Original Article

Asbestos Exposure and Survival in Malignant Mesothelioma: A Description of 122 Consecutive Cases at an Occupational Clinic

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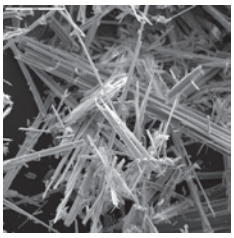

Abstract

Background: The natural history and etiology of malignant mesothelioma (MM) is already thoroughly described in the literature, but there is still debate on prognostic factors, and details of asbestos exposure and possible context with clinical and demographic data, have not been investigated comprehensively.

Objectives: Description of patients with MM, focusing on exposure, occupation, survival and prognostic factors.

Methods: Review of medical records of patients with MM from 1984 to 2010 from a Danish Occupational clinic. Survival was estimated using Kaplan-Meier survival analysis and prognostic factors were identified by Cox regression analysis.

Results: 110 (90.2%) patients were male, and 12 (9.8%) were female. The median (interquartile rang [IQR]) age was 65 (13) years. Pleural MM was seen in 101 (82.8%) patients, and peritoneal in 11 (9.0%); two (1.6%) had MM to tunica vaginalis testis, and eight (6.6%) to multiple serosal surfaces. We found 68 (55.7%) epithelial tumors, 26 (21.3%) biphasic, and 6 (4.9%) sarcomatoid. 12 (9.8%) patients received tri-modal therapy, 66 (54.1%) received one-/two-modality treatment, and 36 (29.5%) received palliative care. Asbestos exposure was confirmed in 107 (91.0%) patients, probable in four (3.3%), and unidentifiable in 11 (9.0%). The median (IQR) latency was 42 (12.5) years. Exposure predominantly occurred in shipyards. The median overall survival was 1.05 (95% CI: 0.96–1.39) years; 5-year survival was 5.0% (95% CI: 2.0%–13.0%). Female sex, good WHO performance status (PS), epithelial histology and tri-modal treatment were associated with a favorable prognosis.

Conclusion: MM continuously presents a difficult task diagnostically and therapeutically, and challenges occupational physicians with regard to identification and characterization of asbestos exposure.

Keywords: Mesothelioma; Asbestos; Exposure; Survival analysis; Prognosis

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Introduction

Malignant mesothelioma (MM) is an uncommon and very aggressive cancer that most frequently originates from mesothelial cells lining the pleural and peritoneal cavities and rarely from the pericardium and tunica vaginalis testis.[1] According to histological morphology, MM can be divided into three groups:

epithelial, biphasic and sarcomatoid. The prognosis for MM is in general poor, and the overall median survival has been reported to be less than a year from time of diagnosis.[2-4]

The idea of a causal relationship between MM and exposure to different types of asbestos fibers was first put forth in the 1960s,[5] and has later been verified by many epidemiological studies.[6] The increasing incidence of MM during the last three to four decades can be ascribed to the large amount of asbestos used for insulation and other purposes in the period from the end of the Second World War until asbestos use was banned in most western countries in the late 20th century. This illustrates the long latency of the disease, which generally ranges between 30 and 50 years.[4,7] The increase in the incidence of MM is far more pronounced in men than in women, which demonstrates the principally occupational etiology of the disease.[8-10] The background incidence of MM seems very low, and has been reported to be in the range of less than 1–2/1 000 000 or lower.[6,11] Induction of MM is not associated with smoking.[12]

The objective of this study was to describe the demographic and clinical data of patients with a diagnosis of MM seen at the Department of Occupational Medicine, Aalborg Hospital, Aarhus University hospital in Northern Denmark, which is an area with a history of extensive occupational asbestos exposure, due to the existence of a large asbestos cement factory and several shipyards. We wish to emphasize information regarding asbestos exposure and occupation, and explore possible differences in the distribution of clinical and demographic data by level of asbestos exposure. Moreover, we intend to establish the median survival time and evaluate the prognostic value of certain patient- and tumor-related variables.

Patients and Methods

We identified all patients diagnosed with MM in the period 1984–2010 from the database of the occupational clinic (n=135) regardless of their primary site or histological subtype. We included patients with a premortal histological or cytological diagnosis that was "definite/most likely" (n=111) or "probable" (n=10), as well as one patient with no pathological diagnosis but very strong clinical and radiological suspicion. Twelve patients were excluded on the basis of negative histology or change of the diagnosis to benign pleural disease or metastatic adenocarcinoma or lymphoma. One patient was excluded because he died prior to diagnosis. This resulted in a study group of 122 patients.

