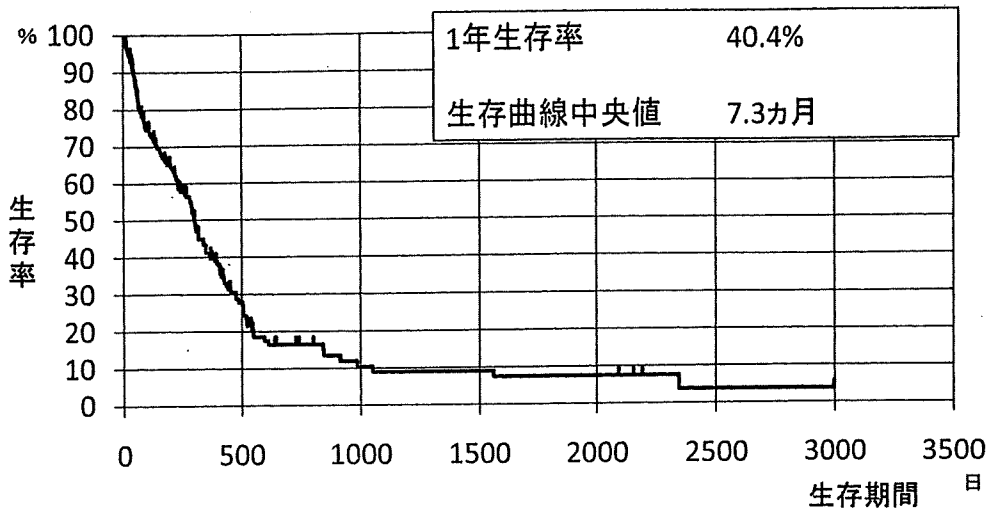

図1　胸膜中皮腫症例の生存曲線

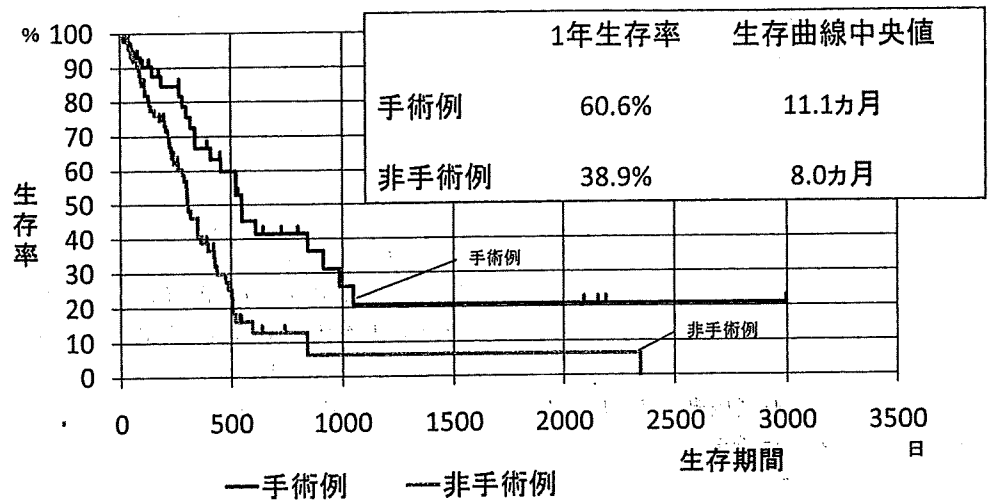

図2　胸膜中皮腫症例の生存曲線

表5　職業性ばく露が疑われる症例における職種別頻度

職業歴調査症例	171
造船所内の作業	34
建設作業	20
配管作業	15
断熱作業	12
電気工業作業	12
石綿製品製造業	10
機械器具製品製造業	10
運転手	6
車両製造業	5
解体作業	4
倉庫内の作業	4
自動車製造・補修業	3
板金作業	3
その他の石綿関連作業	8
計	146 (85.4%)

表6　石綿ばく露が疑われる初回ばく露年齢・期間・潜伏期間

調査項目	中央値	範囲	平均値	標準偏差
胸膜中皮腫				
初回ばく露年齢	21.0	15～50	23.7	8.0
石綿ばく露期間（年）	30.0	1～55	27.3	14.8
潜伏期間（年）	43.0	14～64	42.6	9.5
肺がん				
初回ばく露年齢	20.0	14～50	24.0	7.9
石綿ばく露期間（年）	34.0	2～60	31.6	12.7
潜伏期間（年）	48.5	18～71	47.2	10.6

期間，潜伏期間の中央値はそれぞれ20歳，34年，48.5年であった（表6）．画像所見は胸膜プラーク105例，石綿肺46例などであった（表7）．石綿小体は61例で測定され，乾燥肺1gあたりの石綿小体数は1,000本未満13例，1,000～4,999本12例，5,000本以上36例であった．

考　案

中皮腫による死亡者が増加し，石綿による疾病が社会問題化した中で我々は全国労災病院の中皮腫症例を中間

表7　石綿ばく露に関連する画像所見

所見	胸膜中皮腫（%）	肺がん（%）
症例数	180	135
石綿肺	4（ 2.2%）	46（34.6%）
胸膜プラーク	92（51.1%）	105（78.9%）
石灰化	38	68
円形無気肺	2（ 1.1%）	6（ 4.5%）
びまん性胸膜肥厚	6（ 3.3%）	3（ 2.3%）
胸水貯留	148（82.2%）	30（22.6%）

表8　肺内石綿小体数*)（胸膜中皮腫）

胸膜プラーク	あり	なし	計
計測症例	30	15	45
平均	62,223	5,687	43,378
標準偏差	121,458	10,114	102,381
最大	526,082	30,500	526,082
最小	79	239	79
1,000 未満	5（16.7%）	5（33.3%）	10（22.2%）
1,000 ～ 4,999	3（ 10%）	7（46.7%）	10（22.2%）
5,000 以上	22（73.3%）	3（ 25%）	25（55.6%）

*)乾燥肺 1g あたりの本数

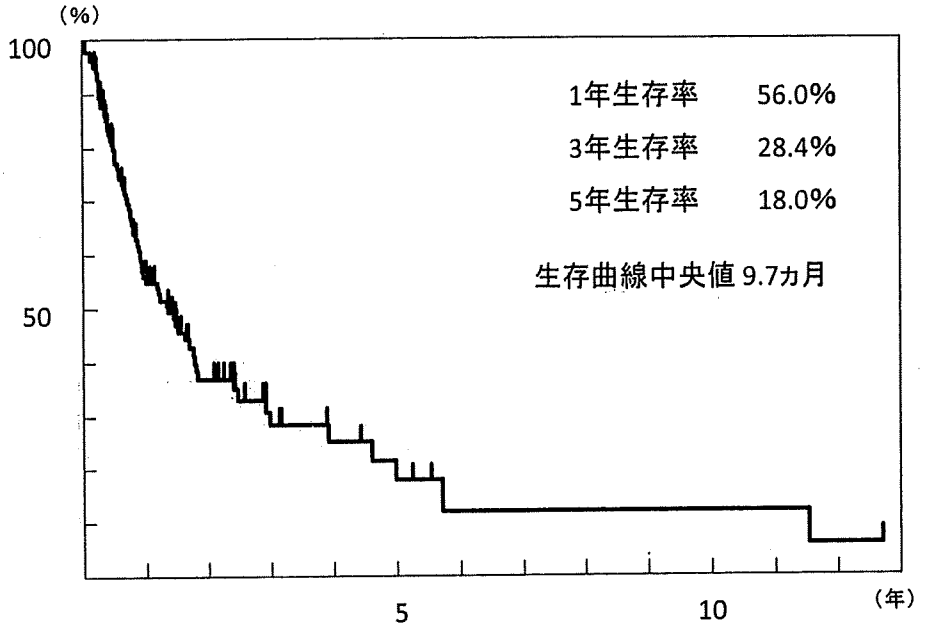

図3　石綿肺がん症例の生存曲線

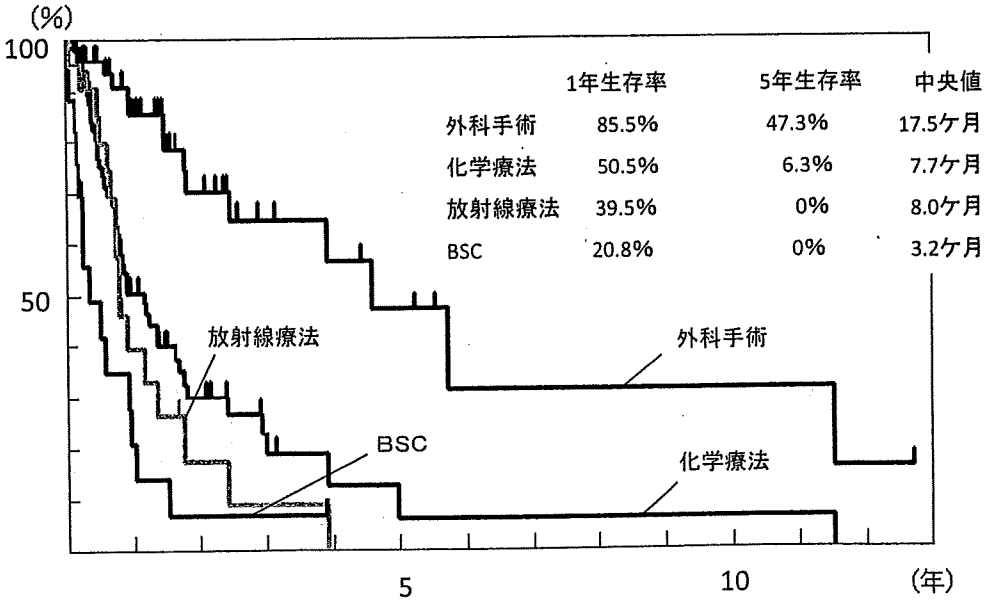

図4　石綿肺がん症例の治療法別生存曲線

報告としてまとめ[3]，今回，症例を追加して検討した．性別では男女比が5.1：1であり，厚生労働省人口動態統計に[4]よる報告に比較して男性が多い傾向を示した．年齢の中央値は67歳であり岸本ら[5]が報告した瀬戸内海沿岸地方での報告と同様であったが，厚生労働省の報告書[6]の61歳に比べ高い傾向であった．厚生労働省の症例はすべてが労災認定されている症例であり，職業性ばく露がみられる症例の方が若く発症する可能性が示唆された．原発部位は，Hillerdal[7]や佐々木ら[8]の報告と同様であった．診断は組織診が行われる比率，局所麻酔下の胸腔鏡が施行される比率が中間報告[3]と比べ高くなっており，診断する医師が中皮腫を念頭に検査を行っているためと思われた．胸水中ヒアルロン酸値の陽性率は39.4%であり陰性であった場合でも中皮腫を否定できないことが確認された．胸膜中皮腫の組織型は肉腫型が28%と通常の報告と比べ肉腫型の比率が高かった[7]が分類不能例もあり，十分な検体が採取できる胸腔鏡などを用いた生検が望まれる．生存曲線を検討すると現時点では手術適応となる早期診断例を増やすことが重要と思われる．胸膜プラークは石綿ばく露の良い指標であるが胸膜プラークがみられない症例でもヘルシンキクライテリア[9]で職業性石綿ばく露と考えられる乾燥肺1gあたり1,000本以上の症例もみられた．胸水が82.2%にみられ，胸水症例では詳細な職歴調査を行い，胸膜プラークがみられない場合でも中皮腫を疑うことが重要である．

