

## Malignant pleural mesothelioma in the Southwestern part of The Netherlands

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**ABSTRACT:** This report is the result of an analysis of the medical records of 124 patients presenting with a malignant pleural mesothelioma. Information about asbestos exposure was available in 104 of them, which appeared to be positive in 95 (91%). The median duration of exposure was 34 yrs. The median latent period was 41 yrs. The median survival was 11 months while different ways of treatment could not prolong survival. The most common radiologic findings were pleural effusions, while in some patients contralateral effusions or pleural thickening was found. Pleural plaques or asbestosis were seen in a minority of the patients. In this series a relatively high percentage of mixed type mesotheliomas was found (56%). Large biopsies will often show both epithelial and connective tissue type elements. Concerning diagnostic procedures we recommend beginning with cytology of pleural fluid, which can easily be obtained together with an Abrams biopsy. If this does not give a definite diagnosis thoracoscopy or thoracotomy will be indicated.

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Many studies have confirmed the relationship between asbestos exposure and the occurrence of malignant mesothelioma [1, 2]. It is now clear that exposure to asbestos may lead to a number of pathologic conditions, including benign abnormalities [3, 4] and involvement of sites other than lung or pleura. A long latency period of up to sixty years between the first exposure to asbestos and the development of a malignant mesothelioma has been described. Incidence rates for pleural mesothelioma among men are increasing [5-7]. The substantial increase of the frequency of pleural mesothelioma among males *versus* the stable trend for females argues against any large impact due to diagnostic or coding changes [8].

Many shipyard workers have been exposed to asbestos in the past (mainly crocidolite) with a consequent increased frequency of malignant mesothelioma. In many coastal regions incidences of mesothelioma are found which are among the worlds highest [9]. This is also true for The Netherlands where two studies have already reported an increased incidence in the Southwestern part of The Netherlands [10, 11]. The study reported here is an analysis of 124 pleural mesotheliomas in the area of Vlissingen and Rotterdam, both known for their large shipbuilding industries.

### Methods

This study is an analysis of 124 patients presenting with malignant pleural mesothelioma. The patients were

seen in two centres. About half of them (71) were seen in the University Hospital in Rotterdam, while the other patients (53) were diagnosed in the Regional Hospital in Vlissingen. These 124 patients probably form about 80-90% of all patients with a malignant mesothelioma in the Southwestern part of The Netherlands.

All mesotheliomas were diagnosed between 1962 and 1985. For the histopathological diagnosis of mesothelioma the recommendations of the Commission of the European Communities were applied [12]. Re-evaluation of all histologic specimens was done by the Dutch Mesothelioma Panel. For certainty of diagnosis the following categories were used.

- a) Definite malignant mesothelioma: no doubt as to the histopathological diagnosis.
  - b) Probable malignant mesothelioma: the reason for the hesitation may be lack of material, poor quality, lack of differentiation, absence of certain histological details.
  - c) Possible malignant mesothelioma: the diagnosis cannot be denied but there is insufficient evidence to come to a positive conclusion.
  - d) Improbable malignant mesothelioma: probably not a mesothelioma but the diagnosis cannot be absolutely denied.
  - e) Definitely not malignant mesothelioma.
- In categories (d) and (e) another diagnosis should be suggested or made. Only the histopathologic categories (a) and (b) were included in the study. The analysis includes, clinical, diagnostic and histologic aspects.

## Results

The study group consisted of 120 men (97%) and 4 women (3%). Sixty nine (56%) mesotheliomas arose on the right side of the thorax, 51 (41%) on the left side, while three (2%) mesotheliomas were bilateral. One patient had simultaneous primary pleural and peritoneal mesothelioma. The median age of the patients at the time of diagnosis was 65 yrs (range 26–86 yrs). Almost 80% (87 out of 112) had ages between 50–75 yrs.

No occupational information was available in twenty patients. Of the other 104 many had been working in a shipyard for at least several years (62 out of 104; 60%). In 95 patients (91%) a positive history of occupational asbestos exposure was found. The median duration of asbestos exposure was 34 yrs (range 1–52 yrs). The latent period, defined as the interval between the beginning of exposure and the occurrence of the first symptoms, also showed a wide range. The median latent period was 41 yrs (range 17–68 yrs).

The histopathologic diagnosis was known in all subjects. The mixed type was the most prevalent mesothelioma found in 68 out of 124 patients (55%). In 40 (32%) patients there was a mesothelioma of the epithelial type, while in 16 (13%) it was of the connective tissue type. In 102 cases the diagnosis was entitled as "definite" whereas the other 22 were "probable".

The most frequent presenting symptoms were dyspnoea (81%), chest pain (73%) and weight loss (66%). Cough was found in 53% of the patients. Superior vena cava occlusion syndrome was one of the presenting symptoms in six cases. In 5 patients (4%) there were palpable lymph nodes on presentation. Swallowing complaints were found in 4 patients (3%).