Clinical and demographic data

We used the unique 10-digit civil registration number assigned to all individuals in Denmark[13] to link data from the following sources: medical records from the occupational clinic, medical records from the treating hospitals, as well as the local and national pathological databases. From these sources, we obtained the following demographic, clinical and pathological data on the study participants: gender, age at diagnosis, survival (days), localization, histological subtype (epithelial, biphasic, sarcomatoid), type of pathological diagnosis (histological, cytological, immunohistochemistry), WHO performance status (PS) (0–1, 2, 3–4), comorbidity (yes, no), and treatment modality.

The date of diagnosis was defined as the date of pathological verification. In cases with diagnosis from necropsy and the case without pathological verification, the date of diagnosis was defined as the date when reasonable clinical suspicion was raised. For 10 (8.2%) patients the exact day of diagnosis was not known, and the 15th was used as a surrogate. Vital status was ascer-

TAKE-HOME MESSAGE

- Malignant mesothelioma (MM) is an uncommon aggressive occupational cancer with a poor prognosis. The incidence of MM is very low.
- Induction of MM is not associated with smoking.
- The incidence of MM is far more pronounced in men than in women.
- Male sex, nonepithelial histology and a poor performance status were significantly associated with a decreased survival.

tained as of September 1, 2010 from medical records from treating hospitals and by contacting general practitioners of the patients.

Localization was defined on the basis of presence of MM in serosal cavities at the time of diagnosis (pleura, peritoneum, tunica vaginalis testis, pleura + peritoneum and/or pericardium).

Comorbidity was present if a patient was diagnosed with symptomatic heart disease, diabetes, an additional malignant neoplasm, stroke, or severe lung disease.

Treatment of MM included operation (extra-pleural pneumonectomy [EPP], decortication/pleurectomy, and orchiectomy), chemotherapy (regardless of type or combination), and radiation therapy (when directed at the primary tumor, not when directed at distant metastases). We categorized treatment into the following groups: best supportive care (palliative care only), one-/two-modality treatment (defined as patients receiving one or two of the above treatments), and tri-modal treatment (defined as patients receiving all of the above treatments).

Exposure and occupational history

The occupational history was acquired from the occupational anamnesis obtained by specialized occupational physicians, when the patient was first seen in the clinic. There was no information available about air measurements (fibers/cm^3) at the workplace or measurements of quantitative asbestos fiber burden of lung tissue for any of the patients in this study. Number of years of exposure, latency, industry, and/or occupation in which asbestos exposure took place was derived from the clinical journals. The latency period was defined as the time between the year of first exposure and the year of diagnosis.

Each patient with known exposure was categorized by an experienced occupational physician, based on the intensity of cumulative exposure, as "low" (<10 fibers/cm^3-year), "moderate" (10–25 fibers/cm^3-year), or "high" (>25 fibers/cm^3-year). This was based upon the occupational anamnesis, the assessment of the occupational physician who first consulted the patient, as well as information from the literature about the level of exposure (fibers/cm^3) in certain types of industries.[14]

Statistical analysis

We computed follow-up time from time of diagnosis to time of death or September 1, 2010, whichever came first. Time to death was used as the primary endpoint. We used Kaplan-Meier survival analysis to estimate cumulative survival for all patients included in the study according to localization (n=122). We used Cox regression analysis to compute mortality rate ratios (MRRs) as a measure of relative risk of death. Our initial analysis demonstrated that none of the two patients with localization of MM to tunica vaginalis testis died during follow-up, and we therefore excluded these two patients from the Cox regression analysis. Several Cox regression analyses were fit-

ted to best identify factors associated with prognosis. We used several of the selected independent variables in accordance with the maximum number accepted due to the total number of observed events. Three Cox regression models were chosen that were best fitted to identify factors associated with prognosis:

1) All patients (except those with localization to tunica vaginalis testis) were included (n=120). The following variables were evaluated for prognostic significance: age at diagnosis, gender, histological subtype (epithelial, sarcomatoid, biphasic, unknown), PS (0–1, 2, 3–4 [categorical variables]), and localization (pleura, peritoneum, pleura + peritoneum and/or pericardium).

2) Patients with histological verification of the diagnosis, known histological subtype and with localization to pleura were included (n=78). The same variables as in (1) were evaluated for prognostic significance (except from localization).

3) Patients with histological verification of the diagnosis, known histological subtype and with localization to pleura were included (n=78). The same variables as in (2) were evaluated for prognostic significance, but this model also included treatment as a prognostic factor (best supportive care, one-/two-modality treatment, tri-modal treatment).Treatment was introduced as a time-updated variable.[15]

For three patients, the exact day of beginning of therapy was not known, and the 15th was used as a surrogate. For two patients, diagnosis was made after treatment had commenced, and therefore the date of diagnosis was used as the date of beginning of therapy.

Ethics

This study has been approved by The Danish Data Protection Agency, J.nr. 2010-41-5141.