石綿肺がん135例の検討では，健診で発見された症例が50例あり健診が重要な位置をしめる．健康管理手帳の発行は，平成19年10月からは胸部レントゲンに石綿による所見がなくとも一定以上の従事歴で健康管理手帳が取得でき，また，平成21年4月からは間接ばく露労働者にも胸部レントゲンで所見がみられれば健康管理手帳が取得できるなど健康管理手帳の取得範囲がひろがり，石綿肺がんの早期発見例が増えることが期待できる．組織型は，症例数が少ない場合扁平上皮がんが多いとする報告[10][11]が多かったが，症例数が多くなるほど組織型は一般肺がんと同様に腺がんが多いとする報告[12]と同じであった．生存曲線は一般肺がんと同様の傾向であり，手術症例の予後は他の治療法を受けた症例の予後に比べて良好であった．

肺がん症例の方が石綿肺，胸膜プラークの所見が多く見られ，また，職種が同じにもかかわらず職業性石綿ばく露の期間も長かった．これらのことは肺がん症例の方が石綿の高濃度ばく露であることを示唆するものと考える．

結　語

両者とも予後の悪い疾患であり，現状では手術適応になる早期発見症例を増やすことが重要である．

本研究は，独立行政法人労働者健康服機構のプロジェクト研究「アスベストばく露によって発生する中皮腫等の診断・治療・予防法の研究・開発，普及」の一環として行われたものである．なお，本研究の要旨は平成20年11月第56回日本職業・災害医学会学術大会にて報告した．

謝辞：著者らとともに直接病院を訪問して調査をしていただいた千葉労災病院　由作俊和先生，東京労災病院　戸島洋一先生，国立病院機構山口宇部医療センター　青江啓介先生に深謝します．

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Clinical Characteristics of Mesothelioma and Asbestos-related Lung Cancer in Japan

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We reviewed the clinical characteristics of 221 cases of mesothelioma and 135 cases of asbestos related lung cancer that were diagnosed and treated from January 2000 to January 2008 at 27 Rosai Hospitals. Specialized chest physicians who were knowledgeable about the compensation system for industrial accidents visited each hospital to collect the cases. Within the total of 221 cases, 83.3% were diagnosed with pleural mesothelioma, and 13.1% with peritoneal mesothelioma. Among pleural mesothelioma cases, 85.4% were considered to be associated with occupational asbestos exposure. The occupations were shipyard work, construction, plumbing, insulation and so on. The mean age was 66.9 years old, and 85.9% of the cases were male; 52% were epitheloid type, 28% were sarcomatoid type and 14% were biphasic type. The median survival time was 7.3 months for the total cases of pleural mesothelioma, and 11.1 months for surgical cases. As for the radiographical findings of asbestos related changes, pleural effusion was noted in many cases accounting for 82.2% of the cases. Hyaluronic acid concentration was over 100,000 ng/ml in 39.4% cases. The mean age of the asbestos related lung cancer was 71.1 years old, and 97% of the cases were male; 57.5% were adenocarcinoma, 29.1% were squamous cell carcinoma and 12.6% were small cell carcinoma. The median survival time was 9.7 months for the cases of asbestos related lung cancer. The tendency of histological type and survival curve were similar to that of the general lung cancer.

Comparing asbestos related lung cancer and mesothelioma cases, we found that the density of occupational asbestos exposure was higher in lung cancer cases. The ratio of asbestosis and pleural plaque were higher and the duration of occupational asbestos exposure was longer in asbestos related lung cancer cases. In both diseases, the prognosis is poor. Therefore, early detection and the increase of surgical cases are most important.

(JJOMT, 57: 190—195, 2009)

Malignant Pericardial Mesothelioma with Response to Chemotherapy

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Key Words: Asbestos, Calretinin, Pemetrexed, Irinotecan.

(*J Thorac Oncol.* 2009;4: 1440–1441)

Malignant pericardial mesothelioma (MPerM) is an extremely rare and lethal cardiac tumor.[1] The prognosis is poor, and treatments such as surgery and radiotherapy have not demonstrated an impact on disease progression. We report a case of MPerM with response to chemotherapy.

CASE REPORT

A 61-year-old woman was referred to our hospital because of dyspnea on exertion. A computed tomography (CT) scan of the chest showed diffuse thickening of the pericardium (Figures 1*A*, *B*). The presence of fluid in the right pleural cavity was apparent, but tumor formation was not found on the pleura or the lung. Cardiac ultrasonography showed impaired left ventricular wall motion and dilatation of the inferior vena cava with loss of respiratory fluctuation. Cytologic examination of the pleural fluid was negative (class II). An open-chest, pericardial biopsy was performed without pleural inspection or biopsy. Microscopic examination of the specimen showed proliferation of mesothelial cells with nuclear atypicality consistent with malignant mesothelioma (Figure 2*A*). Immunohistochemical analyses revealed that the cells were calretinin positive, epithelial membrane antigen positive, and carcinoembryonic antigen negative (Figures 2*B–D*). These findings confirmed the diagnosis of malignant mesothelioma. Systemic chemotherapy consisting of carboplatin (AUC = 5, day 1) and pemetrexed (500 mg/m^2, day 1) was initiated, and regression of the pericardial thickening was exhibited after the second course (Figure 1*C*). The dyspnea on exertion was relieved. Six cycles of the chemotherapy were given; however, 6 months later, pleural fluid accumulated in the left cavity and mesothelioma cells were detected in the fluid. As salvage chemotherapy, irinotecan hydrochloride (60 mg/m^2, days 1, 8, and 15) was administered. A CT scanning of the chest after the second course showed regression of the pericardial tumor and decrease in the amount of pleural fluid. Two months later, the patient died of disease progression, 18 months after the diagnosis. Autopsy was not allowed.

DISCUSSION

MPerM is a rare tumor, which has a reported incidence of 0.0022% in an autopsy series of 500,000 case studies.[2] A clinical sign is constrictive pericarditis. Cardiac ultrasonography may reveal an effusion or myocardial mass. A CT scanning of the chest may also show pericardial effusion, thickening of the pericardium, or pericardial mass formation.[1] However, these findings are nonspecific. In the current case, the CT scanning showed diffuse thickening of the pericardium, indicating constrictive pericarditis, but no tumor formation. MPerM should be noted as one cause of unexplained constrictive pericarditis.

The prognosis for MPerM is poor, and the clinical course is progressive. No clinical trial has yet been conducted and standard treatment has not yet been established. Recently, pemetrexed, a multitargeted antifolate, has demonstrated modest activity against malignant pleural mesothelioma in combination with cisplatin[3] or carboplatin.[4] Irinotecan was also reported to demonstrate a modest activity against pleural mesothelioma in a clinical trial.[5] There is no previous report that these regimens were applied to MPerM, so the current case might be the first report that these regimens have shown clinical activity against MPerM.

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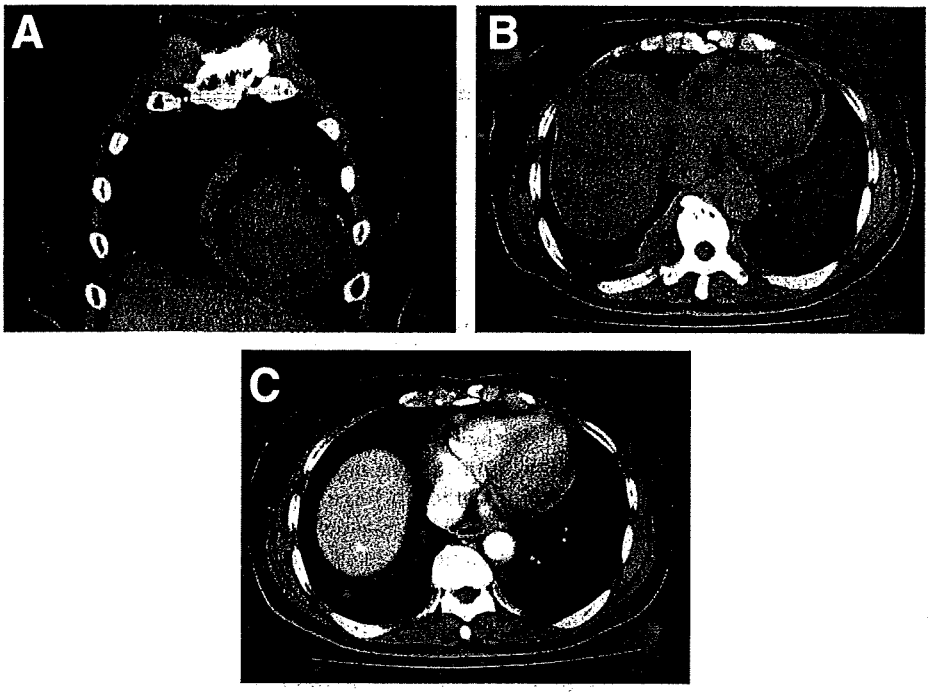

FIGURE 1. CT scan of the chest at the time of diagnosis showing diffuse thickening of the pericardium; (*A*) sagittal and (*B*) horizontal views. After administration of chemotherapy consisting of carboplatin and pemetrexed, (*C*) regression of the pericardial thickening was exhibited.

