A Clinicopathological Study of Lung Cancer Patients with Occupational Exposure to Chrysotile Asbestos Fibers

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Objective **To summarize the features of asbestos-related lung cancer.** ***Patients*** **Thirty-one lung cancer patients with occupational exposure to chrysotile asbestos fibers. They worked or had worked in one asbestos factory or its subcontracters.** ***Result*** **All patients were male with mean age of 60.6 when diagnosed, and all except one were current or ex-'heavy' smokers. Histological types were fairly evenly divided into adeno-, squamous and small cell carcinoma and 24 (78%) of patients showed 'peripheral type' lung cancers. Regarding clinical stages, 20 patients (65%) were classified as III or IV (advanced stage). Tumor shadow(s) was detected on chest X-ray in 22 patients (71%), and in 5 patients with 'negative' chest X-ray, chest CT was necessary to recognize a primary tumor. Seventeen patients (55%) did not undergo periodical check-ups.** ***Conclusion*** **Occupational asbestos exposure is interpreted as one of the important risks for lung cancer and frequent and accurate observation is necessary.**
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Key words: asbestosis, pneumoconiosis, lung cancer

Introduction

The incidence of lung cancer has risen steadily, and it is now the most common lethal visceral malignancy in Japan, surpassing even gastric cancer. Lung cancer is one of the most insidious and aggressive neoplasms, and despite all efforts at early diagnosis and therapy, the survival rate of lung cancer patients remains poor. The etiology of lung cancer is considered epidemiologically to be related to many factors, including cigarette smoking, and asbestos inhalation also (1). We have had extensive clinical experience with many patients employed at an asbestos-related factory and its subcontract works located in a district close to our hospital. These factories have been processing chrysotile asbestos fibers imported from Canada and we have treated 31 lung cancer patients among these workers. We report here a retrospective case study of these patients to summarize and illustrate the features of asbestos-related lung cancer from a clinicopathological standpoint.

Subjects and Methods

This study includes 31 lung cancer patients with occupational exposure to asbestos (chrysotile) fibers. Twenty-three patients worked at the same asbestos factory while the others were employed by a nearby subcontracters. All of these patients were admitted to Nara Medical University Hospital between September 1975 and August 1996. Patients were all male with a mean age of 60.6 year-old (range 42–81) when lung cancer was diagnosed. Diagnosis of asbestosis and asbestos-related pleural changes was based on occupational history, physiological findings and chest X-ray films. The duration of asbestos exposure, smoking history, family history of malignant neoplasms, and chest X-ray findings were noted. Location of the primary lesion of lung cancer, histopathology, clinical stages, therapy, prognosis and the method which made clinical diagnosis of lung cancer were also evaluated.

Results

The overall characteristics of the patients are shown in Tables 1 and 2. The duration of asbestos exposure ranged from 4 to 44 years (mean; 25.5 years), and all patients except one (96.8%) were ex- or current heavy smokers (Brinkman Index >400). Seventeen patients (54.8%) had a family history of malignancy in one to three degrees of relationship. According to the ILO chest X-ray classification of asbestos-related diseases, 3 pa-

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Table 1. Patient Characteristics (1)

