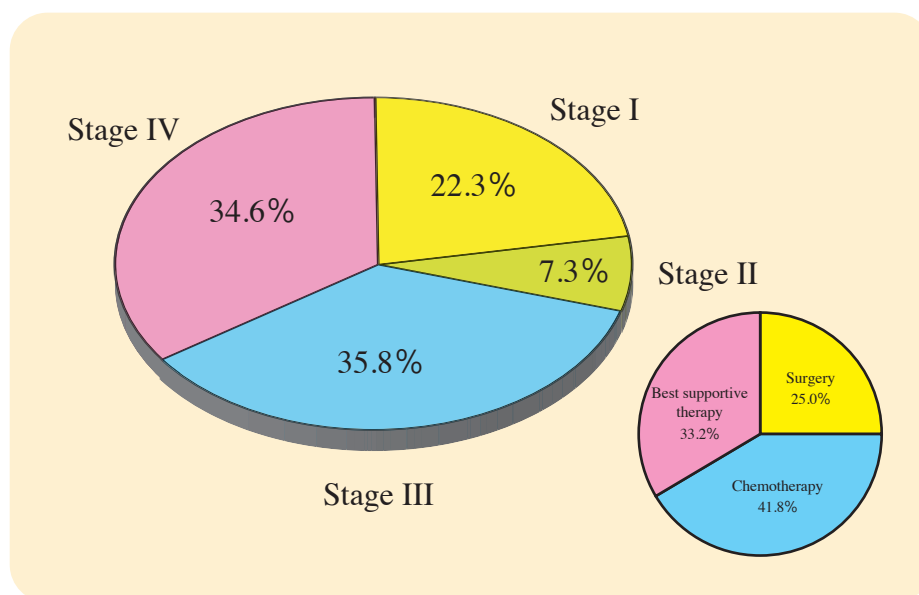


The research and development and the dissemination projects related to
the 13 fields of occupational injuries and illnesses
Field name [Asbestos-Related Diseases]

Survey of Mesothelioma Associated with Asbestos Exposure in Japan

— Clinical characteristics of 221 cases treated in 27 Rosai Hospitals —

Second Report



Clinical Research Center for Asbestos-Related Diseases
Japan Labour Health and Welfare Organization

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【Objective】

Asbestos-related diseases have become a pressing social issue in Japan. In June 2005, a high incidence of mesothelioma was reported among residents in the vicinity of the old Kubota Kanzaki Plant and compensation was paid to those affected. The Rosai Hospital group, a part of the Japan Labour Health and Welfare Organization, rapidly surveyed mesothelioma cases at Rosai Hospitals nationwide in May 2006, and published an interim report* called the “Survey of lung cancer and malignant mesothelioma cases associated with asbestos exposure.” The report closely investigated the relationship between the clinical characteristics of mesothelioma and occupational asbestos exposure. In this report, we further investigated the clinical characteristics of an additional 221 cases of mesothelioma in Japan.

*References

- 1) Kishimoto T., Kimura K., Usami I., et al., Interim report of “Survey of lung cancer and malignant mesothelioma cases associated with asbestos exposure,” Japan Labour Health and Welfare Organization, May 2006.
- 2) Kishimoto T., Kimura K., Usami I., et al., Interim report of “Survey of lung cancer and malignant mesothelioma cases associated with asbestos exposure,” Occupational Health Journal 29: 7-22, 2006.
- 3) Booklet edited by Japan Labour Health and Welfare Organization, Clinical characteristics of mesothelioma in Japan: Summary of 132 patients treated at Rosai Hospital Group, Japan Labour Health and Welfare Organization 2006.

【Methods】

In this report, there were 221 cases clinically or pathologically diagnosed as mesothelioma from January 2000 to January 2008 at 27 Rosai Hospitals.