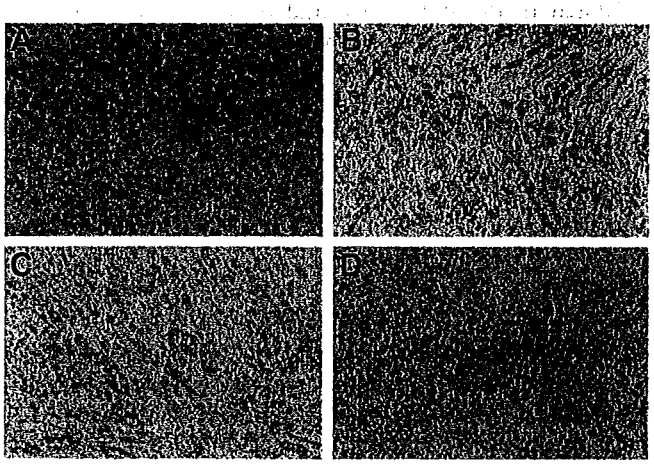

FIGURE 2. *A*, Microscopic examination of the biopsy specimen showed proliferation of mesothelial cells with nuclear atypicality consistent with malignant mesothelioma (hematoxylin-eosin, 40×). *B*, Immunohistochemical analysis revealed positive expression of calretinin (20×), (*C*) epithelial membrane antigen (20×), and (*D*) negative expression of CEA (20×).

In conclusion, MPerM is an extremely rare neoplasm. A combination chemotherapy consisting of carboplatin and pemetrexed or irinotecan monotherapy would be a favorable treatment option against MPerM.

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Accuracy of pathological diagnosis of mesothelioma cases in Japan: Clinicopathological analysis of 382 cases

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ABSTRACT

Incidences of mesothelioma are on the rise in Japan. However, the accurate frequency of mesothelioma occurrence is still unknown. The aim of this study is to clarify the accuracy of pathological diagnosis of mesothelioma. Among the 2742 mesothelioma death cases extracted from the document "Vital Statistics of Japan" for 2003–2005, pathological materials were obtained for 382 cases. After these materials were reviewed and immunohistochemical analyses were conducted, mesothelioma was diagnosed by discussions based on clinical and radiological information. Sixty-five cases (17.0%) were categorized as "definitely not/unlikely" mesotheliomas, and 273 cases (71.5%) were categorized as "probable/definite" mesotheliomas. The percentage of "probable/definite" pleural and peritoneal mesothelioma cases in males was 74.3% and 87.5%, respectively, and that of pleural cases in females was 59.2%; however, the percentage of "probable/definite" peritoneal cases in females was only 22.2%. These results suggest that the diagnostic accuracy of mesothelioma is relatively low in females and in cases of peritoneal and sarcomatoid subtype mesotheliomas; furthermore, approximately 15% of cases of deaths due to mesothelioma in Japan are diagnostically suspicious.

1. Introduction

Mesothelioma is a malignant tumor originating from the mesothelial cells of the pleura, peritoneum, pericardium, and testicular tunica vaginalis. The occurrence of this tumor is associated with occupational and environmental asbestos exposure [1–5]. The frequency of mesothelioma occurrence is on the rise in Japan. The data obtained from the "Vital Statistics of Japan" indicated that there were 500 cases of death due to mesothelioma in 1995, 710 cases in 2000, and 911 cases in 2005. Many of the deaths were due to past usage of asbestos, especially after the 1950s [3,4]. An epidemiological study estimated that there would be approximately 100,000 deaths in Japan due to pleural mesothelioma in the next 40 years, and the peak incidence of mesothelioma would occur during the period 2030–2034 [6]. Therefore, there is an urgent need for accurate diagnosis and treatment of patients suffering from mesothelioma. However, the accurate frequency of mesothelioma occurrence is still unknown because different diagnostic methods and criteria are used in different medical institutes, and no nationwide mesothelioma registry systems have been established in Japan thus far.

Currently, it is recommended that definite mesothelioma diagnosis be possible by histological or cytological analyses by immunohistochemistry using the currently available antibodies [7,8]. However, thus far, these procedures have not been carried out appropriately either in Japan or other countries. In Japan, during the period 2003–2005, a total of 2742 deaths due to mesothelioma were reported in the document "Vital Statistics of Japan," which has been published by the Ministry of Health, Labor and Welfare. However, precise clinicopathological analyses with regard to the accuracy of the diagnosis in these cases have not yet been conducted.

The aim of this study is to review past death cases diagnosed with "mesothelioma" and clarify the accuracy of their pathological diagnosis. In addition, to improve diagnostic accuracy, critical pathological diagnostic problems have been analyzed.

2. Materials and methods

2.1. Patient selection

From the "Vital Statistics of Japan" document for the period 2003–2005, we extracted 2742 deaths that occurred due to

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mesothelioma. In addition, we examined the death certificate files of each of these patients at the Ministry of Health, Labor and Welfare, Japan, after obtaining permission from the Minister for Internal Affairs and Communications, Japan. After examination, we requested all the medical institutes in which mesothelioma cases were reported during this period to submit materials for pathological diagnosis. The materials, including histological and cytological specimens, immunohistochemical slides, unstained slides, paraffin blocks, and formalin-fixed tumor tissues, were obtained for 382 cases (13.9%) from 297 medical institutes with the permission of the families of the deceased and medical institutes. The details of materials obtained are as follows: 46 cytological slides (CS), 21 histology slides stained with hematoxylin and eosin (H&E; SHE), 7 CS and SHE, and 308 CS and/or SHE with immunohistochemistry, including the 237 cases that were analyzed by immunohistochemistry in our department.

The planning of this study was approved by the ethical committee at Okayama Rosai Hospital, Japan.

2.2. Pathological evaluation

After the materials (H&E-stained tissue slides or Papanicolaou or Giemsa stained cytology slides and H&E and immunohistochemically stained tissue slides) were reviewed, immunohistochemical analyses were conducted in cases with unstained slides, paraffin blocks, or formalin-fixed tumor tissues; the analyses were based on the morphology and location of the tumor. Immunohistochemical staining was performed using the Histofine Simple Stain MAX-PO (MULTI) kit (Nichirei, Tokyo, Japan).

Due to limitations with regard to the unstained slides, antibodies against the following markers were initially selected: calretinin (Polyclonal, Zymed, San Francisco, CA, USA), D2-40 (clone D2-40, Nichirei BioScience, Tokyo, Japan), cytokeratin marker (CAM5.2; clone 2A4, Becton-Dickinson, Franklin Lake, NJ, USA), pancytokeratin (clone AE1/AE3, DAKO, Glostrup, Denmark), carcinoembryonic antigen (CEA; clone COL-1, Nichirei), thyroid transcription factor-1 (TTF-1; clone 8G7G3/1, DAKO), and desmin (clone D33, DAKO) when epithelioid or biphasic mesothelioma was suspected [9–11]. Calretinin, D2-40, CAM5.2 (clone 2A4, Becton-Dickinson, Franklin Lake, NJ, USA), pancytokeratin (clone AE1/AE3, DAKO), CEA, and desmin, were selected for the diagnosis of sarcomatoid or desmoplastic mesothelioma [12–15]. Additionally, Wilms tumor gene (WT1; clone 6F-H2, DAKO), thromomodulin (clone 1009, DAKO), epithelial membrane antigen (EMA; clone E29, DAKO), CA19-9 (clone NS19-9, TFB, Tokyo, Japan), epithelial antigen (clone Ber-EP4, DAKO), epithelial-related antigen (clone MOC-31, DAKO), myf-3 (clone 3A11, Novocastra, Newcastle upon Tyne, UK), CD34 (clone QBEnd/10, Novocastra), CD45R (clone 2B11 + PD7/26, DAKO), CD3 (clone PC3/188A, DAKO), CD20 (clone L26, DAKO), and estrogen receptor (ER; clone 1D5, DAKO) were used as appropriate. Antigen retrieval was performed in an autoclave. On the basis of the number of tumor cells observed following immmunohistochemical staining, the tumors were scored using the following semiquantitative system: 0, no or trace staining; score 1+, <5% tumor cells; score 2+, 6–50% tumor cells; score 3+, >51% tumor cells. The definition of a "positive case" in this study is a case with a score of more than 1+. Additional immunohistochemistry of the cytological specimens was not conducted in this study.

2.3. Clinicopathological analysis and categorization of each case

After the independent diagnosis of each case by pathologists (Y.T., K.I., and V.J.A.) according to WHO criteria [16] and clinical analysis by 4 physicians (T.K., K.G., K.A., and N.F.) and 1 radiologist (K.K.), a clinico-pathological discussion was initiated to confirm the final diagnosis. The cases with questionable and/or atypical mesothelioma findings were especially discussed.

For mesothelioma analysis, each case was categorized into either of the 4 subcategories: "inadequate/insufficient" (undetermined due to insufficient materials and information), "definitely not/unlikely" (definitely not mesothelioma and/or unlikely mesothelioma), "possible" (possible mesothelioma), "probable/definite" (probable mesothelioma and/or definite mesothelioma). This conservative category system was used in this study because of the heterogeneous nature of the available diagnostic materials and methods, and because there was, incomplete information and insufficient or inadequate materials for pathological diagnosis that prevented final and certified diagnosis.

2.4. Statistical analysis

A statistical analysis was performed by the Mann–Whitney's *U*-test for the detection of differences in the distribution in each category by various factors. In this analysis, the cases in the "inadequate/insufficient" category were excluded.

3. Results

3.1. Distribution of the 382 "clinical" mesothelioma cases into the diagnostic categories

The distribution of cases in the diagnostic categories "inadequate/insufficiency," "definitely not/unlikely," "probable," and "probable/definite" categories was 19 (5.0%), 65 (17.0%), 26 (6.8%), and 272 (71.2%), respectively. Among the 272 in the "probable/definite" category, 214 cases (78.7%) were considered as "definite" mesothelioma cases.

