膜プラークの検出状況に関するデータは殆どない。本コホートにおいては胸膜プラークを有する割合は 0.4%、「専門的･技術的職業」でないのに胸膜プラークを有する割合は 0.19%であった。今後の検討をする上での基礎データとなると考える。

Ｅ．結論

低線量 CT による肺がん検診を 2004 年 2 月から 2011 年 9 月までに受診した 11519 名中、胸膜プラークの所見を有する頻度は 0.4%であった。また「専門的･技術的職業」でないのに胸膜プラークを有する割合は 0.19%であった。

Ｆ．研究発表

1. 論文発表

1. Kakinuma R, Ashizawa K, Kobayashi T, et al. Comparison of sensitivity of lung nodule detection between radiologists and technologists on low-dose CT lung cancer screening images. Brit J Radiol 2011 (in press)

Ｇ．知的財産権の出願・登録状況（予定を含む）

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

Ⅲ.　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Shiba N, Kusumoto M, et al.	A case of malignant pleural mesothelioma withosseous and cartilaginous differentiation	J Thorac Imaging	26	W30-32	2011
Rice DMB, Asamura H, et al.	Recommendations for Uniform Definitions of Surgical Techniques for Malignant Pleural Mesothelioma: A Consensus Report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group.	J Thorac Oncol.	6(8)	1304-1312	2011
Hiroshima K, Matsuno Y , et . al .	Cytological characteristics of pulmonary pleomorphic and giant cell carcinomas.	Acta. Cytol.	52(2)	173-179	2011
畑中豊、松野吉宏、他	分子病理診断の標準化と精度管理	病理と臨床	29(4)	346-352	2011
Nojiri S, Kishimoto T, et al.,	Survival and prognostic factors in malignantpleural mesothelioma: A retrospective study of 314 patients in thewest part of Japan .	Jpn J Clin Oncol	41(1)	32-39	2011
Maeda M, Kishimoto T, et al.,	Reduction of CXC chemokine receptor 3 in an in vitro model of continuous exposure to asbestos in a human T-cell line, MT-2	Am J Respir Cell Mol Biol.	45	470-479	2011
Kubo T, Kishimoto T, et at.,	Epigenetic silencing of microRNA-34b/c plays an important role in the pathogenesis of malignant pleural mesothelioma.	Clin Cancer Res	17(15)	4965-4974	2011

Ⅳ.　研究成果の刊行物・別刷

Japanese Society of Thoracic Radiology

A Case of Malignant Pleural Mesothelioma With Osseous and Cartilaginous Differentiation

Natsuko Shiba, MD, Masahiko Kusumoto, MD,* Koji Tsuta, MD,† Hirokazu Watanabe, MD,* Shun-ichi Watanabe, MD,‡ Naobumi Tochigi, MD,† and Yasuaki Arai, MD**

Abstract: A 69-year-old man with a history of exposure to asbestos was admitted because of a chest radiographic abnormality. Subsequent findings from computed tomography and a thoracoscopic biopsy suggested malignant mesothelioma. Punctate calcification was observed in the pleural tumor on computed tomography scanning. The patient underwent pleuropneumonectomy, and the tumor was pathologically diagnosed as malignant mesothelioma, sarcomatoid type with osseous and cartilaginous differentiation. Malignant mesothelioma with osseous and cartilaginous differentiation is a rare condition. Punctate calcification in the pleural mass as a lesion distinct from the pleural plaque may indicate osseous or osteosarcomatous differentiation in malignant mesothelioma.

Key Words: malignant pleural mesothelioma, osseous differentiation, cartilaginous differentiation, computed tomography, calcification

(*J Thorac Imaging* 2011;26:W30–W32)

Malignant pleural mesothelioma is a rare primary tumor of the pleura. It is macroscopically classified as localized or diffuse type, and histologically divided into epithelioid, sarcomatoid, desmoplastic, and biphasic types according to the World Health Organization Classification of Tumours, 2004.[1]

Osseous and/or cartilaginous differentiation is an extremely rare presentation in malignant mesothelioma. Osteosarcomatous lesions that appear as dense, punctate calcified foci on computed tomography (CT) scans are rarer still, and only a few cases have been reported.[2–5] Here, we report a case of malignant pleural mesothelioma with osseous and cartilaginous differentiation, in which dense, punctate calcifications were observed on CT scanning.

CASE REPORT

A 69-year-old man who had no significant past medical history was admitted to the department of thoracic surgery. Five months before admission, the patient was asymptomatic but had an abnormal chest radiograph. Results from a subsequent CT scan and thoracoscopic biopsy suggested the diagnosis of malignant mesothelioma. The patient was a building contractor and had been exposed to asbestos for 48 years. There were no significant findings on physical examination. Findings from laboratory tests and tumor markers, including carcinoembryonic antigen, cytokeratin fragment, cancer antigen 19-9, and pro-gastrin-releasing peptide, were within normal range; however, levels of neuron-specific enolase and squamous cell carcinoma antigen were slightly elevated.

Chest x-ray revealed an approximately 10-cm mass with clear margins in the right middle hemithorax and a smaller caudal mass (Fig. 1). In addition, right-sided pleural thickening was observed. CT scanning revealed masses contiguous with the right pleura, and dense, calcified foci were detected in the main tumor (Fig. 2). The calcifications were punctate and uniform (largest diameter, 5 mm) and were diffusely scattered throughout the tumor. Linear calcification also appeared in the pleural plaque. In the lung window setting, the right lung parenchyma was compressed by the pleural tumors, but no tumors were observed within the right lung parenchyma or the left hemithorax. There was no evidence of pulmonary fibrosis.

Right pleuropneumonectomy was performed with chest wall resection. Macroscopic examination revealed multiple nodules and tumors, which arose from the parietal pleura. The largest tumor, which was yellowish white and 9 cm in diameter with clear margins, compressed the right lung adjacent to the tumor (Fig. 3A). Calcifications could be palpated in the tumor and pleura.

Histologic examination revealed a solid growth pattern with oval-to-elongated spindle cells (Fig. 3B). Osteosarcomatous components were scattered in the tumor nests (Fig. 3C), and focal chondrosarcomatous components were observed. Although the tumor invaded the lung parenchyma, most of the tumor grew in the parietal and visceral pleurae. Immunohistochemical examination revealed atypical spindle cells that expressed positive mesothelioma

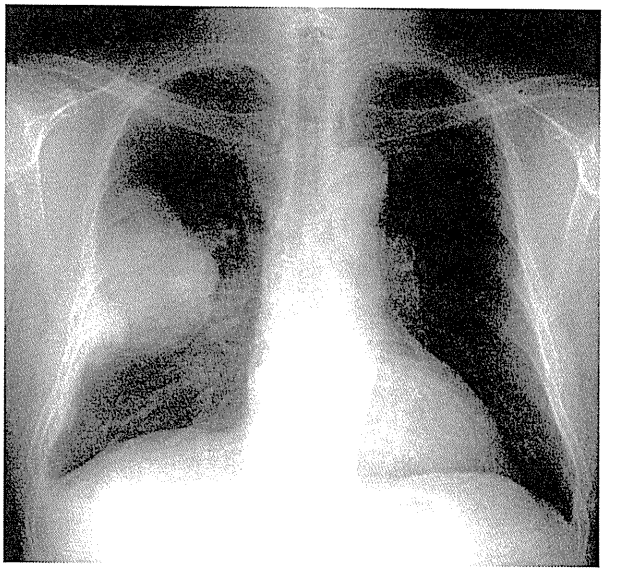

FIGURE 1. Chest radiograph showing well-defined tumor masses in the right hemithorax.