【Results】

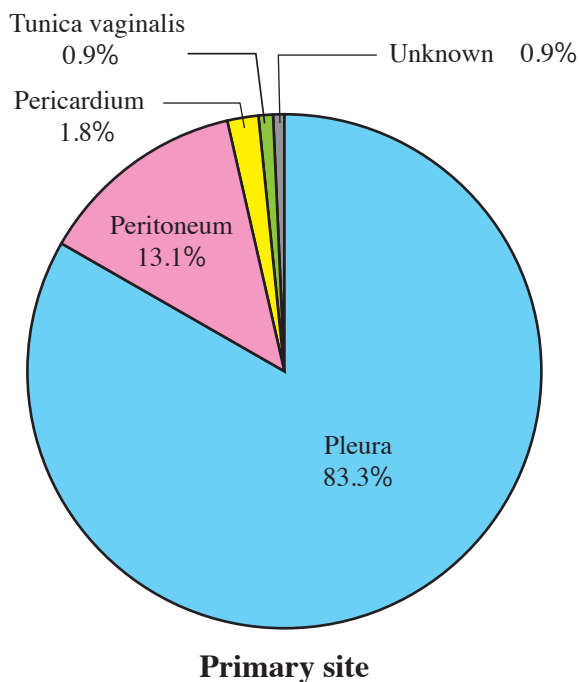
Characteristics of cases

Characteristics of cases by primary site

Primary site	Pleura	Peritoneum	Pericardium	Tunica vaginalis	Total
Number of cases	184 (83.3%)	29 (13.1%)	4 (1.8%)	2 (0.9%)	221*
Age: Mean	66.9	63.0	58.8	51.5	66.1
SD	10.0	12.0			10.5
Sex: Male	158	22	1	2	185 (83.7%)
Female	26	7	3	0	36 (16.3%)

* Includes two cases of unknown origin

Primary site and Sex



The mean age was 66.1 years old. From the total of 221 cases, 83.3% were diagnosed with pleural mesothelioma and 83.7% of the total cases were male.

Motivation for diagnoses

Region	Pleura	Peritoneum	Pericardium	Tunica vaginalis
Subjective symptom	135	26	3	2
Regular health check-up	27	0	1	0
During treatment for other diseases, etc.	22	3	0	0
Total	184	29	4	2

Many cases were identified based on the presence of subjective symptoms.

Subjective symptoms

Pleural mesothelioma	135	Peritoneal mesothelioma	26
Chest/Back pain	55	Abdominal distension	18
Dyspnea	53	Abdominal pain	5
Cough	24	Others	6
Fever	12		
Others	9		

Patients exhibited multiple symptoms.

Chest/back pain and dyspnea were noted frequently in cases of pleural mesothelioma, and abdominal distension was frequently noted in peritoneal mesothelioma.

Methodological procedures for diagnosis

	Pleural mesothelioma	Peritoneal mesothelioma	Pericardial mesothelioma	Mesothelioma of the tunica vaginalis	Total
Number of cases	184	29	4	2	219
Histological diagnosis:	168	21	4	2	195
Thoracotomy/laparotomy	28	4	1	1	34
VATS/Laparoscopy	58	4	2	0	64
Thoracoscopy under local anaesthesia	35	0	0	0	35
Needle biopsy	31	7	1	0	39
Cope needle biopsy	7	0	0	0	7
Autopsy	4	1	0	0	5
Number of histologically diagnosed cases	163	16	4	1	184
Number of histologically non-diagnosable cases	5	5	0	1	11
Cytology	11	6	0	0	17
Unknown	5	2	0	0	7

From 219 cases, 184 (84.0%) were diagnosed histologically.

Hyaluronic acid concentration in pleural or peritoneal effusion

Hyaluronic acid concentration in pleural or peritoneal effusion (ng/ml)

	Pleural mesothelioma	Peritoneal mesothelioma	Total
Number of cases	94	7	101
Mean	197,116	2,184,074	
SD	315,085	4,805,492	
Maximum	1,870,000	13,000,000	
Minimum	211	800	
>100,000 cases	37 (39.4%)	6 (85.7%)	43 (42.6%)

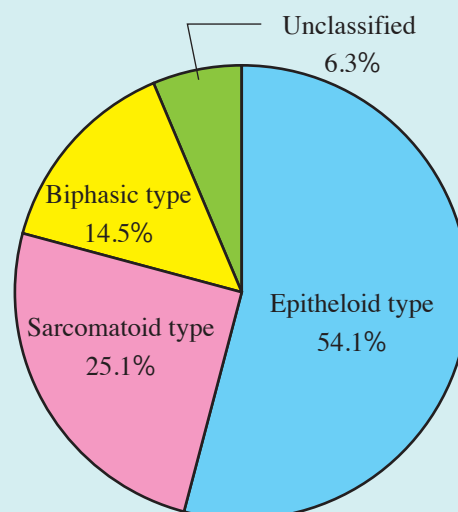
Hyaluronic acid concentration was determined in 94 cases (51.1%) from 184 pleural mesothelioma cases.