3.2. Proportion of cases in each diagnostic category depending on primary tumor sites and gender

By analysis of the primary tumor site, a relatively higher rate of "probably/definite" pleural mesothelioma cases were observed (72.0%) as compared to peritoneal cases (64.0%). On the other hand, a relatively higher rate of "definitely not/unlikely" peritoneal mesothelioma cases was noted (32.0%) compared with the pleural cases (14.8%).

Out of 7 other primary site cases, 6 cases (87.5%), including 4 pericardial cases, 1 testicular tunica vaginalis case, and 2 cases with unknown primary sites, belonged to the "probably/definite" category.

The proportion of cases in each diagnostic category based on the primary tumor site (pleura and peritoneum) and gender is shown in Table 1. A relatively high rate of "probable/definite" pleural mesothelioma was observed among the males (74.3%) and females (59.2%). Further, a high rate of "probable/definite" peritoneal mesothelioma was noted among the males (87.5%) but there were only 4 cases (22.2%) among the females. In conclusion, a relatively high rate of diagnostically suspicious cases was noted in the case of females and in the case of peritoneal mesothelioma.

3.3. Summary of the immunohistochemical profiles of various lesions in each category

A summary of the immunohistochemical results obtained with the markers calretinin, D2-40, cytokeratin (CAM5.2 and/or AE1/AE3), CEA, and TTF-1 in 308 cases analyzed in each category are provided in Table 2.

Table 1
Proportions of cases in each diagnostic category depending on primary tumor sites[a] and gender.

Category	Pleura[b]		Peritoneum[c]	
	Male No. of cases (%)	Female No. of cases (%)	Male No. of cases (%)	Female No. of cases (%)
Inadequate/insufficiency	12(4.3)	7(14.3)	0(0)	0(0)
Definitely not/unlikely	37(13.4)	11(22.4)	3(9.4)	13(72.2)
Possible	22(8.0)	2(4.1)	1(3.1)	1(5.6)
Probable/definite	205(74.3)	29(59.2)	28(87.5)	4(22.2)
Total	276(100)	49(100)	32(100)	18(100)

[a] Excluding 4 pericardial cases, 1 testicular tunica vaginalis case and 2 unknown primary site cases.
[b] $p = 0.40$ by Mann–Whitney's U-test (between male and female pleural cases).
[c] $p < 0.0001$ by Mann–Whitney's U-test (between male and female peritoneal cases).

Table 2
Summary of the immunohistochemical profiles of various lesions in each category.

Pathological diagnosis	Markers					
	Calretinin n (%)	D2-40 n (%)	Cytokeratin[a] n (%)	CEA n (%)	TTF1 n (%)	Desmin n (%)
"Definitely not/unlikely"mesothelioma[b]						
Pulmonary adenocarcinoma	1/8 (12.5)	0/5 (0)	3/4 (75)	5/8 (62.5)	6/8 (75.0)	1/2 (50)
Pulmonary sarcomatoid carcinoma	6/7 (85.7)	3/6 (50.0)	5/6 (83.3)	2/3 (66.7)	0/1 (0)	0/4 (0)
Fibrous pleuritis	4/8 (50)	2/4 (50)	3/4 (75)	ND[c]	ND	4/4 (100)
Serous adenocarcinoma, peritoneum	0/3 (0)	0/3 (0)	3/3 (100)	2/5 (40)	ND	ND
Sarcoma, NOS	1/4 (25)	2/4 (50.0)	1/4 (25)	ND	ND	0/3 (0)
"Possible" mesothelioma						
Epithelioid or biphasic	2/4 (50)	2/4 (50.0)	3/4 (75.0)	0/7 (0)	0/3 (0)	0/1 (0)
Sarcomatoid	3/3 (100)	2/3 (66.7)	2/3 (66.7)	0/3 (0)	0/1 (0)	0/2 (50)
"Probable/definite" mesothelioma						
Epithelioid	132/137 (96.4)	81/84 (96.4)	48/50 (96.0)	3/118 (2.5)	0/43 (0)	7/72 (9.7)
Biphasic	27/30 (90)	15/18 (83.3)	22/22 (100)	0/25 (0)	0/10 (0)	2/17 (11.8)
Sarcomatoid	33/43 (76.7)	15/21 (71.4)	35/35 (100)	0/13 (0)	0/4 (0)	3/31 (9.7)
Desmoplastic	4/4 (100)	2/2 (100)	4/4 (100)	0/1 (0)	ND	0/4 (0)

[a] Including CAM5.2 or AE1/AE3 positivity.
[b] Predominant final diagnoses are indicated.
[c] Not done.

In brief, each of the "probable/definite" mesothelioma and pulmonary sarcomatoid carcinoma subtypes showed a high calretinin positivity (more than 50%). Further, D2-40 positivity in the "possible" and "probable/definite" mesothelioma cases was greater than 50%. In addition, the cases of pulmonary sarcomatoid carcinoma, fibrous pleuritis and sarcoma, NOS were 50% positive. CEA positivity in the case of pulmonary adenocarcinoma, pulmonary sarcomatoid carcinomas, and serous papillary adenocarcinomas invading the peritoneum in females was relatively high (62.5%, 66.7%, and 40%, respectively); however, only 3 "probable/definite" category cases (2.5%) tested positive. Only 6 pulmonary adenocarcinoma cases tested positive for TTF-1.

3.4. Relationship between pathological diagnostic methods and proportion of cases in each diagnostic category

To evaluate the efficiency of the various pathological diagnostic methods for mesothelioma, the proportion of cases in each category were differentiated according to the 4 types of pathological specimens (i.e., only cytology slides with Papanicolaou (Pap) stain (CS), only histological slides with H&E stain (SHE), both CS and SHE, and CS or SHE with immunohistochemistry) (Table 3). The result revealed a higher percentage of cases in the "probable/definite" category for cases with immunohistochemistry than for those without immunohistochemistry.

Table 3
Relationship between pathological diagnostic methods and proportion of cases in each diagnostic category.

Category	Methods			
	CS[a] No. of cases (%)	SHE[b] No. of cases (%)	Both CS and SHE No. of cases (%)	CS and/or SHE with IH[c,d] No. of cases (%)
Inadequate/insufficiency	6(13.0)	2(9.5)	1(14.3)	10(3.2)
Definitely not/unlikely	14(30.4)	3(14.3)	1(14.3)	47(15.2)
Possible	8(17.4)	6(28.6)	1(14.3)	11(3.6)
Probable/definite	18(39.2)	10(47.6)	4(57.1)	240(78.0)
Total	46(100)	21(100)	7(100)	308(100)

[a] CS: cytology specimen with Papanicolaou stain.
[b] SHE: histological slides with H&E stain.
[c] IH: immunohistochemistry.
[d] $p < 0.0001$ by Mann–Whitney's U-test (difference in category proportion by the presence of immunohistochemistry).

Table 4
Correct diagnosis of cases in "definitely not/unlikely" category.

Site	Correct diagnosis	No. of case
Male		
Pleura	Pulmonary adenocarcinoma	14
	Pulmonary sarcomatoid carcinoma	6
	Non-small cell lung carcinoma	1
	Pulmonary carcinosarcoma	1
	Fibrous pleuritis	8
	Sarcoma, NOS	2
	Metastatic renal cell carcinoma	1
	Thymic carcinoma	1
	Malignant lymphoma	1
	Solitary fibrous tumor	1
	Reactive mesothelial hyperplasia	1
Peritoneum	Adenocarcinoma	1
	Renal cell carcinoma	1
	Reactive mesothelial hyperplasia	1
	Total	40
Female		
Pleura	Pulmonary adenocarcinoma	3
	Pulmonary sarcomatoid carcinoma	3
	Non-small cell lung carcinoma	2
	Fibrous pleuritis	1
	Malignant lymphoma	1
	Solitary fibrous tumor	1
	Reactive mesothelial hyperplasia	1
Peritoneum	Serous adenocarcinoma	6
	Adenocarcinoma, NOS	2
	Carcinosarcoma	2
	Sarcoma, NOS	2
	Rhabdomyosarcoma	1
	Total	25

3.5. Correct diagnosis of cases in "definitely not/unlikely" category

Pathological diagnoses of the cases in the "definitely not/unlikely" category are summarized in Table 4. Among the pleural cases in males, pulmonary adenocarcinoma (14 cases), pulmonary sarcomatoid carcinoma (6 cases), and fibrous pleuritis (8 cases) were dominant. Among the pleural cases in females, there were a majority of pulmonary adenocarcinomas (3 cases) and pulmonary sarcomatoid carcinomas (3 cases) similar to the result in the case of the males. Among the peritoneal cases in females, serous adenocarcinomas (6 cases) from the female genital tract were prominent.

Representative cases placed in the "definitely not/unlikely" category are shown in Figs. 1–3.

4. Discussion

The present study involved a clinicopathological analysis of cases where death occurred due to clinical mesothelioma, as per the files from the "Vital Statistics of Japan" for the period 2003–2005. Although a limited amount of information was available for all cases and there was a certain amount of bias depending on the cooperating institutes and submitted materials, we attempted to identify some characteristic problems in the diagnosis of mesothelioma in Japan. Consequently, we decided to consider 65 cases belonging to "definitely not/unlikely" category, and therefore, we assumed that approximately 15% of mesothelioma deaths were diagnostically suspicious, especially in females with peritoneal and sarcomatoid subtype mesothelioma. All the medical institutes from which pathological materials were collected did not provide the slides stained with the recently recommended immunohistochemical panel, and our department could not perform immunohistochemistry with a uniform antibody panel owing to the limitation of submitted materials. Therefore, the error score (i.e., approximately 15%) estimated in this study might be higher than the "actual" error score. However, such comprehensive data concerning the accuracy of mesothelioma diagnosis has not been previously reported in Japan. It is ideal to analyze the autopsy materials to precisely and definitely diagnose clinical "mesothelioma" patients. However, there are limitations to conducting an autopsy in all cases and reevaluating all materials submitted for pathological diagnosis in each medical institute. Therefore, we used the conservative category system, i.e., "inadequate/insufficient", "definitely not/unlikely", "possible", and "probable/definite".