Case	Age/Sex	Chest XP (ILO)	Exposure		Latency period (years)	Smoking history (B. I.)	Family history[a)]	Pleural lesion	Periodical check-up
			Onset (age)	Duration (years)					
1	56/M	0	31	24	25	O	–	+	+
2	48/M	0	25	20	23	810	–	–	+
3	55/M	0	18	37	37	750	–	+	–
4	53/M	1	28	25	25	460	–	+	–
5	56/M	1	21	35	35	1,560	–	–	?
6	58/M	1	16	42	42	580	+	+	+
7	67/M	1	45	23	23	3,260	+	–	+
8	67/M	1	27	30	40	440	+	+	+
9	69/M	1	56	8	13	960	+	–	–
10	71/M	1	26	9	45	800	+	+	+
11	76/M	1	18	44	58	560	+	+	–
12	81/M	1	21	4	60	1,220	–	–	–
13	42/M	2	18	24	24	475	–	+	+
14	47/M	2	24	14	23	625	–	–	–
15	49/M	2	26	23	23	580	–	–	+
16	51/M	2	24	27	27	600	+	+	+
17	53/M	2	18	3	35	460	+	+	–
18	58/M	2	28	30	30	600	+	+	+
19	58/M	2	21	33	37	640	–	+	–
20	59/M	2	37	19	21	800	+	+	–
21	61/M	2	30	27	31	800	+	+	–
22	61/M	2	22	38	39	600	–	–	+
23	63/M	2	29	21	34	900	+	–	+
24	63/M	2	33	17	30	1,290	+	+	–
25	63/M	2	29	27	34	780	+	–	+
26	63/M	2	17	43	46	860	+	–	+
27	68/M	2	29	28	39	900	–	+	–
28	68/M	2	27	30	41	960	–	+	–
29	74/M	2	23	36	51	640	–	+	–
30	54/M	3	30	14	24	620	+	+	–
31	68/M	3	26	35	42	940	+	+	–

[a)] Family history of malignant neoplasm in 1 to 3 degrees of relationship.

tients were classified as grade 0 and these patients were not diagnosed as having asbestosis. The other patients were classified as follows; 9 (29.0%) grade I, 17 (54.8%) grade II, and 2 (6.5%) grade III. Pleural changes on chest X-rays (pleural plaques and/or calcifications) were observed in 20 patients (64.5%), however, these pleural changes did not correlate with the extent of pulmonary fibrosis (ILO classifications). Only 14 (45.2%) were receiving periodic check-ups (factory-based examination for pneumoconiosis) at the time when lung cancer was discovered because these individuals were actively working in asbestos-related factories, and among them, 3 patients with stage I lung cancer were detected by such examinations. The majority of the remaining patients had changed employment to asbestos-unrelated occupations and did not undergo check-ups.

Histopathological types of lung cancer were fairly evenly divided into adenocarcinoma (9 patients; 28.1% of total lesions), squamous cell carcinoma (11; 34.4%), small cell carcinoma (8; 25.0%) and adenosquamous cell carcinoma (4; 12.5%) (Fig. 1). Histological diagnosis of these 4 patients with combined adenosquamous cell carcinoma was based on the autopsy samples. Interestingly, one patient had two cancers (small cell and squamous cell carcinomas) (2). The predominant site of the primary lung cancer lesions were the lower lobes (18 patients, 62.1%) and the 'peripheral' regions (24 patients, 77.4%) of the lungs (Fig. 2). In addition, more than half of squamous cell and small cell carcinomas (54.5% and 62.3%, respectively) originated from peripheral regions of the lung (peripheral type). In 4 patients (12.9%), lung cancer was detected at an early stage (stage I), and three of these individuals underwent surgery successfully. Another case with stage I disease was diagnosed at autopsy. Two patients with squamous cell carcinoma were classed as Stage II and IIIA, but did not undergo surgery because of their decreased pulmonary function. Twenty patients (64.5%) were found to be stage IIIB or IV, therefore the majority of our cases had advanced lung cancer (Fig. 3).

Table 2. Patient Characteristics (2)