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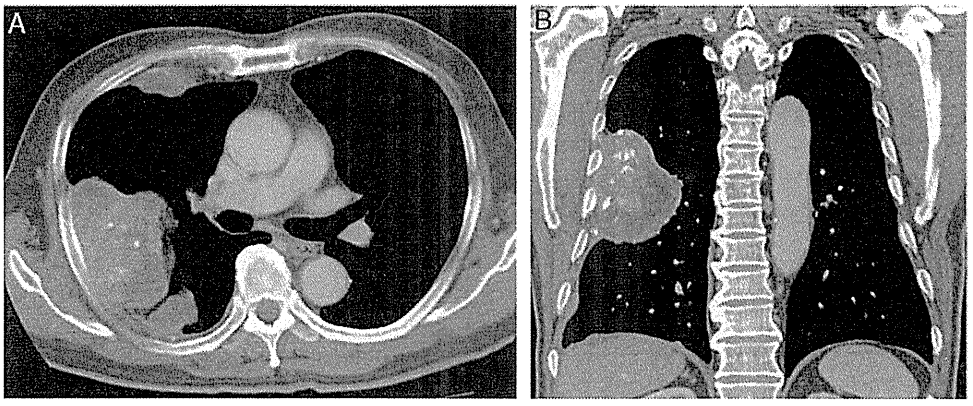

FIGURE 2. A, Axial contrast-enhanced CT scan of the thorax showing masses in the right pleura. Punctate calcifications were detected in the main tumor. B, Coronal reformatted image clearly shows that the tumor arises from the pleura.

markers (calretinin, podoplanin, and Wilms tumor-1), but did not express negative mesothelioma markers (carcinoembryonic antigen, thyroid transcription factor-1, and Ber-Ep4). Asbestos bodies were detected in the lung parenchyma. On the basis of these findings, we diagnosed malignant pleural sarcomatoid mesothelioma with osseous and cartilaginous differentiation.

The patient developed both local recurrence and metastasis and died 19 months after surgery.

DISCUSSION

Malignant pleural mesothelioma is a rarely encountered, high-grade malignant primary tumor. Cases among men have declined in the United States[6]; however, the incidence is increasing in Japan.[7] Development of osseous or cartilaginous differentiation in malignant mesothelioma is very rare, and Goldstein first reported 2 cases in 1979.[8] He suggested that the pluripotentiality of coelomic mesothelium may be the cause of its differentiation toward bone and cartilage, and also proposed the following alternative hypotheses: (1) the cartilage and bone, developed separately from the neoplasm, could be caused by previous tuberculous pleurisy; (2) the mesothelioma might have produced a substance that promoted cartilage and bone formation, directly or by stimulating the parathyroid glands; (3) the cartilage and bone might be integral components of the neoplasm and in parts the spindle cells might be merging or transforming into the cartilage; (4) 2 separate neoplasms may have been present, a mesothelioma with classical tubular formation and a fibrochondrosarcoma; and (5) asbestotic pleural plaques often undergo calcification.

Bolen et al[9] demonstrated the process by which subserous connective tissue cells obtained epithelial characteristics. They suggested that the pathogenesis is caused by the multipotency of mesothelial cells, using the term multipotential subserosal cells, which supports the hypothesis of pluripotent coelomic mesothelium proposed by Goldstein.[8] Yousem and Hochholzer[10] also favored this hypothesis. Our case supports this hypothesis, as there was no evidence of tuberculosis infection or other primary

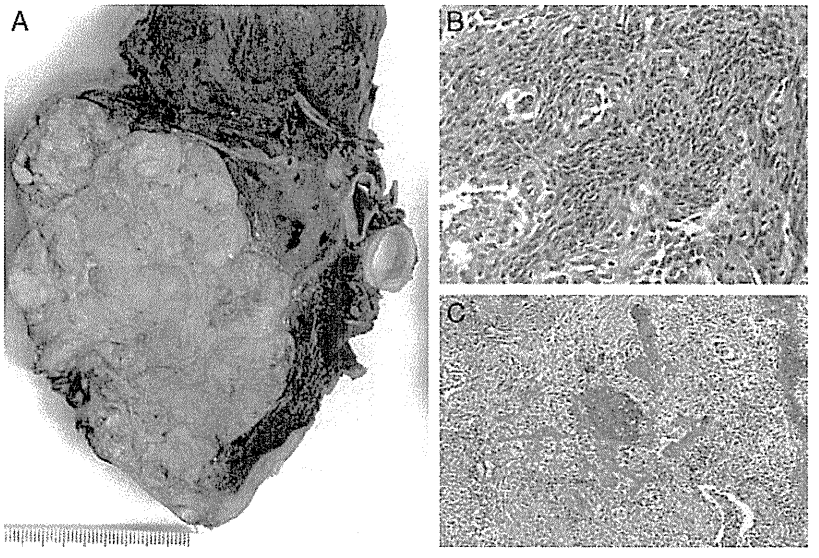

FIGURE 3. A, The cut surface of the largest tumor. The tumor has a diameter of 9 cm, is composed of yellowish white nodules with focal ossification, and is compressing the right lower lobe of the lung. B, Sarcomatoid mesothelioma shows oval-to-elongated spindle cells. C, Irregular-shaped osteoid components with calcium deposition are observed in the nests.

tumors and the osseous lesion was not colocalized with asbestos plaque. However, the possibility of parathyroid hormone influence cannot be excluded.

Of the 2 cases reported by Goldstein,[8] one case showed osteosarcomatous differentiation, and the other showed bone and cartilage differentiation. Sonja et al[11] summarized 27 cases of malignant mesothelioma with heterologous elements. In their report, they suggested that the term "heterologous" should be reserved for tumors that show malignant heterologous elements, such as osteosarcomatous, chondrosarcomatous, or rhabdomyoblastic elements. Pathologically, the differential diagnosis of these cases includes a primary or secondary pleural sarcoma. They concluded that mesothelioma cannot be excluded if cytokeratin staining is negative and should be diagnosed by anatomic distribution. The prognosis after diagnosis of mesothelioma with heterologous elements is similar to that associated with pleural mesothelioma of the sarcomatoid type; survival is approximately 6 months. Our case included heterologous elements such as osteosarcomatous and chondrosarcomatous differentiation.