There are many diseases that must be differentiated from mesothelioma. Epithelioid mesothelioma must be differentiated from pulmonary adenocarcinoma, metastatic adenocarcinoma, peritoneal serous adenocarcinoma, ovarian adenocarcinoma, and reactive mesothelial hyperplasia. Sarcomatoid mesothelioma should be differentiated from pulmonary sarcomatoid carcinoma, true sarcoma arising in the chest wall and parietal pleura, pulmonary primary sarcoma, and various types of intraabdominal sarcomas. The biphasic type must be differentiated from pulmonary biphasic pulmonary blastoma, carcinosarcoma, synovial sarcoma, and carcinosarcoma of the female genital tract (ovary and uterus). The desmoplastic type must be differentiated from fibrous or organizing pleuritis [7,8]. It must be understood that mesothelioma has clinical and pathological heterogeneities and that relatively rare tumors may pose diagnostic difficulties. As expected, the above-mentioned diseases were responsible for mesothelioma death cases, as indicated in Table 4.

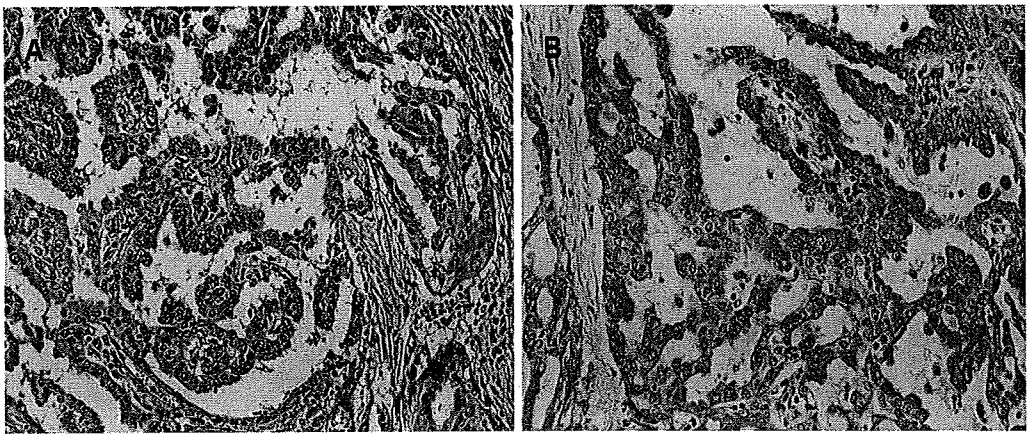

Fig. 1. Pulmonary adenocarcinoma invading the parietal pleura (69-year-old male). (A) Atypical epithelial cells showed a papillary invasive growth pattern (H&E, ×200). (B) Immunohistochemically, the tumor cells were positive for CEA (immunostaining, ×200).

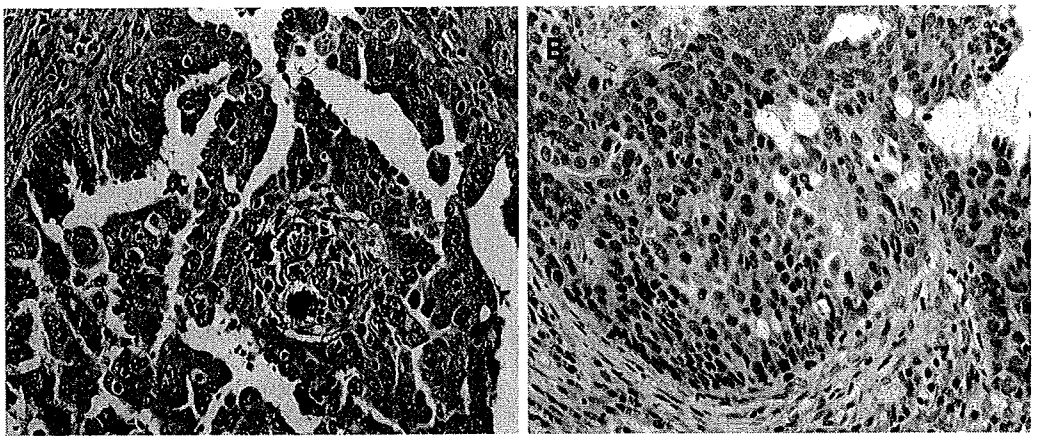

Fig. 2. Serous papillary adenocarcinoma invading the peritoneum (55-year-old female). (A) Atypical epithelial cells show a complex papillary growth pattern with psammoma bodies (H&E, ×200). (B) Tumor cells tested positive for the estrogen receptor (immunostaining, ×200).

Recently, many mesothelial and non-mesothelial markers have been developed to differentiate mesothelioma from other malignant tumors and benign lesions [9–11,13]. Immunoshistochemical analysis is absolutely necessary for the accurate diagnosis of mesothelioma. Therefore, we discussed the differential diagnosis of mesothelioma from pulmonary adenocarcinoma, pulmonary sarcomatoid carcinoma, fibrous pleuritis, and ovarian serous carcinomas, which are the predominant disorders as mentioned in Table 4, especially with regard to the utility of immunohistochemistry using the antibody panel.

In this study, 17 pulmonary adenocarcinomas were misdiagnosed as mesotheliomas (4.5% of 382 cases). Differentiation between epithelioid mesothelioma and pulmonary adenocarcinoma is sometimes difficult. This is because some pleural mesotheliomas invade the pulmonary parenchyma and exhibit lepedic growth [7]. Sometimes pulmonary adenocarcinomas may grow along the visceral and/or parietal pleura, mimicking the growth of malignant pleural mesothelioma; this growth is detected clinically and/or radiologically and it is called "pseudomesotheliomatous adenocarcinoma" [17,18]. Over the last 10 years, many immunohistochemical markers for differentiating between epithelioid mesothelioma and pulmonary adenocarcinoma have been developed [10,19–24]. Ordonez [22,23] stated that calretinin and CK5/6 (or WT1) were positive markers and CEA and MOC-31 (or B72.3, Ber-Ep4, or BG-8) were negative markers. We demonstrated that the combination of CEA, calretinin, and WT1 or thrombomodulin was the best antibody panel for differential diagnosis [10]. Recently, D2-40 or podoplanin was reported to be useful for distinguishing mesothelioma from pulmonary adenocarcinoma [25]. On the basis of these facts, we selected the antibody panel from among calretinin, D2-40, CAM5.2, CEA, TTF-1, and desmin for differential diagnosis. The application of these antibodies will contribute to increase the diagnostic accuracy of epithelioid mesothelioma.

Differentiation between sarcomatoid mesothelioma and pulmonary sarcomatoid carcinoma is still very difficult if no adequate clinical and pathological information is available. The higher number of pulmonary sarcomatoid carcinomas in the "definitely not/unlikely" category may be reflective of the difficulties in the diagnosis of sarcomatoid mesothelioma (Table 4). Pulmonary sarcomatoid carcinoma is described as a poorly differentiated non-small cell lung carcinoma containing a component of sarcoma or sarcoma-like differentiation [7]. At present, no sensitive or specific markers for differentiation of these tumors are available; thus, it is very important to obtain precise clinical and gross pathological findings (i.e., main location of tumor, presence of intrapulmonary nodule, presence of adenocarcinoma or squamous cell carcinoma foci, etc.). However, the primary site must be determined by examination of the surgically resected tumor and/or autopsy materials. Histologically, therefore, the development of new markers for differential diagnosis is necessary. Kushitani et al. [10] indicated that no significant differences exist between tumors in the expression of calretinin, WT1, AE1/AE3, CAM5.2, and EMA. Recently, Hinterberger et al. [14] stated that calretinin and D2-40 immunostaining in the case of sarcomatoid mesothelioma will improve the diagnos-

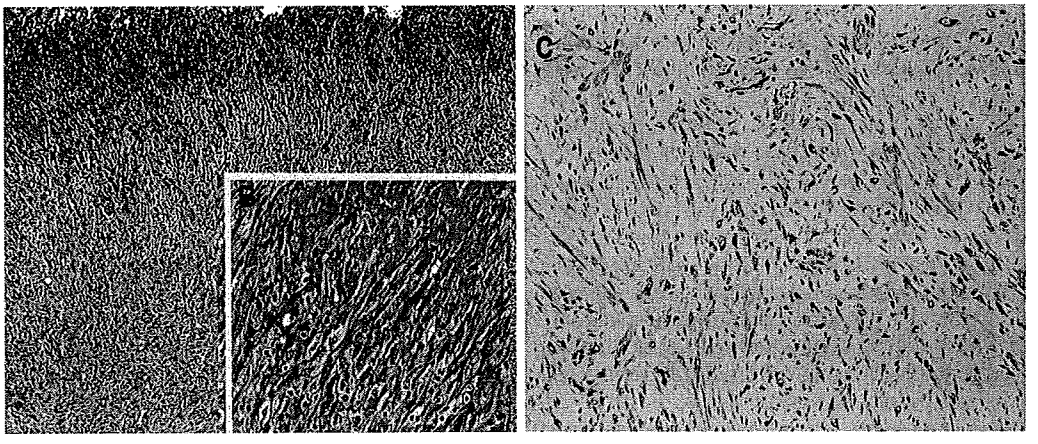

Fig. 3. Fibrous/organizing pleuritis (73-year-old male). (A, B) Spindle-shaped cells proliferating in a "zonation" fashion. The surface of this lesion is composed of fibrin, immature spindle cells, and capillaries (H&E, A: ×40, B: ×200). (C) Some spindle cells tested positive for desmin (immunostaning, ×200).

tic accuracy of spindle-cell lesions in the pleura. In this study, 6 of 7 (87.5%) pulmonary sarcomatoid carcinomas tested positive for calretinin and 3 of 6 cases (50%) tested positive for D2-40. On the other hand, 33 of 43 (76.7%) sarcomatoid mesotheliomas tested positive for calretinin and 15 of 21 cases (71.4%), for D2-40. D2-40 positivity in the case sarcomatoid mesothelioma tended to be higher than that in the case of pulmonary sarcomatoid carcinoma; however, a definite conclusion could not be drawn from the limited number of pulmonary sarcomatoid carcinoma cases in this study.