Case	Location[a]	Histology Type[b]	Histology Method[c]	Stage[d]	Tumor XP	shadow CT[e]	Sputum[f] cytology	Chance[g] of diag.	Therapy[h]	Prognosis (days)[i]
1	RL-P	ad	Op	I	+	+	I	XP	Op	alive
2		sq	A	IV	+	+	V	meta	SC	66
3	LU-P	comb	A	IV	+	+	V	effusion	R	90
4	RL-P	sm	B	IV	–	+	II	meta	SC	28
5	RU-P	sm	B	IIIA	+	+	II	XP	C+R	alive
6	RL-P	sq	Op	I	+	+	V	XP	Op	alive
7	RL-P	comb	A	IIIB	+	+	V	XP	C+R	212
8	LU-C	sq	A	IV	+	+	V	XP	C+R	608
9	RL-P	sm	B	IIIA	+	+	II	XP	C+R	274
10	LL-C	sq	A	IIIB	+	+	II	XP	C+R	273
11	RL-C	sm	A	IIIA	+	+	II	CT	C	81
12	RL-C	sm	A	IV	+	+	V	XP	C	118
13	RU-P	ad	A	IV	+	+	IV	XP	C	153
14	LL-P	ad	A	IV	+		V	mata	SC	122
15	LU-P	ad	A	IIIB	–	–	II	effusion	C	153
16	LL-P	ad	A	IV	+		V	XP	C	122
17	RU-P	sq	A	IIIA	–	+	II	CT	R	547
18	LL-P	sq	A	IV	+		IV	XP	C+R	122
19	LU-P	sm	B	IV	+	+	V	XP	C+R	61
20	RL-P	ad	P	IIIB	–	–	II	effusion	SC	123
21	LL-P	sq	B	IIIB	+		V	XP	C	181
22	LL-P	comb	A	IV	+		V	effusion	C	61
23	RL-P	ad	A	I	–		II	autopsy		
24	RL-P	comb	A	I	–	+	V	sputum	Op	1491
25	LU-P	sq	A	II	+		IV	XP	C	120
26	RU-C	sq	A	IV	+	+	II	XP	C+R	184
27	RL-C	sm	A	IIIA	–	+	V	sputum	C	92
28	LL-P	ad	A	IV	+	+	V	XP	SC	94
29		ad	A		–	–	V	sputum	SC	122
30	LU-C	sq	B	IIIB	–	+	V	sputum	R	61
31	RU-P	sq+sm	A	IIIB	+		V	XP	C+R	304

[a] right (R) or left (L) lung, lower (L) or upper (U) lobe and central (C) or peripheral (P) type. [b] Histological types: adenocarcinoma (ad), squamous cell carcinoma (sq), small cell carcinoma (sm) and adenosquamous cell carcinoma (comb). [c] Final histopathologic diagnosis: autopsy (A), transbronchial biopsy (B), Pleural biopsy (P) and operation (Op). [d] Clinical stages. [e] Positive or negative findings of tumor shadow on chest X-ray (XP) and chest CT (CT). [f] Papanicolaou classification. [g] Chance of diagnosis by chest X-ray (XP), chest CT (CT), or smptoms of metastasis (meta). [h] Surgery (Op), chemotherapy (C), radiotherapy (R), and supportive care only (SC). [i] Survival in days after diagnosis of lung cancer or detection of massive pleural effusion.

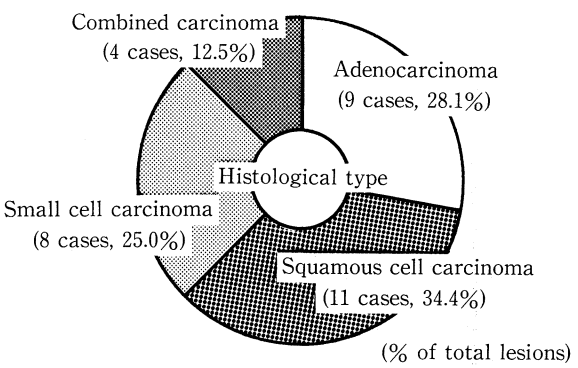

Figure 1. Histological types of lung carcinoma.

Tumor (nodule) shadows were clearly demonstrated on chest X-ray in 22 patients (71%). Chest CT was performed in 23 patients and using chest CT, primary lung tumor (nodule) was easily detected in 20 patients (87% of tested). On the 9 patients with negative chest X-ray, lung tumor (nodule) was pointed out by chest CT in 5 patients. Sputum cytology was positive in 20 patients (64.5%).