Histological type of mesothelioma

Histological type of mesothelioma

	Pleural mesothelioma	Peritoneal mesothelioma	Total
Number of cases	184	29	221*
Number of examined cases out of total number of patients above	175	26	207
Epitheloid type	91	18	112
Sarcomatoid type	49	2	52
Biphasic type	25	4	30
Unclassified	10	2	13

*Pericardium, Tunica vaginalis, and unclassifiable cases were included.



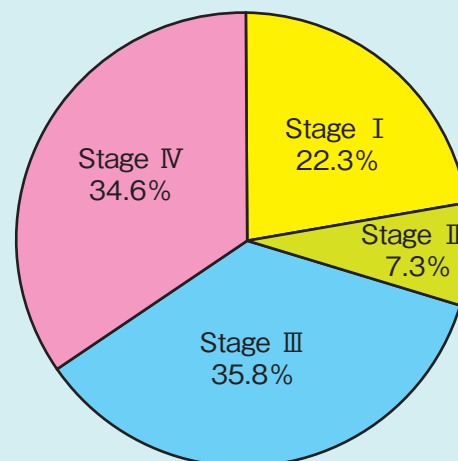
From 207 cases, 112 (54.1%) were epitheloid type, 52 (25.1%) were sarcomatoid type, 30 (14.5%) were biphasic type, and 13 (6.3%) were unclassified.

Staging of pleural mesothelioma (IMIG classification)

Staging of pleural mesothelioma

	Stage I	Stage II	Stage III	Stage IV	Total
Number of cases	40	13	64	62	179
Treatment:					
Surgery	18	6	19	1	44
Chemotherapy	3	3	30	37	73
Best supportive therapy	15	4	13	24	56
Unknown	4	0	2	0	6

Five cases were excluded where the stage was unknown.



29.6% were diagnosed at an early stage (Stage I or II). Better efforts to establish early detection are important.

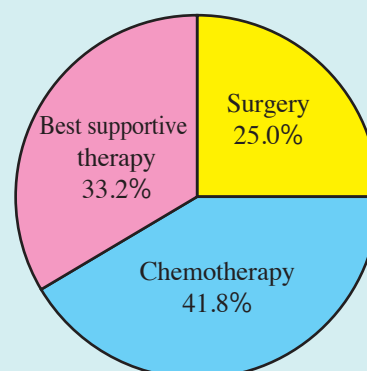
Treatment of mesothelioma

Treatment of mesothelioma

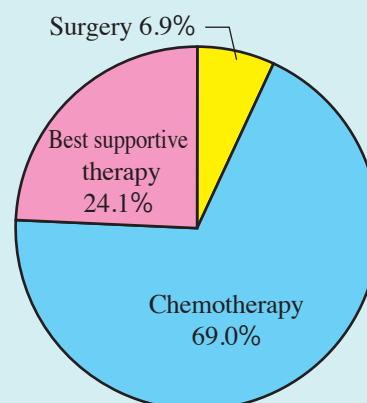
	Pleural mesothelioma	Peritoneal mesothelioma	Total
Number of cases	184	29	213
Surgery	46	2	48
Chemotherapy	77	20	97
Best supportive therapy	61	7	68

One case each of pericardial mesothelioma and of mesothelioma of the tunica vaginalis were surgically resected.

Surgical resection was performed in 25.0% of pleural mesothelioma cases and 6.9% of peritoneal mesothelioma cases.