Several reports have described imaging findings of pleural mesothelioma, but only 3 reports mentioned tumor calcifications detected by CT scanning.[2–5] Arnold et al[2] reported 2 cases of diffuse malignant mesothelioma that presented with large and dense calcified pleural masses, which were visualized on CT scan. In this report, it was described that the diagnosis of osteocartilaginous differentiation in diffuse malignant mesothelioma was based on the past history of asbestosis exposure, the typical radiographic appearance of encasing pleural tumor, the histopathologic features of malignant mesothelioma, and the absence of any osteogenic sarcoma or chondrosarcoma elsewhere. In this case, large calcification inside the main tumor was not seen, but punctate calcification was evident on CT scanning. Calcification of benign pleural plaque and osseous differentiation in mesothelioma could be distinguished by their shape and location. Calcification of benign pleural plaque is linear and is located on thickened pleural plaque, whereas osseous differentiation in mesothelioma is punctate or large and is located inside the tumor. The radiologic differential diagnoses of malignant pleural tumor with calcification include lung cancer with pleural dissemination, sarcoma derived from pleura, and metastatic lung or pleural tumor, such as colorectal cancer, osteosarcoma, and chondrosarcoma.

In conclusion, we report a case of malignant mesothelioma with osseous and cartilaginous differentiation. The punctate calcifications in the pleural tumor, distinct from the pleural plaque, may indicate osseous or osteosarcomatous differentiation in malignant mesothelioma.

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Recommendations for Uniform Definitions of Surgical Techniques for Malignant Pleural Mesothelioma

A Consensus Report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group

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Introduction: Extrapleural pneumonectomy has been well defined; however, surgeons vary regarding the surgical extent and goals of "pleurectomy/decortication" (P/D). We explored mesothelioma surgeons' concepts of P/D with the aim of unifying surgical nomenclature.

Methods: A web-based survey was administered to surgeons who operated on malignant pleural mesothelioma (MPM) for diagnosis, staging, palliation, or cytoreduction. One hundred thirty surgeons from 59 medical centers were included. Surgeons who did not perform surgery for MPM within the last year were excluded.

Results: There were 62 (48%) respondents from 39 medical centers in 14 countries. The mean number of patients with MPM seen annually at each medical center was 46, and the mean annual number of cytoreductive procedures performed per surgeon was 8. Most (88%) agreed that the goal of cytoreductive surgery should be macroscopic complete resection of tumor. P/D was defined as resection of parietal and visceral pleura with the aim of achieving macroscopic complete resection by 72% of respondents. If the diaphragm or pericardium required resection, 64% preferred the term "radical P/D," whereas "P/D" (40%) or "total pleurectomy" (39%) was preferred if these structures were not removed. Most surgeons believed that extrapleural pneumonectomy (90%) or "radical P/D" (68%) could provide adequate cytoreduction, whereas only 23% thought that P/D could.

Conclusions: There was significant variation regarding surgical nomenclature for procedures for MPM. The International Staging Committee of the International Association for the Study of Lung Cancer and the International Mesothelioma Interest Group recommend that P/D should aim to remove all macroscopic tumor involving the parietal and visceral pleura and should be termed "extended" P/D when the diaphragm or pericardium is resected.

Key Words: Mesothelioma, Pleural neoplasm, nomenclature, Surgery.

(*J Thorac Oncol.* 2011;6: 1304–1312)

Surgery for malignant pleural mesothelioma (MPM) may include relatively minor procedures for diagnosis and staging, more involved debulking operations for palliation, and extensive cytoreductive procedures where the goal is to lengthen survival by reducing the intrathoracic tumor burden to microscopic levels. The latter is usually accomplished either by extrapleural pneumonectomy (EPP) or by a procedure that is presently classified as "pleurectomy/decortication" (P/D), generally as part of a multimodality treatment regimen. Although the surgical technique of EPP has been standardized, there is a variation among surgeons with respect to what is involved in P/D.[1–5] For some mesothelioma surgeons, P/D refers to a surgical procedure that aims to remove all macroscopic tumor from the affected hemithorax.[6] This typically includes resection of the entire parietal and

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Disclosure: The authors declare no conflicts of interest.

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visceral pleura, with resection of portions of the pericardium and diaphragm if involved by tumor. Others refer to this extensive procedure as a "radical" P/D, reserving the term P/D for resection of only the parietal and visceral pleura.[7,8] Still others use the term P/D to describe a palliative procedure where the intention is debulking of tumor to ameliorate pain and pleural effusion and improve respiratory mechanics.[9] Occasionally, operative reports will describe P/D when little more than a thoracotomy and generous pleural biopsy has been performed.

In collaboration with the International Mesothelioma Interest Group (IMIG), the International Association for the Study of Lung Cancer (IASLC) recently formed a subcommittee of the International Staging Committee to improve the current staging system for MPM. The mesothelioma subcommittee "Mesothelioma Domain" of the International Staging Committee recently completed an analysis of a large retrospective database and is now developing an international, multidisciplinary, and multi-institutional cohort study that will collect information on extent of disease, personal and demographic characteristics, comorbid illness, treatment, and survival of newly diagnosed patients with MPM. Because there is considerable variation regarding the surgical management of mesothelioma, and in particular P/D, the mesothelioma subcommittee thought that it was important to arrive at definitions of surgical procedures for MPM that would be unambiguous and broadly acceptable to most thoracic surgeons. To arrive at a consensus regarding surgical definitions, a survey was conducted among surgeons who perform surgery for MPM.

METHODS

A web-based questionnaire was created by members of the IASLC mesothelioma subcommittee using a commercially available, online survey designer (www.surveymonkey.com). Unlike a recent survey of surgical opinion in mesothelioma, which included thoracic surgeons regardless of their level of experience with the disease, we polled only surgeons who had a clinical or research interest in MPM and who were presumed able to offer expert opinion.[10,11] Surgeons were identified by having published on MPM during the past 5 years, by affiliation with a medical center known to specialize in MPM, by affiliation with the IMIG, or by peer reference. One hundred thirty surgeons from 59 centers worldwide were identified and asked to complete the electronic survey. The survey was designed to examine prevailing views about nomenclature for various surgical resections commonly performed for pleural mesothelioma and concepts regarding cytoreduction (Figures. 1–4). In addition to multiple-choice options, most questions also offered respondents an opportunity to add text-based comments. We explored opinions regarding use of the terms "partial pleurectomy," "pleurectomy/decortication," "total pleurectomy," and "radical pleurectomy/decortication." Because EPP has been standardized from a procedural standpoint, we did not further explore terminology for this operation. The survey collected data over a 3-week period from October 11 through October 29, 2010. Two reminders were sent electronically to participants during this period. Responses from thoracic surgeons who did not perform any type of surgery for MPM (including either surgery for diagnosis, staging, palliation, and/or cytoreduction) were censored from further analysis. Responses were analyzed according to the raw data, and results were reviewed with the members of the IASLC Mesothelioma Domain and the Advisory Board, and consensus achieved before the manuscript was prepared. It was then submitted to all members of the IASLC Staging Committee and to board members of the IMIG for approval before the manuscript and recommendations were finalized.