The radiological findings are reported in table 1. Ipsilateral pleural effusion and pleural thickening were found most frequently.

The diagnostic procedures used are shown in table 2. Compared to aspiration of pleural fluid and Abrams biopsy, thoracoscopy and thoracotomy were carried out less often, but they gave positive findings in a high percentage (87% and 91%, respectively).

Therapy mainly consisted of symptomatic treatment. Recurrent pleural effusions were terminated by drainage. In a number of patients radiotherapy, chemotherapy, surgery or immunotherapy (interferon) were tried.

Table 1. – Radiographic findings in 124 patients with malignant pleural mesothelioma on presentation

	n	%
Pleural effusion		
ipsilateral	109	88
contralateral	6	5
Pleural thickening		
ipsilateral	95	77
contralateral	19	15
Pleural plaques		
ipsilateral	10	8
contralateral	8	6
Extensive contraction of the chest	17	14
Rib destruction	18	15
Asbestosis	2	2

No significant effect on survival could be obtained. Fourteen patients (11%) did not receive any treatment at all. The average survival was  $16.5 \pm 13$  months (median 11 months). Only five patients were alive 5 yrs after the diagnosis was made. Figure 1 shows the survival percentages. The 1-yr survival is less than 50% (47%).

Table 2. – Diagnostic techniques

Technique performed	n	Positive
Pleural fluid cytology	105	63 (60%)
Abrams biopsy	85	58 (68%)
Thoracoscopy	45	39 (87%)
Thoracotomy	21	19 (91%)
Bronchoscopy	3	0 (0%)

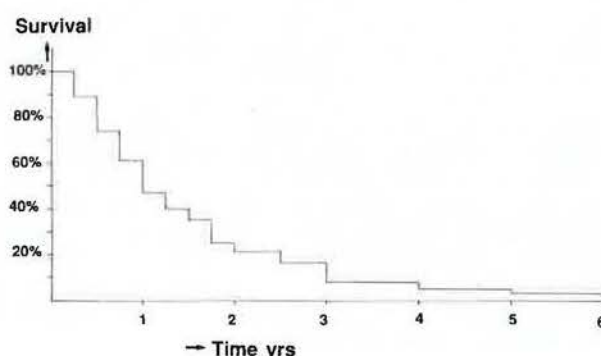


Fig. 1. – Survival time of 124 patients with malignant mesothelioma.

Table 3. – Autopsy-findings of 28 subjects with mesothelioma

Site of Metastases	Examined n	Positive
Diaphragm	26	22 (85%)
Pericardium	24	17 (65%)
Liver	25	15 (60%)
Thoracic lymph nodes	24	13 (54%)
Abdominal lymph nodes	26	10 (38%)
Kidneys	25	7 (28%)
Spine	23	4 (17%)
Brain	25	1 (4%)
Other	24	11 (46%)

Non-narcotic analgesics were able to relieve the pain in 63 patients (of the 98 patients given non-narcotic analgesics). When, however, in a later stage pain became more severe, opiates had to be given in 49 patients. In one patient chordotomy was performed while epidural anaesthesia was given in another patient, both with good results. Eight patients had pain relief after local radiotherapy.

The autopsy findings in 28 patients were available and are listed in table 3. Metastases in the liver (60%) and abdominal lymph nodes (38%) were found most frequently.

## Discussion

In this study we analysed the clinical, diagnostic and histologic findings in 124 patients with malignant pleural mesothelioma. The incidence in men is usually several times that in women [13] as is demonstrated in this study. Malignant pleural mesothelioma usually affects people between 45–75 yrs [14]. The median age of our subjects at the time of diagnosis was 65 yrs, while 87 patients (78%) were between 50–75 yrs of age. The duration of the asbestos exposure could be calculated from the occupational files of most patients. The median exposure was 34 yrs (range 1–52 yrs). The latent period was at least 17 yrs (median 41 yrs), which is in the same range as in other studies [15]. The survival from the time of the first symptoms to death was short (median 11 months). Although some authors have found different survival times for the various cellular subtypes we did not find a significant difference [16].

In 68 patients (55%) pleural mesotheliomas with a histopathologic diagnosis of mixed type were found. Compared to other series this is rather high. The histopathologic diagnosis of mesothelioma is a difficult one. A strong inter-observer variability is a well-known phenomenon [17, 18]. There is a considerable risk of misdiagnosing mesothelioma as pulmonary adenocarcinoma if only a small biopsy is examined. Furthermore, in investigating only small portions of tumour, there is considerable risk of missing one component. When large portions of tumour tissue are investigated, the chances of finding both epithelial and connective tissue components are high. Several phenotypic markers have been studied for their efficacy in the differentiation of mesothelioma from other (metastatic) malignancies, but they are still of only complementary importance [19]. We believe that an adequate histopathologic classification can only be reached by examination of a large biopsy, performed by an experienced pathologist. The material should be searched intensively for malignant elements of both epithelial and connective tissue character. Then higher numbers of mixed type mesothelioma will be found. Support for this statement was obtained by comparing the percentages of epithelial or connective tissue type with mixed type in the diagnostic procedures where small portions of tumour (cytology of pleural fluid and Abrams biopsy) or large portions of tumour were obtained (thoracoscopy, thoracotomy, obduction). We found that if only a "small portion technique" had been performed the mixed type was present in 40% of the patients, whereas in a "large portion technique" this increased to 73%.