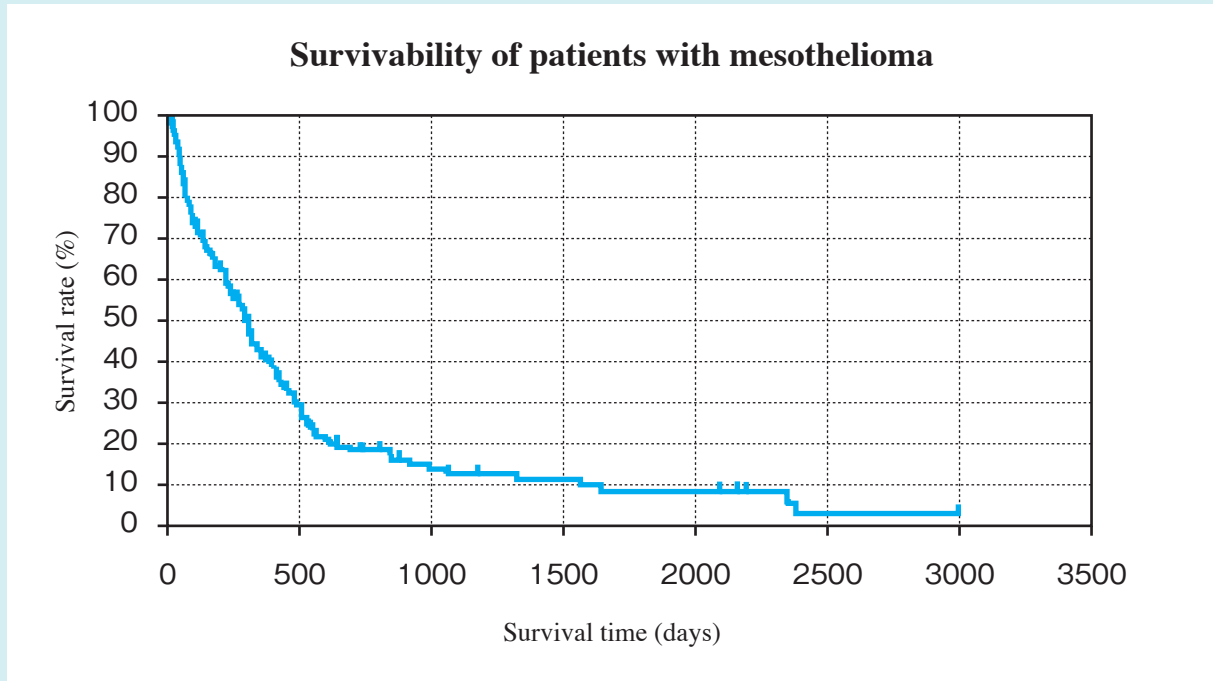


Pleural mesothelioma

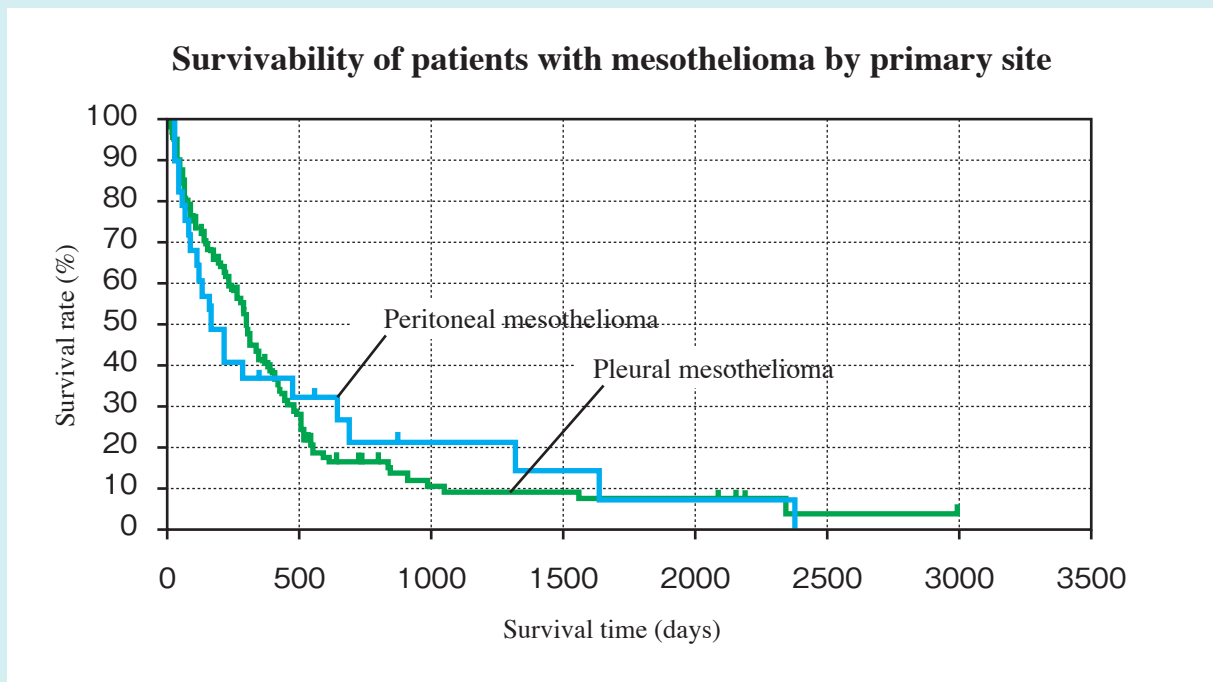


Peritoneal mesothelioma

Survival time

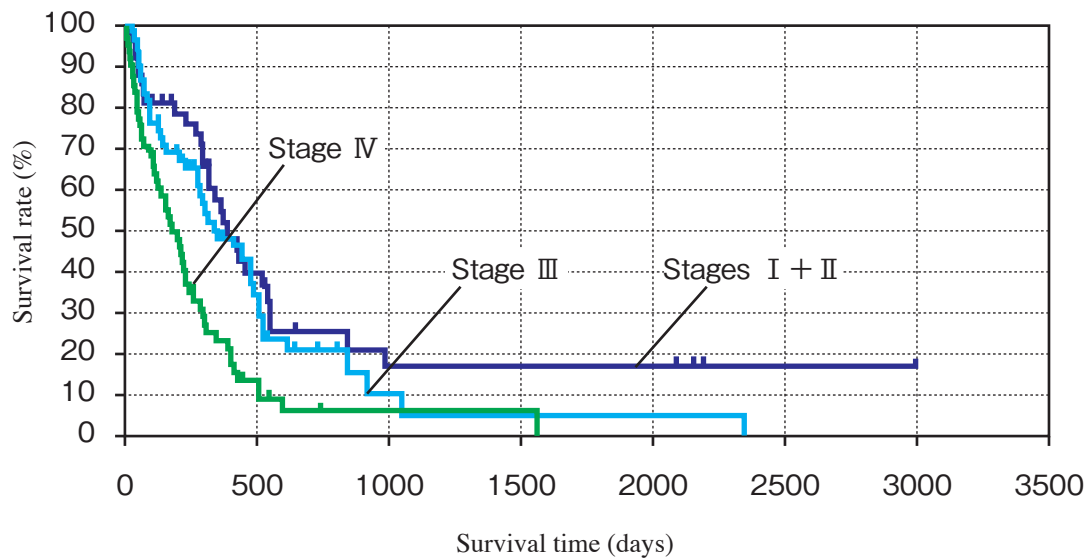