RESULTS

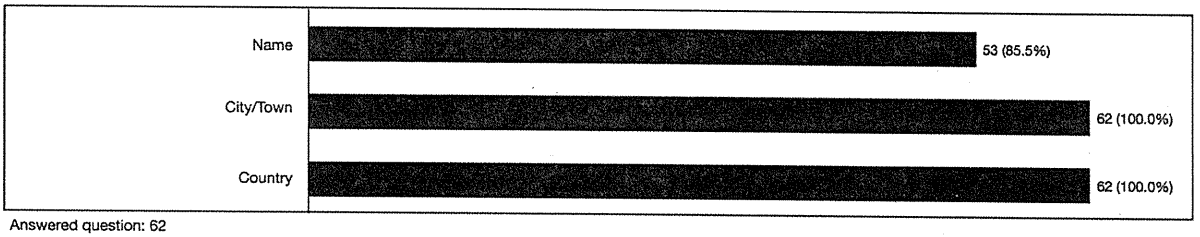
Respondents

The survey was sent through email to 130 thoracic surgeons, of which 62 (47.7%) responded. Respondents were affiliated with 39 different medical centers in 14 countries. Most were from centers in Europe (47%) or North America (42%) with only six (10%) responders from Asia and one from Australia (Table 1). Three participants did not perform any type of surgery for MPM and were censored from further analysis (Figure 1). One respondent provided incomplete data leaving a total of 58 respondents who provided analyzable data. The mean number of patients with MPM seen annually at participating centers was 40 (median, 32; range, 3–150), and the mean number of mesothelioma surgical cases annually performed by respondents ($n = 58$) was 20 (median, 16; range, 2–80). Ninety-eight percent of surgeons performed surgery for diagnosis, 82% for surgical staging, 85% performed cytoreductive surgery, and 71% performed surgery for palliation. Only 34 of 58 surgeons (59%) performed surgery for all four indications. Three (5%) surgeons performed palliative surgery but not cytoreductive surgery. Of surgeons who practiced cytoreductive surgery ($n = 49$), the mean number of cases performed within the 12-month period preceding the survey was 10.4 (range, 1–30).

Surgical Definitions

Most respondents (95%) felt that there was a need to refine surgical nomenclature to account for the procedural differences between P/D for palliation and P/D performed for macroscopic complete resection (MCR) or maximal cytoreduction (Figure 2). Thirty-nine of 58 (67%) respondents defined "partial pleurectomy" as a partial debulking of tumor for palliative purposes. Of these, 21 (36%) considered it to include resection of both parietal and visceral tumor, whereas the others considered it to include removal of only parietal tumor. Ten (17%) surgeons considered "partial pleurectomy" to be a subtotal removal of parietal and visceral tumor for palliation with the expectation of leaving gross residual disease behind, and another four (7%) defined the procedure as the removal of all gross parietal and visceral tumor with the intention of achieving an R0 or R1 resection without removal of the diaphragm or pericardium. Only three (5%) respondents felt that it should be defined as resection of parietal pleura for diagnostic purposes only. Forty-two of 58 (72%) respondents considered the term "P/D" to imply resection of all gross parietal and visceral tumor with the objective of achieving resection of all macroscopic disease. Of these, 18 (31%) considered the procedure to also include resection of the diaphragm and/or pericardium even if in-

Question 1. Please enter your name (optional), city and country:



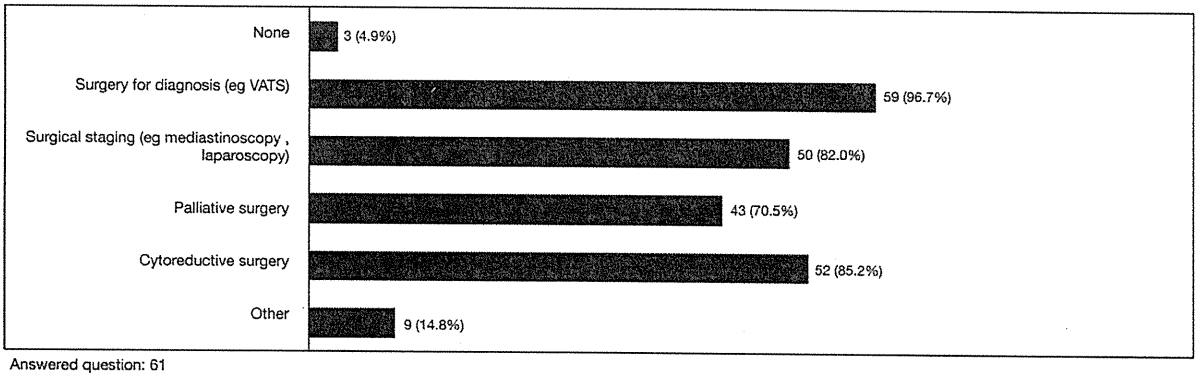
Answered question: 62
Skipped question: 0

Question 2. How many patients with malignant pleural mesothelioma were registered at your institution in the last 12 months?

Answer Options	Response Average	Response Total	Response Count
Number	40.4	2,381	60

Answered question: 62
Skipped question: 0

Question 3. I currently perform the following types of surgery for mesothelioma (answer all that apply):



Answered question: 61
Skipped question: 1

Question 4. How many patients with malignant pleural mesothelioma did you perform surgery on in the last 12 months (for diagnosis, staging, palliation or cytoreduction?

Answer Options	Response Average	Response Total	Response Count
Number	20.0	1,158	58

Answered question: 58
Skipped question: 4

Question 5. How many patients with malignant pleural mesothelioma did you perform cytoreductive surgery on in the last 12 months?

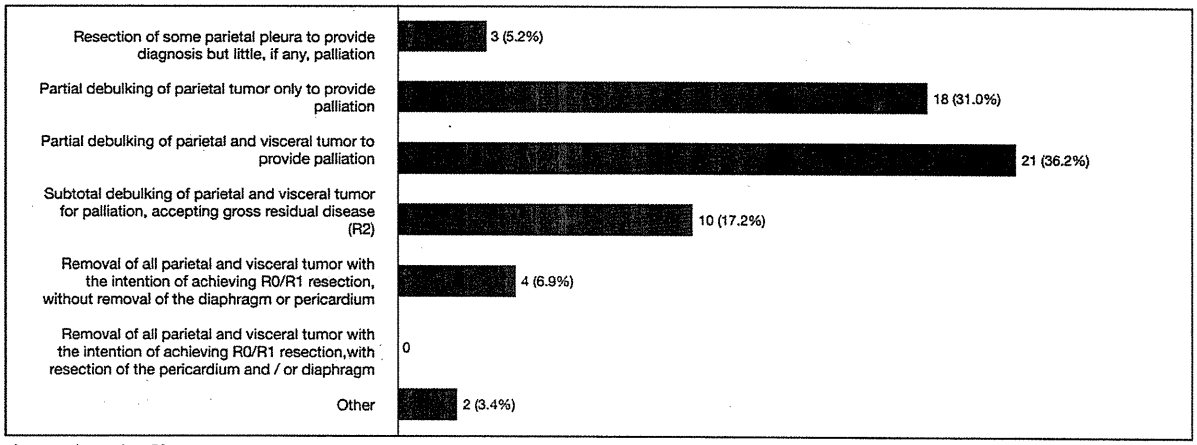
Answer Options	Response Average	Response Total	Response Count
Number	8.8	512	58

Answered question: 58
Skipped question: 0

FIGURE 1. Questions 1 to 5. Demographic and practice information of the respondents.