The most frequently found presenting symptoms in our series of dyspnoea, pain and weight loss are the usual clinical characteristics of pleural mesothelioma [20, 21]. A less common symptom is cough. Six patients presented with the superior vena cava occlusion syndrome. This means that this may not be as infrequent as was suggested by others [22].

Pleural effusions were detected radiologically in no less than 90% of the patients presenting with malignant mesothelioma. Long-term pleural effusions are due in 10% to a malignant mesothelioma [23]. As in our series,

the pleural effusion usually masks the tumour. Aspiration of the fluid may disclose the malignancy. In this series of patients it is found that asbestos exposure may also cause benign pleural thickening since this sign was found in 15% of the patients on the contralateral side of the thorax. Furthermore, it is obvious that pleural plaques and asbestosis are not premalignant lesions since they were found in a minority of the patients presenting with a malignant pleural mesothelioma and the occurrence is not increased as compared to the asbestos-exposed population generally.

Cytology of the pleural fluid was positive for malignant mesothelioma in 60%. An Abrams biopsy could make a definite diagnosis of mesothelioma in 68%. In only seven cases was diagnosis based on cytology alone. Thoracoscopy and thoracotomy were positive in a much higher percentage. This pattern is not unusual [24]. In our view the best procedure to be followed is to start with cytology of the pleural fluid, which can easily be obtained together with an Abrams biopsy. If this does not give a definite diagnosis, thoracoscopy or thoracotomy is indicated.

The results of several treatment programmes have been poor [25–27]. Patients with a survival of more than two years are only found incidentally. In our study, treatment consisted of a mixture of all modalities. Only surgery and immunotherapy seemed to prolong survival, but due to the fact that all sorts of selection-bias can have taken place, this cannot be regarded as a valid statement.

In previous years a number of reports emphasized the frequent occurrence of metastases in patients with malignant mesothelioma. Metastatic spread does not seem to be linked with histologic type according to some [28], while others found that distant metastases were more frequent in connective tissue type tumours [29]. In this study distant metastases were found in mixed type tumours in 13 cases (68%). The numbers of other histologic types are too small to pronounce upon this matter. The most frequent sites of spread outside the thorax were the liver (60%) and abdominal lymph nodes (38%). Compared to other studies these percentages are rather high. The rarity of brain metastases is confirmed (4%) [30].

In conclusion, in this series of malignant pleural mesotheliomas a relatively high percentage of mixed types is found. This is probably due to the availability of large portions of tumour specimens for histologic examination. If cytology of the pleural fluid and an Abrams biopsy do not give a definite diagnosis, we recommend that thoracoscopy with biopsies should be the diagnostic procedure of choice since this method delivers positive findings in a high percentage of patients.

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*Mésothéliome pleural malin dans le Sud-Ouest des Pays-Bas. T. van Gelder, H.C. Hoogsteden, M.A. Versnel, E.J. van Hezik, J.P. Vandenbroucke, H.T. Planteydt.*

**RÉSUMÉ:** Ce travail est le résultat de l'analyse des dossiers médicaux de 124 patients atteints de mésothéliome pleural malin. Chez 104 d'entre eux, l'on a pu obtenir des informations concernant l'exposition à l'asbeste, qui s'avère positive chez 95 (91%). La durée médiane d'exposition fut de 34 ans. La période médiane de latence fut de 41 ans. La survie médiane est de 11 mois; les différentes techniques thérapeutiques n'arrivent pas à prolonger la survie. Les anomalies radiologiques les plus communes sont les épanchements pleuraux, alors que chez certains patients l'on a noté des épanchements contro-latéraux ou un épaississement pleural. Les plaques pleurales ou les images d'asbestose ne furent rencontrées que chez une minorité des patients. Dans cette série, nous avons trouvé un pourcentage relativement élevé de mésothéliomes du type mixte (56%). Des biopsies larges montrent fréquemment des éléments tissulaires de type épithélial et conjonctif. En ce qui concerne les procédures de diagnostic, nous recommandons de commencer par l'examen cytologique du liquide pleural, qui peut être facilement obtenu en même temps que la biopsie à l'aiguille d'Abrams. Si un diagnostic de certitude n'est pas acquis, la thoracoscopie ou la thoracotomie est indiquée. *Eur Respir J.*, 1989, 2, 981–984.