The other problem is differential diagnosis between desmoplastic mesothelioma and fibrous pleuritis. In this study, 9 of 65 cases (13.8%) in the "definitely not/unlikely" category were considered to be fibrous pleuritis. Churg et al. [26] provided a summary of distinguishing desmoplastic mesothelioma from fibrous pleuristy (pleuritis) and/or organizing pleuritis in their review article. They showed that fibrous pleuritis typically exhibits "zonation" with high cellularity and cytologic atypia toward the pleural space and increasing fibrosis with decreasing cellularity and lesser atypia toward the chest wall. On the other hand, sarcomatous (desmoplastic) mesothelioma does not exhibit this type of zonation and is sometimes accompanied with bland necrosis and overtly sarcomatous foci. To differentiate between these 2 diseases, a relatively large amount of tissue and/or pleural whole layer tissues is necessary for a thoracoscopic biopsy. Churg documented that needle biopsy is generally inadequate, because "small" thoracoscopic biopsy may not be sufficient to evaluate "zonation" [16].

In this study, 10 carcinomas, i.e., serous papillary adenocarcinomas, adenocarcinoma, NOS, and carcinosarcomas of the genital tract or peritoneum were included in the case of peritoneal cases in females, and only 4 cases were categorized as "probable/definite" epithelioid mesothelioma. The ratio of peritoneal mesotheliomas in Japanese females among all mesothelioma cases is reportedly higher than that in Western countries [27]. In females, the most difficult differential diagnosis is that between peritoneal epithelioid mesothelioma and serous papillary adenocarcinoma of the ovary and/or peritoneum [28]. Baker et al. [29] described the morphological differences between peritoneal epithelioid mesothelioma (PEM) and serous papillary adenocarcinoma (SC). Peritoneal mesothelioma often invades the peritoneal cavity with multiple nodule formation, associated with ascites, or occasionally forms a localized abdominal mass, including mass formation in the ovary [30]. Therefore, SC of ovarian or peritoneal origin [28] is the most important and difficult malignant tumor for differentiation due to the clinical and histological similarities in the 2 cases [29]. Recently, reports on the application of immunohistochemistry for differential diagnosis have emerged. Attanoos et al. [31] described that calretinin and Ber-EP4 are useful discriminant markers for distinguishing PEM in women from SCs and peritoneal carcinoma. Ordonez [9,32] reported that combinations of best positive markers (D2-40 and calretinin) and negative markers (Ber-EP4, MOC-31 and ER) were useful for discriminating between the 2 tumors. The relatively high rate of misdiagnosed cases among clinically diagnosed female peritoneal mesothelioma clinically is a problematic issue. We described calretinin and thrombomodulin as positive markers and Ber-EP4, MOC-31, CA19-9, and ER as negative markers with relatively high sensitivity and specificity [11]. Chemotherapy and/or radiotherapy can significantly improve patient survival and decrease recurrence, especially in primary and secondary SC, as compared with PEM [33–35]. However, Sugarbaker et al. recently reported a remarkable prolongation in the median survival of peritoneal mesothelioma patients treated with an intensive local-regional treatment strategy that included cytoreductive surgery with peritonectomy and hyperthermic intraoperative intraperitoneal chemotherapy; the prolongation was also reported for some patients that received early postoperative intraperitoneal chemotherapy [36]. Therefore, appropriate antibody selection for immunohistochemistry and for sampling a relatively large amount of tumor tissue by laparotomy are necessary for early and precise diagnosis [37]. The application of immunohistochemistry for cytology materials (ascites) is also effective, especially for the epithelioid type mesothelioma [38].

There are various methods to obtain mesothelioma cells and tissues, such as cytology, needle biopsy, and biopsy under thoracoscopy or laparoscopy. Among these methods, pleural or peritoneal biopsy under thoracoscopy or laparoscopy is a reliable method to obtain sufficient tumor tissue from the pleura and peritoneum for accurate pathological diagnosis [39,40].

Cytology from body cavity fluids is also useful for cancer diagnosis; however, morphological observation only by Papanicolaou, Giemsa, and PAS staining would not be sufficient, even for experienced pathologists [41]. In particular, as small amounts of tumor cells from sarcomatoid or desmoplastic mesothelioma are shed into the body cavity, diagnosis by only cytology is impossible [7]. In this study, of the 46 cases for which only the cytological tests were performed, 18 cases (39.2%) (all of epithelioid subtype) belonged to the "probable/definite" category according to the cytological and radiological features, the level of hyaluronan in body fluids, and so on. The cytological criteria for epithelioid mesothelioma were based on classical morphological features such as high cellularity, uniform cell population, intercellular gap, central or paracentral nucleus, multinucleation with atypia, villosity, nuclear pleomorphism, and so on. [41]. On the other hand, 5 cases where cytology specimens were stained by immunohistochemistry, including calretinin, D2-40, CEA, TTF-1, and so on, were included in this study and among them 3 cases (60%) (all of epithelioid subtype) belonged to "probably/definite" category. Therefore, it is assumed that cytology with immunohistochemistry using an appropriate antibody panel may increase the accuracy of mesothelioma diagnosis, especially in the case of epithelioid type mesothelioma [38]. Lyons–Boudreaux recommended the use of D2-40 and MOC-31, which are sensitive and specific markers for mesothelial and epithelial cells, respectively, to improve the diagnostic accuracy with body cavity effusions [38]. Pu et al. reported the utility of WT1, p63, MOC31, and cytokeratin (K903 and CK5/6) immunostains in differentiating adenocarcinoma, squamous cell carcinoma, and malignant mesothelioma in pleural effusions [42]. However, no effective markers are available thus far with sensitivity and specificity high enough to differentiate between epithelioid mesothelioma and benign mesothelial lesions (reactive mesothelial and reactive hyperplasia cells), because the diagnosis of epithelioid mesothelioma is based on the "invasiveness of mesothelial cells" [16]. Therefore, we considered that the cases of the "probable/definite" category among the "cytology-only" category in this study should belong to the "probable" mesothelioma category and not to the "definite" category. We supposed that body fluid cytology is useful for mesothelioma diagnosis; however, adequate tissue sampling by biopsy and immunohistochemistry using an appropriate antibody panel are necessary for "definite" mesothelioma diagnosis. Recently, Hanley et al. reported the utility of anti-L523S antibody (antibody to K homolog domain containing protein overexpressed in cancer (KOC)) in combination with calretinin and CK5/6 for differentiating reactive mesothelial cells from malignant mesothelioma and metastatic carcinoma [43]. Further efforts to evaluate new markers useful for differentiating mesothelioma especially from benign mesothelial lesions are required.

In conclusion, it is ascertained that the diagnosis of mesothelioma in females and in the case of peritoneal and sarcomatoid subtype cases has relatively low diagnostic accuracy, and approximately 15% of the deaths by mesothelioma in Japan are diagnostically suspicious. Therefore, precise pathological procedures, including immunohistochemistry using an appropriate antibody panel selected based on histology and clinical information, are necessary for accurate mesothelioma diagnosis. Moreover, the nationwide mesothelioma registration system must also be

established for obtaining precise data on mesothelioma for epidemiological study. These efforts will help promote early detection and therapy of mesothelioma and facilitate significant improvements in patient prognoses.

Conflict of interest statement

None.

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胸膜中皮腫の臨床的検討

—岡山労災病院における81例の検討—

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胸膜中皮腫の臨床的検討
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Malignant Pleural Mesothelioma
—A Clinical Study of 81 Patients from Okayama Rosai Hospital—

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ABSTRACT —— ***Objective.*** We examined the clinical features and prognosis of malignant pleural mesothelioma. ***Subjects.*** From 1993 to 2008, 81 patients from the Main Center for Asbestos-related Disease for Diagnosis and Treatment, Okayama Rosai Hospital, were enrolled. ***Results.*** Of the 81 patients, 74 were men and 7 were women with an average age of 66.0 years old. A past history of exposure to asbestos was confirmed in 71 patients (87.7%). Seventy-one patients (87.7%) presented with symptoms. A definitive diagnosis was obtained by pleural biopsy in 55 patients (67.9%) within 4.5 months (median) from the first visit. Chemotherapy and/or radiotherapy were performed in 40 patients. Operation was performed in 24 patients. Best supportive care alone was carried out in 17 patients. The median survival of all patients was 10.8 months. The overall 5-year survival rate was 5.0%. The overall 1- and 3-year survival rates after operation were 65.1% and 23.2% respectively, while the median survival was 13.2 months. With chemotherapy only, the overall 1- and 3-year survival rates were 39.2% and 0% respectively, while the median survival was 10.8 months. There were significant differences in survival rates between the resection and chemotherapy only groups ($p = 0.04$). In a multivariable analysis by the Cox proportional hazards model with controls for performance status, clinical stage, operation, chemotherapy and N factor, non-resected patients had a higher hazard ratio (1.622) than resected patients. ***Conclusion.*** Extrapleural pneumonectomy is a prognostic factor in malignant pleural mesothelioma. The establishments of diagnosis at an early stage, the development of adjuvant therapy and more effective chemotherapy are required for the improvement of survival in patients with malignant pleural mesothelioma.