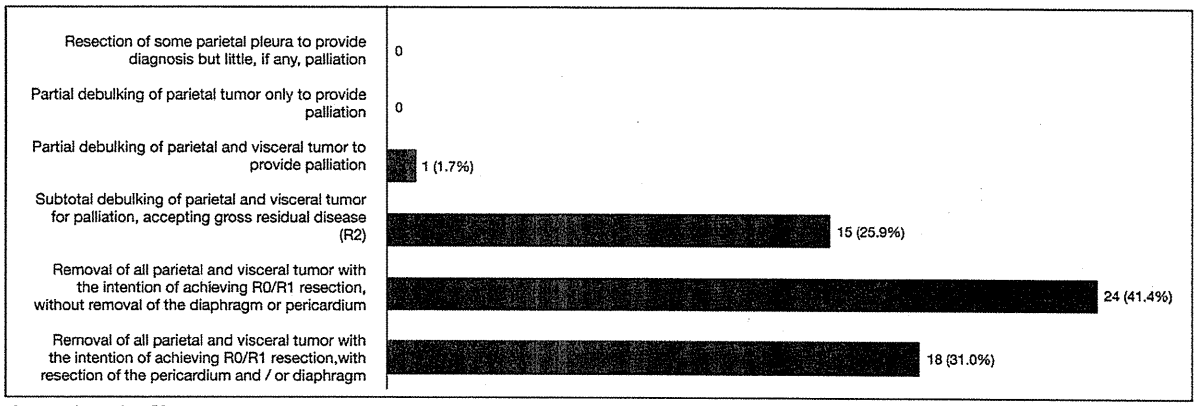
volved by tumor. Nevertheless, 15 (26%) surgeons considered "P/D" to be a subtotal removal of parietal and visceral tumor for palliation with the expectation of leaving gross residual disease behind (R2), and one (2%) respondent defined the procedure as a partial debulking of parietal and visceral tumor for palliation.

Question 6. In your opinion which of the following procedures would describe a 'partial pleurectomy' the best?



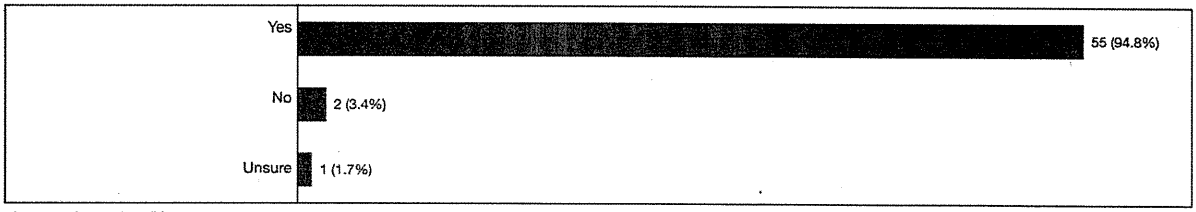
Answered question: 58
Skipped question: 0

Question 7. In your opinion which of the following procedures would describe a 'pleurectomy / decortication' the best?



Answered question: 58
Skipped question: 0

Question 8. Do you think there is a need to develop terminology that would differentiate between the extent of resection associated with pleurectomy/decortication for palliation versus complete macroscopic resection (cytoreduction)?

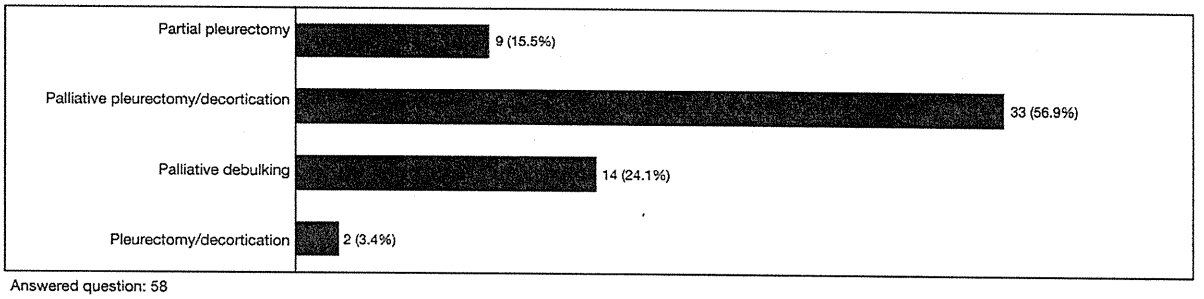


Answered question: 58
Skipped question: 0

FIGURE 2. Questions 6 to 8. Opinions regarding definition of partial pleurectomy and pleurectomy/decortication.

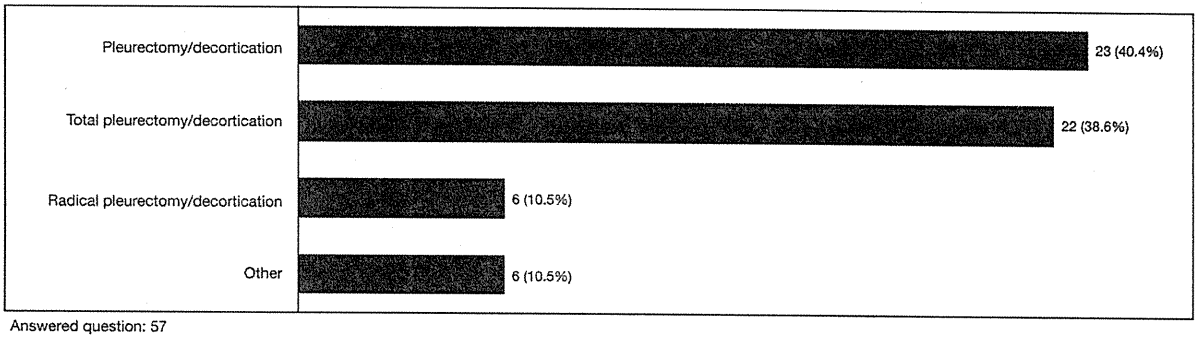
To further explore opinions regarding the extent of "P/D," two scenarios were provided where the intent was to resect parietal and visceral tumor so that no residual macroscopic tumor remained (Figure 3). In one scenario, the diaphragm and pericardium were resected, and in the other scenario they were not. With regard to the first (diaphragm and/or pericardial resection), the majority (64%) referred to the procedure as "radical P/D." Eleven (19%) surgeons preferred the term "total pleurectomy" and only three (5%) used "P/D." One surgeon considered this a "partial resection." To describe the second scenario (no diaphragm or pericardial resection), 23 (40%) chose the term "P/D," whereas 22 (39%) preferred "total pleurectomy." Only six (10.5%) surgeons called this procedure a

Question 9. In a patient who undergoes parietal and visceral pleural resection for palliative purposes only, without the intention of achieving complete macroscopic resection, which of the following terms do you think is most appropriate?