The median survival time was 300 days when including all types of mesothelioma.



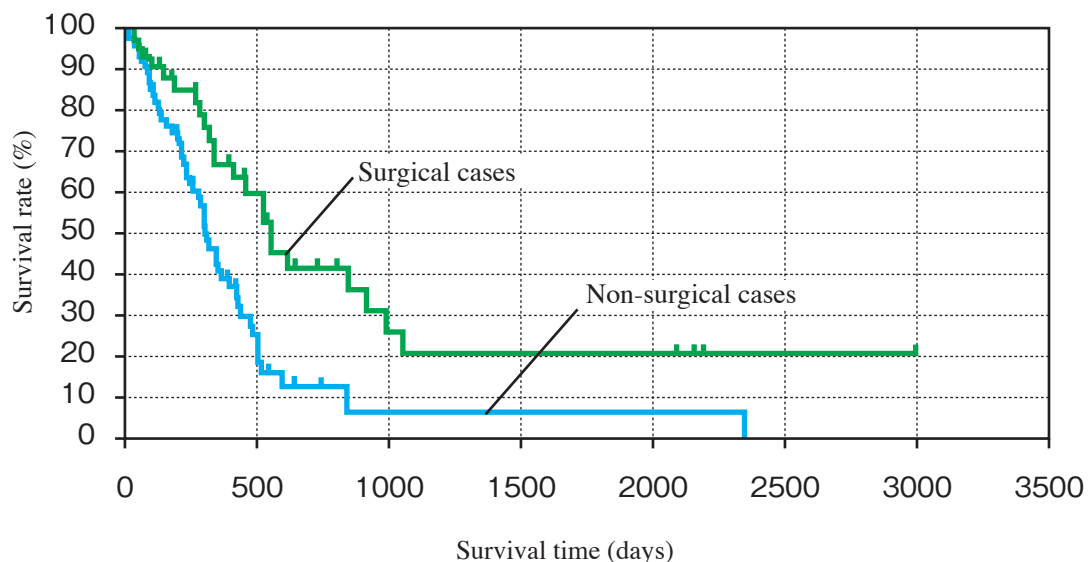
The median survival time was 299 days for cases of pleural mesothelioma, and 170 days for cases of peritoneal mesothelioma.