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KEY WORDS —— Malignant pleural mesothelioma, Extrapleural pneumonectomy, Prognosis

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要旨 —— **目的.** 胸膜中皮腫の臨床像および予後について検討した. **対象.** 1993～2008年に診断・治療した胸膜中皮腫81例を対象とした. **結果.** 男性74例, 女性7例で, 平均年齢は66.0歳であった. アスベストばく露歴を71例（87.7%）に認め, 症状発見が71例（87.7%）であった. 確定診断は, 55例(67.9%)が胸膜生検で得られた. 初診から診断までに平均4.5ヶ月を要した. 治療は, 化学療法もしくは放射線療法が40例, 手術療法が24例, 対症療法が17例に行われた. 予後に関しては, 全症例の生存期間中央値は10.8ヶ月で5年生存率が5.0%であった. 手術療法の1年および3年生存率は65.1%と23.2%で, 生存期間中央値は13.2ヶ月であった. また, 化学療法の1年および3年生存率は39.2%と0%で, 生存期間中央値は10.8ヶ月であり, 手術療法と化学療法の生存率

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の間に統計学的有意差を認めた（p＝0.04）．Cox 比例ハザードモデルを用いた多変量解析では，手術の有無による相対危険率は 1.622 であった．**結論．**胸膜肺全摘術の有効性が認められたが，依然予後不良の疾患であり，早期発見と有効な治療法の確立が急務であると考えられた．

索引用語 —— 胸膜中皮腫，胸膜肺全摘術，予後

はじめに

胸膜中皮腫は稀な腫瘍であるが，この 10 年間に症例数は増加し，2025 年ごろにピークに達すると推測されている．[1]

2006 年 3 月 27 日から「石綿による健康被害の救済に関する法律」が施行され，中皮腫に対する社会的関心がいっそう高まってきた．胸膜中皮腫の臨床像や予後に関して多数例を検討した報告は少ない．今回われわれは，当院で経験した胸膜中皮腫の臨床像および予後について検討したので報告する．

対象と方法

1993～2008 年 9 月までの期間に，病理組織学的に胸膜中皮腫と診断された 81 例を対象とした．臨床病理学的には，性別，年齢，石綿ばく露歴，胸水の有無，胸水中のヒアルロン酸値，胸痛の有無，症状発現から診断までの期間，performance status（以下，PS），組織型，罹患側，臨床病期，主な治療内容について検討した．病期分類は International Mesothelioma Interest Group（IMIG）病期分類に拠った．手術適応は，I，II 期および完全切除可能と考えられる一部の III 期とし，術式は胸膜肺全摘術とした．2007 年 1 月に Pemetrexed（MPA）が承認されてから化学療法として Cisplatin（CDDP）＋Pemetrexed を第一選択としている．生存率は診断時を起点として 2008 年 9 月 30 日現在での転帰を調査し，Kaplan-Meier 法を用いて算出し，有意差検定には log-rank test を用いた．群間比較には t および x^2 検定を用いた．多変量解析には Cox 比例ハザードモデルを用いた．いずれの検定も $P<0.05$ をもって有意差ありとした．

結　果

胸膜中皮腫 81 例の性別内訳は，男性 74 例，女性 7 例で，平均年齢は 66.0 歳（38～93 歳）であった．職歴および生活歴から石綿ばく露が推定された例は 71 例（87.7%）であった．診断時に胸水を認めた例は 53 例（65.4%）で，胸水中ヒアルロン酸値は 48 例で測定され，7～2550 μg/ml で，100 μg/ml 以上[2]の高値を示したものが 17 例であった．症状発見は 71 例（87.7%）で，特に胸部痛があるものは，40 例（49.4%）であった．最初の医療機関受診日から確定診断が得られるまでの期間は 0～67.4 ヶ月，中央値 2.0 ヶ月，平均 4.5 ヶ月であった．PS は，0～1 が 63 例（77.8%）であった．病理組織型は上皮型 50 例（61.7%），肉腫型 21 例（25.9%，線維形成型 8 例），二相型 8 例（9.9%），不明 2 例（2.5%）であった．罹患側は，右側 43 例（53.1%），左側 38 例（46.9%）であった．臨床病期に関しては，III 期以上の進行例が 52 例（64.2%）であった．主な治療は，化学療法が 36 例（44.4%）に，化学＋放射線療法が 1 例（1.2%）に，手術療法は 24 例（29.6%）で，全例に胸膜肺全摘術が行われた．その他，放射線療法が 3 例（3.7%）に，対症療法が 17 例（21.0%）に行われた（Table 1）．

診断は，全例病理組織学的検査により得られた．その検体採取法としては胸膜生検が 55 例（67.9%）に行われた．胸水細胞診や針生検での診断は 25 例に行われ，そのうち 22 例が III 期以上の症例であった（Table 2）．

Table 1. Patient Characteristics

No. of patients		81
Gender	Male	74
	Female	7
Mean age (years)		66.0 ± 10.6 (SD)
Asbestos exposure (patients)		71 (87.7%)
Pleural effusion		53 (65.4%)
Hyaluronic acid (≥100 μg/ml)		17
Chest pain		40 (49.4%)
Duration to diagnosis (months)		4.5 ± 9.0
Performance status	0-1	63 (77.8%)
	≥2	18 (22.2%)
Histologic type	Epithelioid	50 (61.7%)
	Sarcomatoid	21 (25.9%)
	Biphasic	8 (9.9%)
	Unknown	2 (2.5%)
Affected side	Right	43 (53.1%)
	Left	38 (46.9%)
Clinical stage (IMIG)	I	14 (17.3%)
	II	15 (18.5%)
	III	24 (29.6%)
	IV	28 (34.6%)
Treatment	Chemotherapy	36 (44.4%)
	Chemotherapy＋Radiotherapy	1 (1.2%)
	Operation	24 (29.6%)
	Radiotherapy	3 (3.7%)
	Best supportive care	17 (21.0%)

Table 2. Methods of Diagnosis of Malignant Pleural Mesothelioma

Methods	No. of cases	Stage I	Stage II	Stage III	Stage IV
VATS	34 (42.0%)	4	9	11	10
Thoracoscopic pleural biopsy	21 (25.9%)	9	3	8	1
Percutaneous needle biopsy	17 (21.0%)	1	1	5	10
Cytologic study of pleural fluid	8 (9.9%)	0	1	0	7
Autopsy	1 (1.2%)	0	1	0	0

VATS: video assisted thoracic surgery under general anesthesia, Thoracoscopic pleural biopsy: thoracoscopy under local anesthesia.

Table 3. Characteristics of Patients Receiving Operation or Chemotherapy

		Operation (24)	Chemotherapy (37)	P-value
Gender	Male	23	32	
	Female	1	5	0.331
Mean age (years)		62.6 ± 6.4 (SD)	64.6 ± 11.3 (SD)	0.221
Performance status (PS)	0-1	24	26	
	≥2	0	11	0.001
Clinical stage (IMIG)	I	4 (16.7%)	4 (10.8%)	
	II	14 (58.3%)	0 (0.0%)	
	III	6 (25.0%)	14 (37.8%)	
	IV	0 (0.0%)	19 (51.4%)	0.002
Histological type	Epithelioid	16 (66.7%)	26 (70.3%)	
	Sarcomatoid	6 (25.0%)	7 (18.9%)	
	Biphasic	2 (8.3%)	2 (5.4%)	
	Unknown	0 (0.0%)	2 (5.4%)	0.588
Affected side	Right	13 (54.2%)	18 (48.6%)	
	Left	11 (45.8%)	19 (51.4%)	0.564
Adjuvant method	EPP	11		
	EPP + CT	9		
	CT + EPP	1		
	EPP + RT	1		
	EPP + CT + RT	1		
	EPP + IPT*	1		
Containing chemotherapy	Gemcitabine + Vinorelbine		16	
	Pemetrexed + Cisplatin		13	
	Gemcitabine + Cisplatin		6	
	Platinum containing		21 (56.8%)	
	Gemcitabine containing		22 (59.5%)	
	Pemetrexed containing		13 (35.1%)	

EPP: extrapleural pneumonectomy, CT: chemotherapy, RT: radiotherapy, *IPT: intrapleural hypotonic treatment, Platinum containing: platinum compounds containing chemotherapy, Gemcitabine containing: gemcitabine compounds containing chemotherapy, Pemetrexed containing: pemetrexed compounds containing chemotherapy.

手術症例24例の検討では，リンパ節郭清は，22例（91.7%）に縦隔リンパ節郭清が行われ，4例（18.2%）に縦隔リンパ節の転移が認められた．全例に胸膜生検部の全層切除を行ったが，2例に腫瘍細胞が認められた．生検診断から手術までの平均期間は29.9日（11～55日）であった．補助療法は，術後化学療法が9例，術前化学療法が1例，術後放射線療法が1例，術後化学＋放射線療法が1例，術中胸腔内化学療法が1例に行われた．術後に昇圧剤を必要とする心不全，心房細動などの合併症が9例に発生し，morbidity 37.5%，術後関連死亡が1例（急性呼吸促迫症候群の発症）で mortality 4.2% であった．化学療法の検討では，使用された主な抗癌剤としては，Gemcitabine + Vinorelbine 16例，Cisplatin + Pemetrexed 13例，Cisplatin + Gemcitabine 6例であった．

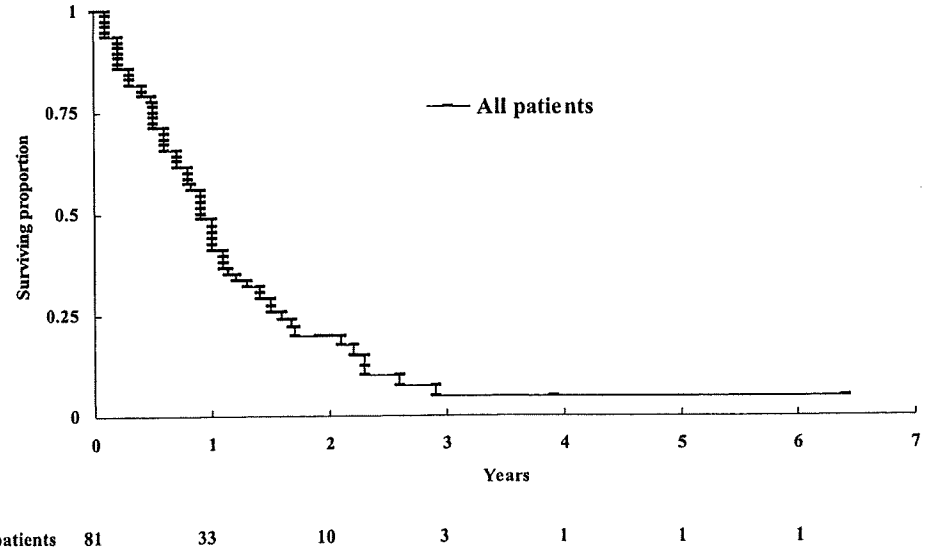

Figure 1. Overall survival of the patients with malignant pleural mesothelioma.