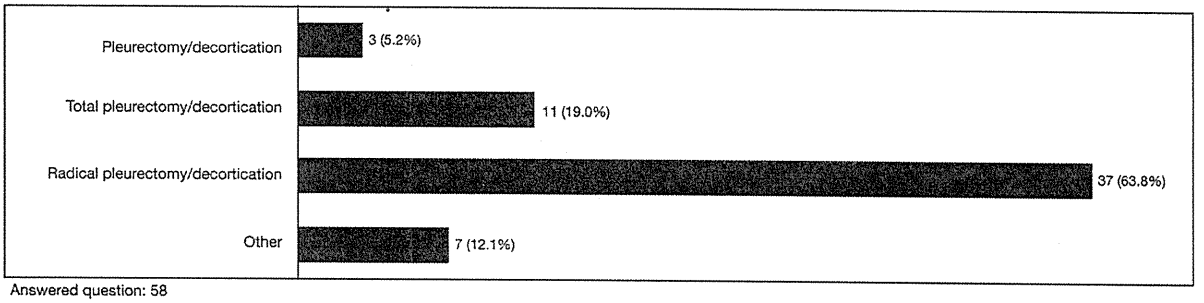
Answered question: 58
Skipped question: 0

Question 10. In a patient who undergoes parietal and visceral pleural resection (but not resection of the pericardium or diaphragm) with the intention of achieving macroscopic complete resection which of the following terms do you think is most appropriate?



Answered question: 57
Skipped question: 1

Question 11. In a patient who undergoes parietal and visceral pleural resection with the intention of achieving a macroscopic complete resection and the diaphragm and/or the pericardium is resected, which of the terms do you feel is most appropriate to use?



Answered question: 58
Skipped question: 0

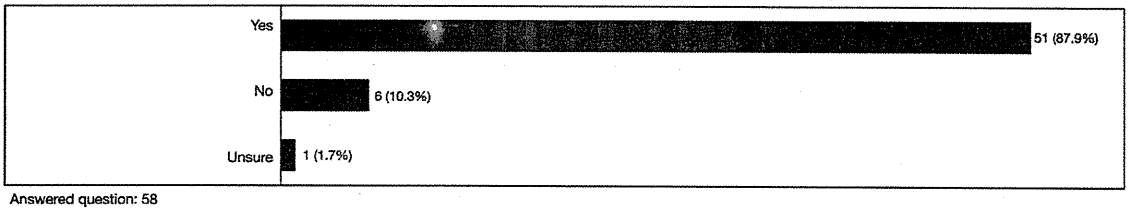
FIGURE 3. Questions 9 to 11. Opinions regarding the surgical extent of pleurectomy/decortication.

"radical P/D." Two (3.4%) respondents used the term "palliative debulking" and another two (3.4%) used "partial pleurectomy." One (1.7%) respondent preferred the term "subtotal P/D."

Cytoreduction

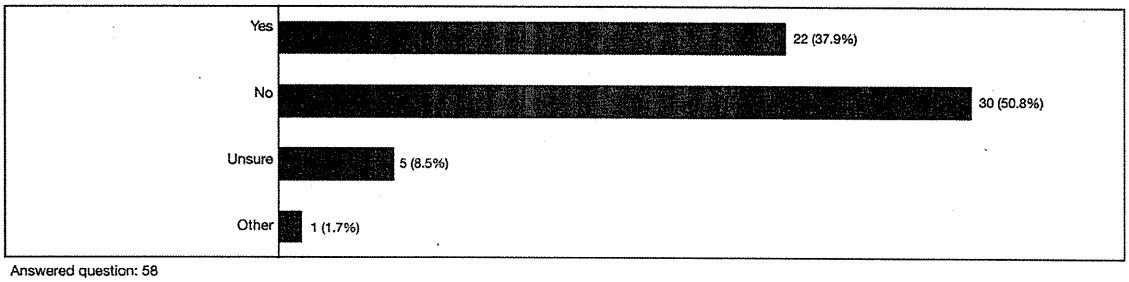
Fifty-one (88%) respondents agreed with the premise that the goal of cytoreductive surgery in MPM should be the removal of all visible or palpable tumor (R0 or R1) or a "macroscopic complete resection" (MCR) (Figure 4). When asked which cytoreductive procedure was capable of providing MCR, 51 (90%) chose EPP and 39 (68%) "radical P/D," but only 13 (23%) thought that "P/D" could. One of the factors that influence performance of P/D versus EPP is whether tumor involves the fissures. Twenty-two (38%) respondents agreed that P/D could usually provide a MCR if tumor involved the fissure, however, 30 (51%) did not. In addition, the majority of respondents (86%) did not believe that video-assisted thoracoscopic surgery was capable of providing as complete a cytoreduction as an open procedure. Nevertheless, three (5%) respondents did, and another agreed that it could in patients with stage I disease. The remaining four respondents were uncertain.

Question 12. The goal of cytoreductive surgery for malignant pleural mesothelioma should be the removal of all visual and palpable tumor, in other words, a macroscopic complete resection (R0/R1):



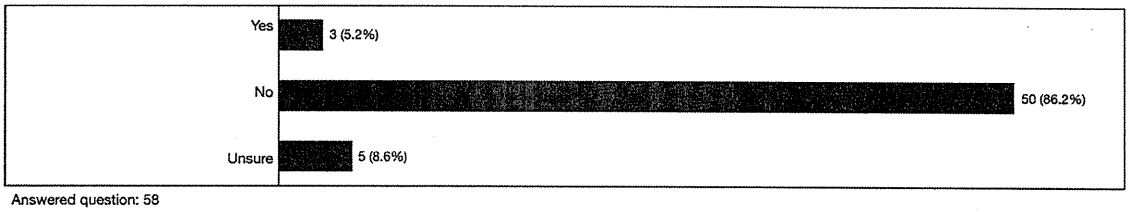
Answered question: 58
Skipped question: 0

Question 13. In a patient with tumor involving the fissure(s) pleurectomy / decortication can usually achieve macroscopic complete resection:



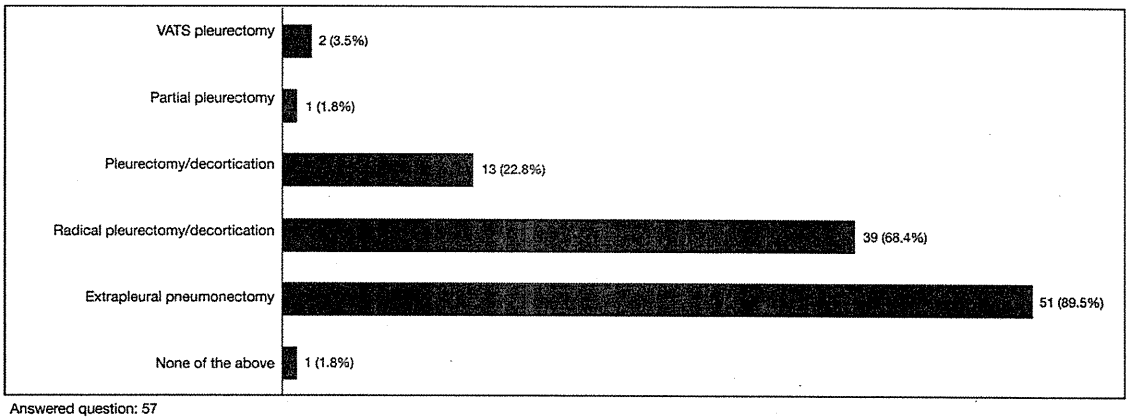
Answered question: 58
Skipped question: 0

Question 14. VATS pleurectomy / decortication can usually achieve as as good a tumor cytoreduction as open pleurectomy / decortication:



Answered question: 58
Skipped question: 0

Question 15. Which of the following procedures do you consider capable of providing adequate cytoreduction (R0/R1)?