Survivability of patients with mesothelioma by stage



The median survival time was 386 days for patients in Stages I + II, 338 days for those in Stage III, and 178 days for those in Stage IV. There was no significant difference between the survival curves of Stages I + II and Stage III, but the survival rate of the patients in Stages I + II was significantly better than that for those in Stage IV ($p < 0.01$).

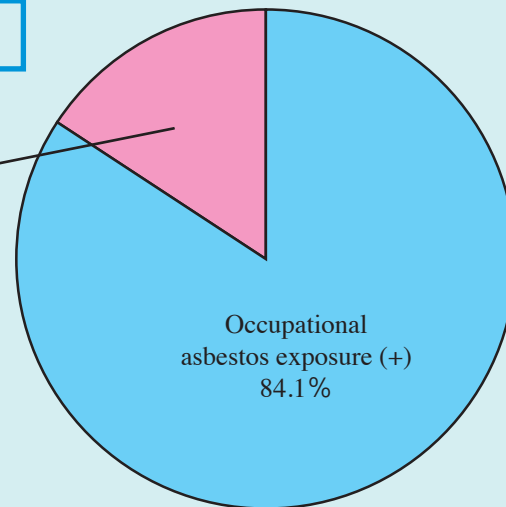
Survivability of patients with pleural mesothelioma by treatment



The median survival time was 549 days for the surgically resected cases and 305 days for the non-resected cases. There was a statistically significant difference ($p < 0.05$).

Occupational asbestos exposure

Occupational
asbestos exposure (-)
15.9%



Frequency of occupational asbestos exposure

	Pleural mesothelioma	Peritoneal mesothelioma	Total
Cases	171	24	201 *
Shipyards work	34	3	37
Construction	20	2	22
Insulation	12	4	19*
Plumbing	15	0	15
Asbestos product manufacturing	10	5	15
Electrical industry	12	1	13
Mechanical device manufacturing	10	0	11 *
Driver	6	1	7
Vehicle manufacturing	5	0	5
Dismantling	4	1	5
Work in warehouse	4	0	4
Car manufacturing/repair	3	0	3
Sheet metal work	3	0	3
Other asbestos-related work	8	2	10
Total identified cases	146 (85.4%)	19 (79.2%)	169 (84.1%)
Number of unidentified cases	25	5	32

* Four cases of pericardial mesothelioma and two cases of mesothelioma of the tunica vaginalis were included.

The occupational history was investigated in 201 of the 221 mesothelioma cases. Among these cases, 169 (84.1%) were considered to be associated with occupational asbestos exposure.

Duration of asbestos exposure, age at initial exposure, and latent period

Duration of asbestos exposure, age at initial exposure, and latent period

Primary site	Item	No. of cases	Median	Range	Mean	SD
Pleura	Duration of exposure (years)	144	30	1-55	27.3	14.8
	Age at initial exposure	140	21	15-50	23.7	8.0
	Latent period (years)	143	43	14-64	42.6	9.5
Peritoneum	Duration of exposure (years)	18	21	6-52	26.8	15.6
	Age at initial exposure	17	21	16-35	22.9	5.5
	Latent period (years)	17	45	28-62	43.4	8.8
Total*	Duration of exposure (years)	164	30	1-55	27.6	14.9
	Age at initial exposure	159	21	15-50	23.6	7.8
	Latent period (years)	162	43	14-64	42.5	9.5

* One case of mesothelioma of the tunica vaginalis and one case of unknown origin were included.

The latent period was 42.6 years for cases of pleural mesothelioma and 43.4 years for cases of peritoneal mesothelioma.

