patients underwent local therapy with intrapleural infusion of cis-diamminedichloroplatinum (50–100 mg). Postoperative systemic chemotherapy was performed in 8 patients (treatment was given to patients who could tolerate it after surgery unless they refused additional chemotherapy). The regimen of chemotherapy was carboplatin + paclitaxel for 7 patients, and carboplatin + gemcitabine for 1 patient.

Three patients died due to recurrence of lung cancer and 1 patient died of hepatocellular carcinoma. These 3 patients with the disease recurrence had carcinomatous pleuritis at 4, 5, and 11 months after surgery, respectively. The 5-year survival rate after surgery in the PLC-positive group and the PLC-negative group was 54.7% and 79.0%, respectively (Fig. 1). There was a tendency toward unfavorable prognosis in the PLC-positive group ($P = 0.098$).

Discussion

Lung cancer represents one of the most common and aggressive solid tumors, and reducing the mortality of lung cancer remains an important issue. A complete surgical resection is considered to be the

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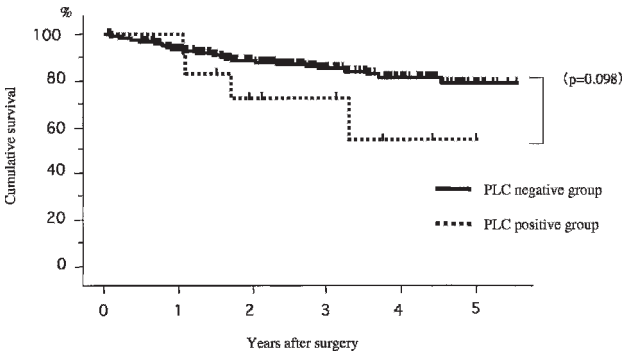

Fig. 1 Comparison of the 5-year survival rate after surgery between the PLC-positive and PLC-negative groups. The postoperative 5-year survival rate in the PLC-positive group was 54.7%; however, that of the PLC-negative group was 79.0%.

first line of treatment for individuals with stages I to II NSCLC. According to previous reports, the positive rates of PLC at thoracotomy were 4.5% to 22.6%.[11–13] However, some cases show positive PLC despite the absence of pleural invasion. A possible explanation of this phenomenon is that lung cancer cells not only directly involve the visceral pleura but also invade lymph vessels and enter the thoracic cavity via the lymph pathway on the lung surface. Positive PLC findings are reported to be significantly correlated with lymphatic permeation and vascular involvement of tumor cells.[11,13] The present study observed that there was significantly more microscopic vascular invasion in PLC-positive cases, consistent with these previous reports.

The presence of malignant cells in the pleural cavity without apparent pleural effusion suggests the aggressive biologic behavior of the tumor, including cell exfoliation, migration, and extravasation. The prognosis of PLC-positive cases has been described as unfavorable compared with PLC-negative cases in many reports. The initial recurrence is expected to occur in the thoracic cavity, but simultaneous distant metastasis is also observed in many recurrent cases.[11–14] Therefore, positive PLC needs to be incorporated into the pathologic staging. A meta-analysis of the correlations of the positive findings of PLC with survival showed it to be a significant independent adverse prognostic factor, thereby suggesting that it was appropriate to upstage patients by one T category on the basis of an analysis after stage-adjusted survival.[14] PLC positivity is an unfavorable prognostic factor, as observed in many reports; therefore, our findings indicate that it should be performed as an essential intraoperative examination.

Some investigators have reported PLC after lung resection to be a more important independent prognostic predictor than PLC after lung resection.[15–17] Patients with positive PLC after lung resection have a significantly greater association with pleural recurrence than those with positive PLC before lung resection.[17] The positive findings of PLC after lung resection may occur because surgical manipulation allowed exfoliation of tumor cells into the pleural cavity. In particular, mediastinal lymph nodes dissection damages lymphatic connections and, therefore, impairs the lymphatic drainage through the intrapulmonary lymphatic channel to the mediastinal nodes, which might accelerate exfoliation of cancer cells. However, the results of PLC after lung resection are influenced by surgical procedures. Dresler *et al* reported that PLC after lung resection had no significant prognostic value.[18]

No consistent therapeutic strategy has been established for PLC-positive cases. Macroscopic pleural dissemination is an indicator to discontinue pulmonary resection, because pleural dissemination was classified as M1 in the 7th edition of UICC TNM staging system.[9] Aokage *et al* showed significantly better prognosis of PLC-positive patients compared with patients with pleural dissemination.[19] Only 3 patients in the current series (23%) had recurrence of carcinomatous pleuritis, thus suggesting that positive findings of PLC should be distinguished from clearly established dissemination. The 5-year survival rate exceeded 50% in our results following the scheduled surgery, showing that the exclusion of PLC-positive cases based on the surgical indications is inappropriate.

It might be necessary to add local chemotherapy for intrapleural recurrence in patients with positive PLC. The Japanese Clinical Oncology Group conducted a randomized trial to determine the efficacy of intrapleural hypotonic cisplatin treatment for patients with positive PLC.[20] They reported no statistically significant difference in the overall survival and disease-free survival between the 2 groups, but the appearance of carcinomatous pleuritis was suppressed by the hypotonic cisplatin treatment. Muraoka *et al* also reported that intrapleural hypotonic cisplatin treatment had a preventive effect on carcinomatous pleuritis but had no survival benefit.[21]

Satoh *et al* analyzed the recurrence patterns in patients with positive PLC results. They reported that 25 of 41 patients (72%) with recurrence had distant metastases, whereas pleural recurrence was observed only in 8 patients (25%).[13] These findings

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suggest that systemic adjuvant therapy may be necessary to improve outcome of surgical resection. It is difficult to accumulate a sufficient number of patients to determine the efficacy of adjuvant chemotherapy because of the low rate of positive PLC. Further multicenter studies are necessary to evaluate the benefits of performing multimodal treatment in these patients.

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