Answered question: 57
Skipped question: 1

FIGURE 4. Questions 12 to 15. Opinions regarding surgical goals and technical ability to achieve macroscopic complete resection.

TABLE 1. Geographic Distribution of Physicians Who Responded to the Online Survey

Country	No. of Responses	Percentage
United States	23	37.1
United Kingdom	10	16.1
Japan	6	9.7
Italy	5	8.1
Spain	3	4.8
Canada	3	4.8
Turkey	2	3.2
Switzerland	2	3.2
Germany	2	3.2
Belgium	2	3.2
Greece	1	1.6
Australia	1	1.6
Netherlands	1	1.6
France	1	1.6

DISCUSSION

The first description of P/D is attributed to Fowler[12] who reported the successful treatment of a man with chronic empyema and bronchopleural fistula in 1893. Nevertheless, it was not until 20 years later when four patients successfully underwent P/D at the Mayo Clinic that the procedure began to gain popularity and gradually superceded thoracoplasty as the preferred method for the initial treatment for chronic empyema and trapped lung.[13] It is worth noting that "decortication" involved freeing of the fibrinous rind away from the visceral pleura and not resection of the visceral pleura itself. In the 1950s and 1960s, parietal pleurectomy was used for the treatment of spontaneous pneumothorax,[14,15] and in 1963, Jensik et al.[16] at the University of Chicago reported the use of parietal pleurectomy for treatment of malignant pleural effusions, showing a 96% freedom from recurrence in 50 patients. As meticulously described by Beattie,[17] parietal pleurectomy began with creation of an extrapleural plane before insertion of a rib spreader, with continued dissection "up over the apex of the thoracic cavity, and down to and around the lung hilum." Once the upper half of the parietal pleura had been freed, it was excised, and the lower half then dissected down to the costophrenic sulcus. It was noted that it was usually impossible to remove the diaphragmatic pleura which was left attached to the intact diaphragm.

The first report of pleural resection for MPM was by Martini et al.[18] in 1975 who described outcomes of parietal pleurectomy in 83 patients with malignant pleural effusions, of which 14 had mesothelioma. At 1 year, 79% of patients were noted to have been alive, with little or no clinical limitation in pulmonary reserve, and the median survival of those with MPM was 16 months. A year later, this series was expanded to include 33 patients with MPM who had a median survival of 21 months. It should be noted that in these early descriptions of pleurectomy for mesothelioma "all pleura covering the rib cage and mediastinum (was) removed," but attempts were not made to remove the visceral pleura or resection of the diaphragm or pericardium.[19] The operation became referred to as "subtotal parietal pleurectomy" as neither the visceral, diaphragmatic nor pericardial pleurae were removed.[20]

Coincidentally, EPP (also termed pleuropneumonectomy) for MPM began to be performed, its proponents arguing that pleurectomy could not possibly achieve the same degree of tumor clearance as EPP, largely because with pleurectomy tumor frequently remained on the diaphragm, pericardium, and the visceral surfaces and fissures of the lung.[21,22] Perhaps in response to this challenge, pleurectomy evolved in some surgeons' hands into a more extensive procedure than had been described previously. In 1989, Rusch and Livingston[23,24] described "radical decortication" in conjunction with intrapleural chemotherapy and, in the article that followed, P/D was defined as parietal pleurectomy with either partial or complete visceral pleurectomy according to the extent of tumor involvement. The diaphragm and/or pericardium were frequently resected and reconstructed but with preservation of the underlying peritoneum. Variations on this theme have been reported by others, the common thread being resection of tumor involved parietal and visceral pleurae.[25] In one of the larger and more recent series, Richards et al.[4] from the Brigham and Women's Hospital described P/D as resection of the parietal and visceral pleurae along with involved areas of the pericardium and diaphragm. As described by others, the intended goal was to obtain a MCR, arbitrarily defined as tumor residual less than 1.0 cm.[3,5,26] The clear intent of these cytoreductive procedures is to resect all gross tumor while preserving underlying lung parenchyma. This has not gained unanimous acceptance however. For example, Butchart[9] has referred to P/D as "debulking" surgery which did not include resection of the diaphragm. The term P/D is still frequently applied to procedures that remove some parietal and visceral pleural tumor and yet which are strictly palliative in intent leaving behind considerable amounts of gross tumor. Perhaps, this is why in an effort to differentiate the more intensive cytoreductive procedure from less extensive ones several authors have recently applied the qualifier "radical" when referring to a maximally cytoreductive P/D.[7,8] Thus, 35 years after the initial description, there remains some ambiguity regarding the definition of P/D for MPM.

The overall response rate to our survey was less than 50% but is on a par with response rates of other recent web-based surgical surveys. The thoracic surgeons who completed the survey were experienced in MPM surgery—performing what would be considered a high volume of operations for this rare disease. Respondents were primarily from North America and Europe, so it can be argued that the findings may be biased toward Western practice, but this primarily reflects the incidence of MPM and the geographic location of centers involved in surgical and multimodality treatment for MPM. The survey confirmed significant variation among thoracic surgeons regarding the definition of P/D. When pleural resection was performed for palliative purposes, most respondents did not refer to the procedure as "P/D" but rather used terms such as partial pleurectomy, palliative debulking, or palliative P/D. Thus, based on the

findings of the survey, P/D seems to imply a level of completeness or thoroughness of tumor resection that did not apply to debulking or palliative procedures. Nevertheless, when the diaphragm or pericardium had to be resected to achieve MCR, most surgeons (64%) favored the term "radical" P/D.

Finally, we explored the opinion regarding completeness of resection achievable with surgery for mesothelioma. The majority of surgeons polled believed that MCR should be the goal of cytoreductive surgery, regardless of whether that involves EPP or a lung-preserving operation. This is certainly in line with the current surgical philosophy of high-volume centers.[3,5,26] Furthermore, most agreed that either "radical P/D" or EPP could provide MCR in appropriately selected patients, but most responders did not consider that P/D (without diaphragm or pericardial resection) could do so. Nevertheless, this clearly depends on the extent of the disease.