Radiographical findings of asbestos-related changes

Radiographical findings of asbestos-related changes

Region	Pleura	Peritoneum	Pericardium	Tunica vaginalis	Total
Number of cases	184	29	4	2	219
Evaluated cases	180	25	4	2	211
Radiographical changes					
Pulmonary asbestosis	4	5	0	0	9 (4.3%)
Pleural plaque	92	14	0	0	106 (50.2%)
Hyaline degeneration	54	6			60
Calcification	38	8			46
Round atelectasis	2	0	0	0	2 (0.9%)
Diffuse pleural thickening	6	0	0	0	6 (2.8%)
Pleural effusion	148	10	4	0	162 (76.8%)

Pleural effusion was noted in many cases accounting for 76.8% of the cases, and pleural plaque was present in 50.2% of the cases.

Number of asbestos bodies in the lung

Number of asbestos bodies in the lung (per gram of dry lung tissue)

Pleural plaque	Present	Absent	Total
Total cases	106	105	211
Cases examined	30	15	45*
Mean	62,223	5,687	43,378
SD	121,458	10,114	102,381
Maximum	526,082	30,500	526,082
Minimum	79	239	79
< 1,000	5 (16.7%)	5 (33.3%)	10 (22.2%)
1,000 - 5,000	3 (10.0%)	7 (46.7%)	10 (22.2%)
>5,000	22 (73.3%)	3 (20.0%)	25 (55.6%)

*All 45 cases were diagnosed with pleural mesothelioma.

From the 45 cases with pleural mesothelioma in which asbestos bodies in the lung were counted, 1,000 or more intrapulmonary asbestos bodies per gram of dry lung tissue were detected in 25 of 30 cases with pleural plaque (83.3%), and 10 of 15 cases without plaque (66.7%).

(Discussion)

Compared to the interim report of the “Survey of lung cancer and malignant mesothelioma cases associated with asbestos exposure” published in May 2006, we found the important points given below.

1. In the interim report, 89 of 117 cases (76.1%) provided information regarding asbestos exposure in the occupational history; however, this increased to 84.1% (169/201) in this report. The awareness of physicians to obtain a detailed occupational history may have increased.
2. The disease was identified during a regular health check-up in 12 of 132 cases (9.1%) in the interim report, and in 28 of 219 cases (12.8%) in this report. This shows an increase in the proportion of detection at regular health check-ups.

3. Histological diagnosis was obtained in 78.8% of the cases in the interim report and 84.0% of the cases in this report. This indicates that the physicians are utilizing histological testing more often and recognizing the importance of histological diagnosis.
4. Thoracoscopy under local anesthesia was performed in 13.4% of the cases in the interim report, and increased to 19.0% of the cases in this report. This indicates that thoracoscopy under local anesthesia has been performed more widely as a diagnostic procedure.
5. The level of medical care for mesothelioma has been improving in Japan, but the proportion of diagnosis at Stages I and II remained low (29.6%) in this report, and the survival rate was poor. Development of procedures for early detection and further educational activities in general practice are necessary.

Comparison between interim and current reports

	Interim report (Jan 2000-Feb 2006)	Current report (Jan 2000-Jan 2008)	Cases during Mar 2006-Jan 2008
Occupational asbestos exposure	76.1% (89 of 117 cases)	84.1% (169 of 201 cases)	95.2% (80 of 84 cases)
Diagnosed during regular health check-up	9.1% (12 of 132 cases)	12.8% (28 of 219 cases)	18.4% (16 of 87 cases)
Histologically diagnosed cases of pleural mesothelioma	78.8% (104 of 132 cases)	84.0% (184 of 219 cases)	92.0% (80 of 87 cases)
Measurement of pleural hyaluronic acid concentration in pleural mesothelioma cases	38.4% (43 of 112 cases)	51.1% (94 of 184 cases)	70.8% (51 of 72 cases)
Thoracoscopy under local anesthesia in pleural mesothelioma cases	13.4% (15 of 112 cases)	19.0% (35 of 184 cases)	27.8% (20 of 72 cases)

All items were markedly improved during the period between the interim and current reports (March 2006-January 2008).

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The research is a part of the research and development and the dissemination projects related to the 13 fields of occupational injuries and illnesses of the Japan Labour Health and Welfare Organization.

※ Field name: Asbestos-Related Diseases

Theme name: The research and development and the dissemination related to diagnosis, treatment, and prophylaxis of mesothelioma induced by asbestos exposure.