Results

Clinical and demographic data

Of the 122 patients in the study group, 110 (90.2%) were male and 12 (9.8%) were female. The median (interquartile range [IQR]) age at diagnosis was 65 (13) years. MM of the pleura was established in 101 (82.8%) patients (right pleura [55.0%], left pleura [37.6%], bilateral [4.6%], unknown [2.8%]). Eleven (9.0%) patients had peritoneal MM, two (1.6%) had localization to the tunica vaginalis testis, and eight (6.6%) patients had localization to pleura + peritoneum and/or pericardium.

Histological subtype was epithelial in 68 (55.7%) patients, biphasic in 26 (21.3%), sarcomatoid in six (4.9%), and unknown in 22 (18.0%) patients. Certain histological verification of the diagnosis was present in 98 (80.3%) patients, whereas six (4.9%) had a probable histological diagno-

Table 1: Selected demographic and clinical data stratified by exposure level. Patients with probable exposure (n=4) were not included.

	No known exposure	Known exposure	p value
Total	**11**	**107**	
Gender, n (%)			
Male	4 (36.4)	102 (95.4)	<0.001†
Female	7 (63.6)	5 (4.6)	
Histological subtype, n (%)			
Epithelial	6 (54.5)	59 (54.6)	
Biphasic	3 (27.3)	23 (22.2)	0.950†
Sarcomatoid	0 (0)	6 (5.6)	
Unknown	2 (18.2)	19 (17.6)	
Site of disease, n (%)			
Pleura	6 (54.5)	94 (88.0)	
Peritoneum	1 (9.1)	8 (7.4)	0.003†
Tunica vaginalis testis	2 (18.2)	0 (0)	
Pleura + other*	2 (18.2)	5 (4.6)	
Median (IQR) age at diagnosis	56 (36)	66 (12)	0.122‡

*Other: Peritoneum and/or pericardium
†Calculated by Fischer's exact test
‡Calculated by Kruskal-Wallis test

sis, and 18 (14.8%) patients had no histological diagnosis. Among the patients with no histological diagnosis, 13 (72.2%) had a cytological diagnosis. This resulted in 111 (91.0%) patients with a definite histological or cytological diagnosis, and a group of 11 (9.0%) patients with a paraclinically non-verified but probable diagnosis. Immunohistochemistry was performed in 116 (95.1%) patients.

PS was good (0–1) in 90 (73.8%) patients, while 15 (12.3%) had a moderate PS (2), and 17 (13.9%) patients had a poor PS (3–4). Presence of comorbidity was established in 51 (41.8%) patients.

Tri-modal therapy was given to 12 (9.8%) patients, while 66 (54.1%) received a combination of one or two of chemotherapy, radiation therapy and operation; no treatment, apart from palliative care, was given to 36 (29.5%) patients. The treatment modality was unknown in eight (6.6%) patients.

Table 1 shows selected demographic and clinical data stratified by exposure level (known exposure [n=107], no known exposure [n=11]). There was a significant difference between the sex ratio in the two groups, with a male:female ratio of 1:1.75 in the group with no known exposure, and a male:female ratio of 20.4:1 in the group with known exposure. Furthermore, there was a significant difference in the distribution of localization between the two groups, with pleural localization making up a larger percentage of the group with known exposure (88.0%) compared to the group with no known exposure (54.5%). We observed an equal distribution of epithelial and non-epithelial histology between the two groups; there was no difference in age at diagnosis.

Table 2: Distribution of industries and occupations in which asbestos exposure took place.

Industry/occupation	n (%)
Shipbuilding industry	43 (29.9)
Unskilled laborer	11
Machinist	9
Carpenter/joiner	6
Electrician	5
Shipbuilder	4
Plumber/pipe fitter	3
Smith	3
Welder	3
Others	6
Construction industry	31 (21.5)
Carpenter/joiner	15
Electrician	4
Insulation installer	4
Unskilled laborer	3
Bricklayer	2
Plumber/pipe fitter	1
Others	3
Dansk Eternit-Fabrik	24 (16.7)
Unskilled laborer	15
Machinist	5
Other	5
Iron and metal	13 (9.0)
Machinist	7
Smith	4
Boilermaker/boiler attendant	3
Automobile industry	9 (6.3)
Scrap merchant	2 (1.4)
Agriculture	2 (1.4)
Leisure-time exposure	1 (0.7)
Others	19 (13.2)

Only patients with known (n=107) or suspected (n=4) asbestos exposure were included. Some patients worked in and were consequently registered in more than one industry and/or occupation, which resulted in a higher number of observations (n=144) than patients (n=111).