To determine which combination of the non-invasive diagnostic techniques (e.g., chest X-ray, CT and sputum cytology) is most useful for detecting lung cancer, we compared these 3 methods (Table 3). As described above, chest X-ray or sputum cytology alone could detect lung tumor shadow or cancer cells in approximately 65–70%. By combining these two methods, there was a marked increase in the rate of lung tumor/cancer

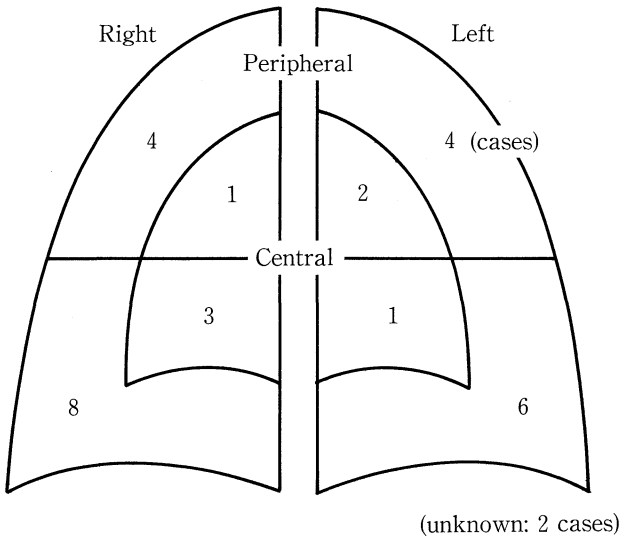

Figure 2. Primary lesion of lung carcinoma.

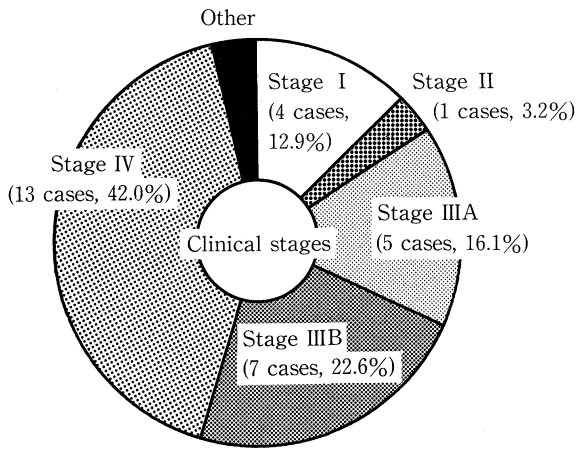

Figure 3. Clinical stages of lung cancer.

Table 3. Correlation of Findings Among 3 Methods

Chest X-ray (Tumor shadow)		Sputum cytology		Chest CT (Tumor shadow)
+22 cases (71.0%)	<	+16 cases (51.6%)	<	+9 cases (39.2%) −0
		−16 (19.4%)	<	+6 (26.1%) −0
−9 (29.0%)	<	+4 (12.9%)	<	+3 (13.0%) −1 (4.3%)
		−5 (16.1%)	<	+2 (8.7%) −2 (8.7%)

detection (83.9%). Furthermore, when all 3 methods were employed, it resulted in a 91.3% detection rate. In the 4 patients where both chest X-ray and sputum cytology were negative, chest CT demonstrated the lung tumor in 2 cases while the others exhibited massive pleural effusions. In the latter cases, the diagnosis of lung cancer was made at autopsy or by surgical pleural biopsy. Although one patient was diagnosed as having cancer solely by sputum cytology, multiple lung tumors appeared and developed rapidly (in 4 months) and the primary site of lung cancer could not be determined accurately, even at autopsy. The initial abnormality leading to the diagnosis of lung cancer was as follows; detection of tumor shadows on chest X-ray, including check-up examination, in 17 patients (54.8%), massive pleural effusion in 4 patients (12.9%), positive sputum cytology in 4 patient (12.9%) and chest CT for further examination of asbestosis (to evaluate the extension of fibrosis) in 2 patients (6.5%). In three patients (9.7%) symptoms of metastasis, such as bone pain, facilitated the clinical diagnosis of lung cancer.

Three patients underwent surgery, as described above, and 2 have survived. Twenty-one patients (67.7%) received chemotherapy and/or radiotherapy, and the remaining 6 patients (19.4%) were treated conservatively because of their poor general condition. In summary, patients who were not surgically treated died between 1 and 20 months after being diagnosed as having lung cancer (median 4.1 months).