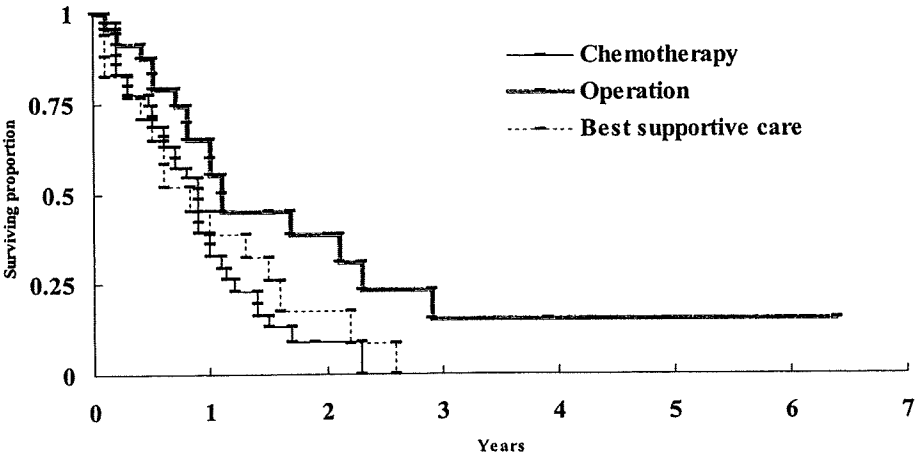

Figure 2. Overall survival of malignant pleural mesothelioma is shown stratified by treatment. BSC: best supportive care.

手術療法と化学療法の臨床病理学的背景因子を比較すると，PS と IMIG 臨床病期に有意差が認められた（Table 3）.

予後についてみると，全例の 5 年生存率は 5.0% で，生存期間中央値は 10.8 ヶ月であった（Figure 1）. 主な治療法別では，手術療法の 1 年生存率 65.1%，3 年生存率 23.2%，5 年生存率 15.4% で，生存期間中央値は 13.2 ヶ月であった. 化学療法単独の 1 年生存率 39.2%，2 年生存率 8.7%，3 年生存率は 0% で，生存期間中央値は 10.8 ヶ月であった（Figure 2）. 手術療法と化学療法の生存率の間に有意差を認めた（$p=0.04$）.

Cox の比例ハザードモデルによる予後因子の解析では，単変量解析で PS，臨床病期，手術の有無の各因子に有意差がみられた（Table 4）. 単変量解析で有意差がみられた 3 因子に，化学療法の有無，リンパ節転移の有無を加えた 5 因子について多変量解析を行ったところ PS，臨床病期，手術の有無が独立した予後因子であった. また，手術の有無による相対危険率は 1.622 であった（Table 5）.

考　察

これまでの胸膜中皮腫の臨床像に関する報告として

Table 4. Univariate Analysis of Potential Prognostic Factors for Malignant Pleural Mesothelioma: Cox's Proportional Hazards Model

Variable		No. of patients	Hazard ratio	95% confidence interval	P-value
Age (years)	< 70	48	1.000		
	≥ 70	33	1.171	0.619-3.841	0.925
Gender	Male	74	1.000		
	Female	7	1.212	0.524-2.841	0.471
Performance status	0-1	63	1.000		
	≥2	18	2.200	1.285-2.745	0.009
Chest pain	No	41	1.000		
	Yes	40	1.205	0.882-3.841	0.346
Basis for	Symptoms	71	1.000		
	X-ray findings	10	0.800	0.725-2.377	0.207
Asbestos exposure	Yes	71	1.000		
	No	10	1.135	0.577-2.764	0.885
Histological type	Epithelial	50	1.000		
	Non epithelial	31	0.789	0.553-1.981	0.132
Affected side	Right	43	1.000		
	Left	38	1.250	0.765-2.241	0.195
Clinical stage (IMIG)	I + II	29	1.000		
	III + IV	52	1.974	1.225-4.716	0.003
Operation	Yes	24	1.000		
	No	57	1.645	1.280-4.652	0.007
Chemotherapy	Yes	37	1.000		
	No	44	1.444	0.988-1.841	0.053
Containing platinum	Yes	21	1.000		
	No	16	1.112	0.548-1.592	0.347
Containing gemcitabine	Yes	22	1.000		
	No	15	1.286	0.643-2.510	0.288
Containing pemetrexed	Yes	13	1.000		
	No	24	0.959	0.431-1.678	0.257
N factor	N (−)	63	1.000		
	N (+)	18	1.375	0.785-2.765	0.078

N factor: metastasis of lymph nodes.

Table 5. Multivariate Analysis of Potential Prognostic Factors for Malignant Pleural Mesothelioma by Cox's Proportional Hazards Model

Variable	No. of patients	Hazard ratio	95% confidence interval	P-value
PS				
0-1	63	1.000		
≥2	18	2.195	1.183-2.935	0.003
Clinical stage (IMIG)				
I-II	29	1.000		
III-V	52	1.500	1.243-2.368	0.024
Operation				
Yes	24	1.000		
No	57	1.622	1.283-2.145	0.028
Chemotherapy				
Yes	37	1.000		
No	44	1.245	0.878-2.231	0.054
N factor				
N (−)	63	1.000		
N (+)	18	1.221	0.695-1.913	0.375

は，4710例の文献報告例を集積したHillerdalによる報告がみられる.[3] しかし，わが国の多数例での報告は，Takagiらの全国調査による189手術例の報告がみられるのみであった.[4] 最近の報告では，東山らの全国アンケート調査による外科治療成績,[5] 由佐らによる多施設共同研究グループによる臨床的検討の報告,[6] 単施設としては当院の報告がある.[7]

アスベストばく露は本症の主要な原因とされており，今回の検討でも87.7%にアスベストばく露歴を認め，その関与が示唆された．しかし，明らかなアスベストばく露の職業歴を認めない例もある．当院でも，造船所の近隣に住む郵便配達人，造船所で就労する夫をもつ専業主婦，教員，銀行員などの胸膜中皮腫患者を経験しており，詳細な生活歴なども聴取する必要があると考えられた．

発見動機について，71例(87.7%)が症状による医療機関への受診であり，胸部X線による検診が普及しているわが国においても本症の早期発見が困難であることが窺われた．しかし，胸膜中皮腫が認識されるようになり2004年以降の当院における症状発見は49.0%と症状発見例が減少している．

診断についてみると，最初の医療機関から診断までに平均4.5ヶ月と長時間を要していた．その理由として，初診の医療機関での胸膜中皮腫に対する認識不足や，胸水細胞診や経皮的針生検での本症の診断の困難さが窺われた.[2] 近年，胸腔鏡下に直接病変を観察しながら十分量の腫瘍組織が採取されるようになり，確定診断法は向上した．

本症の治療に関しては，標準的な治療法が確立されていないのが現状である．われわれの施設の基本的な治療方針として，腫瘍の進展と全身状態から切除可能と思われる例には手術を主体として行い，可能であれば術後化学療法を行うこととし，手術不能例には全身化学療法を主とした治療を行うこととしている．本症に対する手術術式は，Sugarbakerら[8]の報告に代表されるように胸膜肺全摘術を行っている．その2年生存率は10～38%で，手術関連死亡率が3.8～31%と報告されている.[8-11] Takagiらのわが国における手術例の調査では，116例の胸膜中皮腫に対する胸膜肺全摘術について，その2年および5年生存率はそれぞれ29.7%，9.1%で手術死亡率6%と報告されている.[4] 玄馬らは，2003～2005年までの人口動態統計で把握された中皮腫による死亡例2742例のうち，胸膜中皮腫502例の検討で，胸膜肺全摘術の生存期間中央値が11.1ヶ月，2年および5年生存率はそれぞれ21.0%，1.6%と報告している.[12] 東山ら[5]の全国アンケート調査による報告においても，2年生存率は33%であり，Takagiら[4]の報告とあわせてもわが国における胸膜中皮腫に対する外科的成績がこの20年間にほとんど変わっていないことが示唆され，治療の困難さが窺われた．術式に関しては，胸膜肺全摘術の他に胸膜切除・剥皮術も行われているが，最近報告された663例の外科手術症例のレビューによると，胸膜肺全摘術と胸膜切除・剥皮術との比較で生存率および術死率ともに胸膜肺全摘術の方が不良であり,[10] Mayo Clinicにおける検討でも術後合併症を考慮すると胸膜肺全摘術の有効性は明らかでないと結論されている.[11] Takagiらおよび東山らの報告でも，胸膜肺全摘術が占める割合は，手術症例の61%と55%で，胸膜肺全摘術と胸膜剥皮術などの縮小手術施行例の術後成績もほぼ同等であった.[4,5] 現在，英国で胸膜肺全摘術の生存に対する意義を明らかにするための前向きの臨床試験（The MARS trial：mesothelioma and radical surgery）が進行中であり，結果に興味があるところである.[13] 手術適応に関しては，III期も手術適応の一部と考えられているが，当院の手術症例における検討では，I期はIII期と比較して有意に生存率が良いが，III期に関しては，手術療法と化学療法において有意差を認めておらず，手術の決定は慎重に行わなければならないと考えている.[14] 生存率の改善には，手術に補助療法を追加する必要があると考えられているが，胸膜肺全摘術という大きな侵襲を伴う治療後に，全身化学療法や放射線療法を追加できる例は限られているのが現状と思われ,[15] 今回の検討においても胸膜肺全摘術に補助療法を行えた症例は54.2%にすぎなかった．東山らの報告でも，術前導入療法のあるものが10%で，術後補助療法が44%であった.[5] 2007年American Society of Clinical OncologyにおいてRuschらにより，CDDP/MPAによる術前化学療法後に胸膜肺全摘術を行う第II相試験が発表されたが,[16] より患者への負担が少なく，より効果的な治療法の開発も望まれる.[17,18]

本症の予後因子としては，年齢，アスベストばく露歴，血小板数，組織型，病期などが報告されている.[19] われわれの多変量解析の結果では，PS，臨床病期，手術の有無が独立した予後因子であったが，玄馬らの報告でも無症状発見，臨床病期，胸膜肺全摘術およびプラチナベースの化学療法が予後因子であった.[12]

結　語

治療と予後に関する今回の検討では，現在のところ満足できる結果は得られていないが，胸膜肺全摘術の有効性が認められた．予後改善のための今後の課題としては，早期発見できる体制，適正な手術適応の設定や施設の限定，補助療法の多施設共同による症例の集積と検討が急務であると考えられた．