RECOMMENDATION

On the basis of the survey data, which represented the opinions of experienced MPM surgeons from multiple centers in different geographical regions, the IASLC Mesothelioma Domain and the IMIG have recommended the following terminology to be used in the forthcoming Mesothelioma Staging Project:

a. EPP: en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm. In cases where the pericardium and/or diaphragm are not involved by tumor, these structures may be left intact.
b. Extended P/D: parietal and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or pericardium. The IASLC Mesothelioma Domain suggests use of the term "extended" rather than "radical" in this instance as the latter implies a completeness of resection with added therapeutic benefit. There is currently insufficient evidence that resection of the pericardium and diaphragm provides either.
c. P/D: parietal and visceral pleurectomy to remove all gross tumor without diaphragm or pericardial resection.
d. Partial pleurectomy: partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumor behind.

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Cytological Characteristics of Pulmonary Pleomorphic and Giant Cell Carcinomas

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

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

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

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

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

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

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

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

Materials and Methods

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

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

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

Results

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

Clinical Findings and Clinical Courses

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

Cytological Findings

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

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

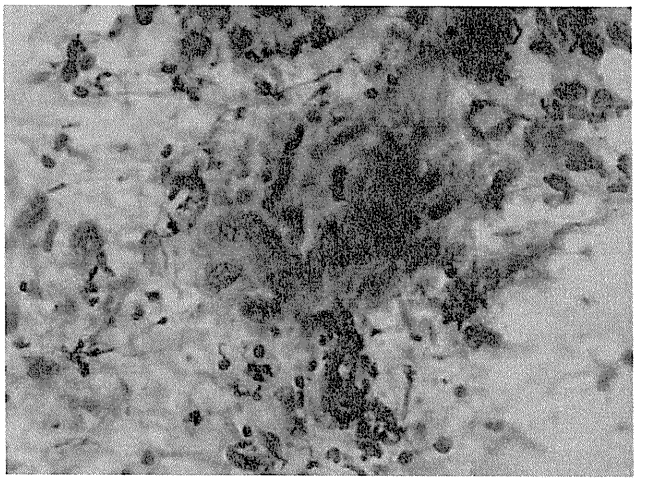

Fig. 1. Touch imprint cytology of the resected tumor from case 10. Pleomorphic spindle cells were observed in a necrotic background. Papanicolaou stain, ×40.

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

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

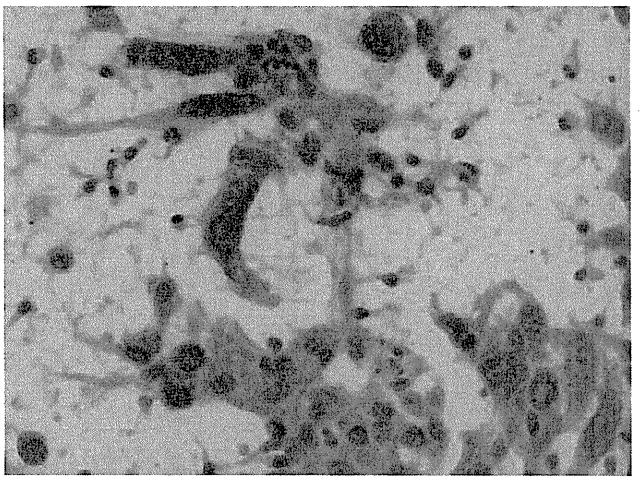

Fig. 2. Transbronchial brushing cytology of case 9. Pleomorphic spindle cells were arranged in loose clusters. Papanicolaou stain, ×40.

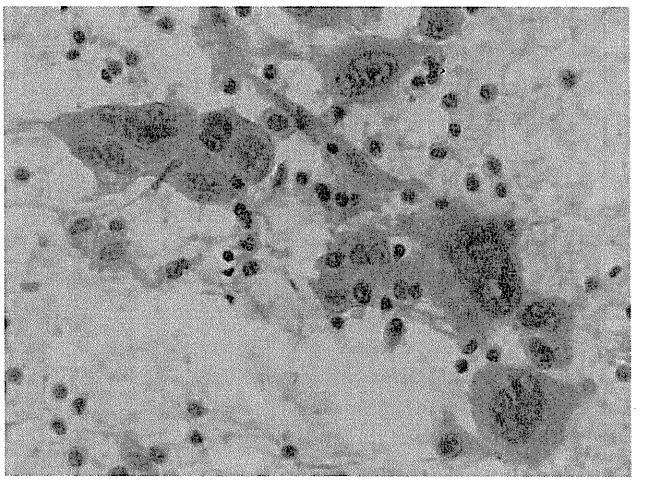

Fig. 3. Multinucleated cells were arranged in loose clusters in a background of lymphocytes (case 1). Papanicolaou stain, ×40.

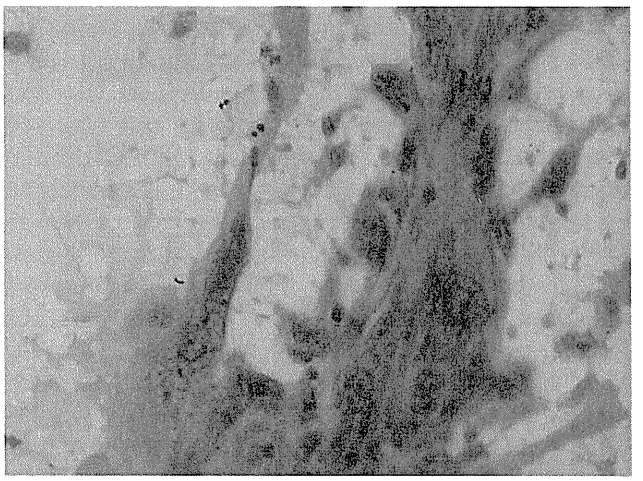

Fig. 4. Transbronchial brushing cytology of case 9. Pleomorphic spindle cells were arranged in fascicles. Papanicolaou stain, ×40.

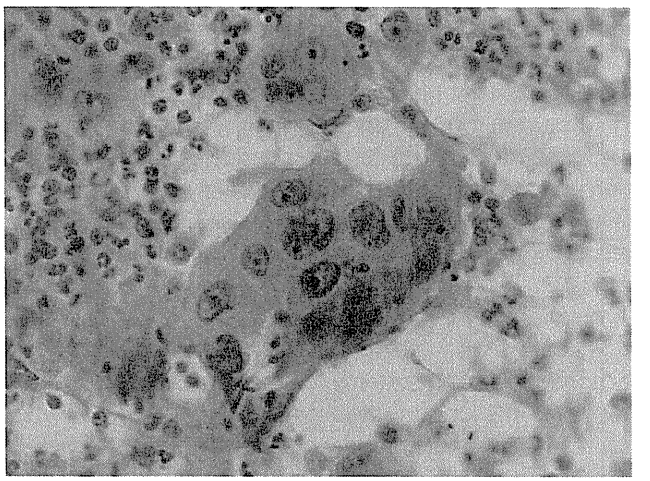

Fig. 5. Cohesive clusters of atypical epithelial cells were observed in a background of neutrophils (case 2). Papanicolaou stain, ×40.

Discussion

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