Discussion

The relationship between lung cancer and asbestosis was first described by Lynch and Smith in 1935 (3) and confirmed epidemiologically by Doll in 1955 (1). The incidence of lung cancer developing in patients with asbestosis has recently been reported to be between 10 and 20% and we have shown that morbidity from asbestos-related cancer is 8.3 times higher than the expected value in Japan (4). Selikoff and Lee (5) and other investigators (6, 7) have reported that smoking increases the incidence of lung cancer in asbestosis patients, and in the present study, all patients except one were heavy smokers. Numerous studies have implicated amphibole asbestos fibers as especially important in risk of carcinogenesis, while chrysotile is considered as less hazardous and is therefore more widely used. Carcinogenesis by inhaled amphibole asbestos fibers has been demonstrated in non-smokers; however, chrysotile can also act as a direct cause of malignancy (8–10).

Histopathologically, Whitwell et al reported that adenocarcinoma developed preferentially in asbestosis patients (11), while Kannerstein and Churg found there was no disproportionate increase in this histology in comparison with asbestos unrelated lung cancer patients (12). The present results are consistent with this finding. Although both squamous cell and small cell carcinoma were the predominant histological types of the 'central type' lung cancer, most of our patients, including those with these histological types showed a 'peripheral type' lung cancer. Recently, some studies have investigated whether asbestosis (pulmonary fibrosis caused by asbestos inhalation) is

necessary and always present in asbestos-exposed lung cancer patients, and have concluded that asbestos fibers can cause lung cancer even without pulmonary fibrosis (13). However, many patients in our study had asbestosis and it is difficult to conclude whether this somewhat different location of the primary lesions were attributed to an effect of asbestos exposure itself or to pulmonary fibrosis related to asbestos.

Since asbestos-exposed people are interpreted as a high risk group for lung cancer, efforts at early diagnosis should be promoted. However, it can be difficult to detect tumor shadows on chest X-ray at an early stage, because of abnormal background shadows caused by the pulmonary fibrosis and pleural lesions present in many patients. In the present study, a majority of patients were in the advanced clinical stages of lung cancer and two patients with squamous cell carcinoma who were classed as stage II and IIIA were inoperable because of their decreased pulmonary functions. These results illustrate the difficulty of both detection and treatment of asbestos-related lung cancer. Regarding diagnosis, tumor shadows were detected on chest X-ray in only 71% of patients, indicating that chest X-ray alone could not reliably detect lung cancer at an early stage in asbestosis patients. Therefore the non-invasive techniques of sputum cytology and chest CT are necessary adjuncts to facilitate diagnosis of lung cancer, especially in patients with a negative chest X-ray. In this study, although many patients were examined by chest CT scan, the accuracy of the evaluation varied and some patients in the early period of the study were not examined by CT at all. As described, in patients who were able to undergo surgery, lung cancers were generally detected at periodic check-ups, however, many patients did not undergo periodic evaluation. Of course, the overall value of the periodic examinations or screening for lung cancer is controversial, because the 5-year survival rate of lung cancer patients remains quite low. Moreover, many patients in the present study who underwent periodic check-ups did not have a lung cancer detected at an early stage, indicating the importance of accuracy and the quality of the check-up program. Clearly early diagnosis of malignancy is necessary for improved and successful treatment of such an aggressive disease. Recently, many technical advances have occurred, especially the increased resolution of chest CT scans and the helical CT technique, and these have improved the results of periodic screening in clinical trials. Furthermore, we now have many diagnostic advanced skills including endoscopy, radioactive examinations and blood examinations such as tumor markers that may also lead to improved and earlier diagnosis and therapy.

The patients in our series resembled those in previous reports of asbestos-related lung cancer. However, it is noteworthy that these Japanese patients were almost all from the same factory with occupational exposure to imported chrysotile asbestos fibers, a type of asbestos which is interpreted to be less hazardous. It is quite possible that other types of asbestos fibers were inadvertently mixed in with the imported materials (14). Based on this retrospective case study, and its relevance to the important public health problem of lung cancer, we conclude that individuals occupationally exposed to asbestos, are at a significantly high risk of lung cancer, and should undergo frequent and accurate evaluation in order to diagnose lung cancer at the earliest possible stage (9).

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