Exposure and occupational history

We found that 11 (9.0%) patients had no known asbestos exposure, four (3.3%) had probable asbestos exposure and 107 (87.7%) patients had known asbestos exposure. Of the patients with documented exposure, 51 (47.6%) had low cumulative exposure, 35 (32.7%) had moderate cumulative exposure, and 21 (19.6%) had high cumulative exposure. The total time of exposure ranged from a few days to

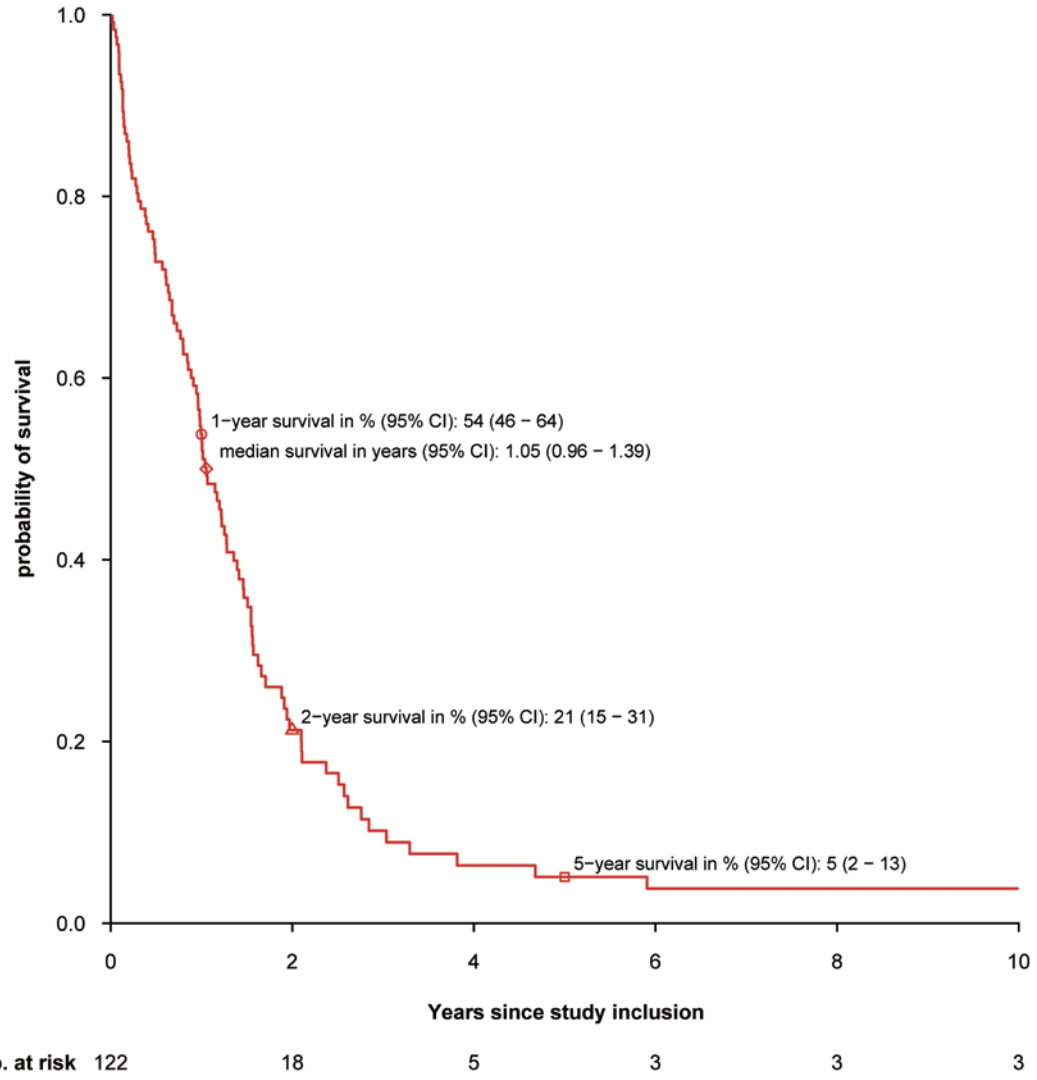

Figure 1: Overall survival

over 40 years. The median (IQR) latency period was 42 (12.5) years. When distributed by localization of MM, we found that there was a significantly (p=0.009) longer median latency among patients with pleural MM (43 [IQR: 12] years) compared to patients with MM of the peritoneum (36 [IQR: 19] years) whereas there was no difference in latency when stratified by level of cumulative asbestos exposure.

Table 2 illustrates the distribution of industries and occupations in which asbestos exposure took place. The shipbuilding industry accounted for almost 30% of the cases of known asbestos exposure, whereas the construction industry accounted for 21.5%. The large asbestos cement factory, Dansk Eternit-Fabrik A/S accounted for 16.7% of employments with asbestos exposure. One patient had a leisure time exposure, whereas the remainders of exposures were occupational in origin. No

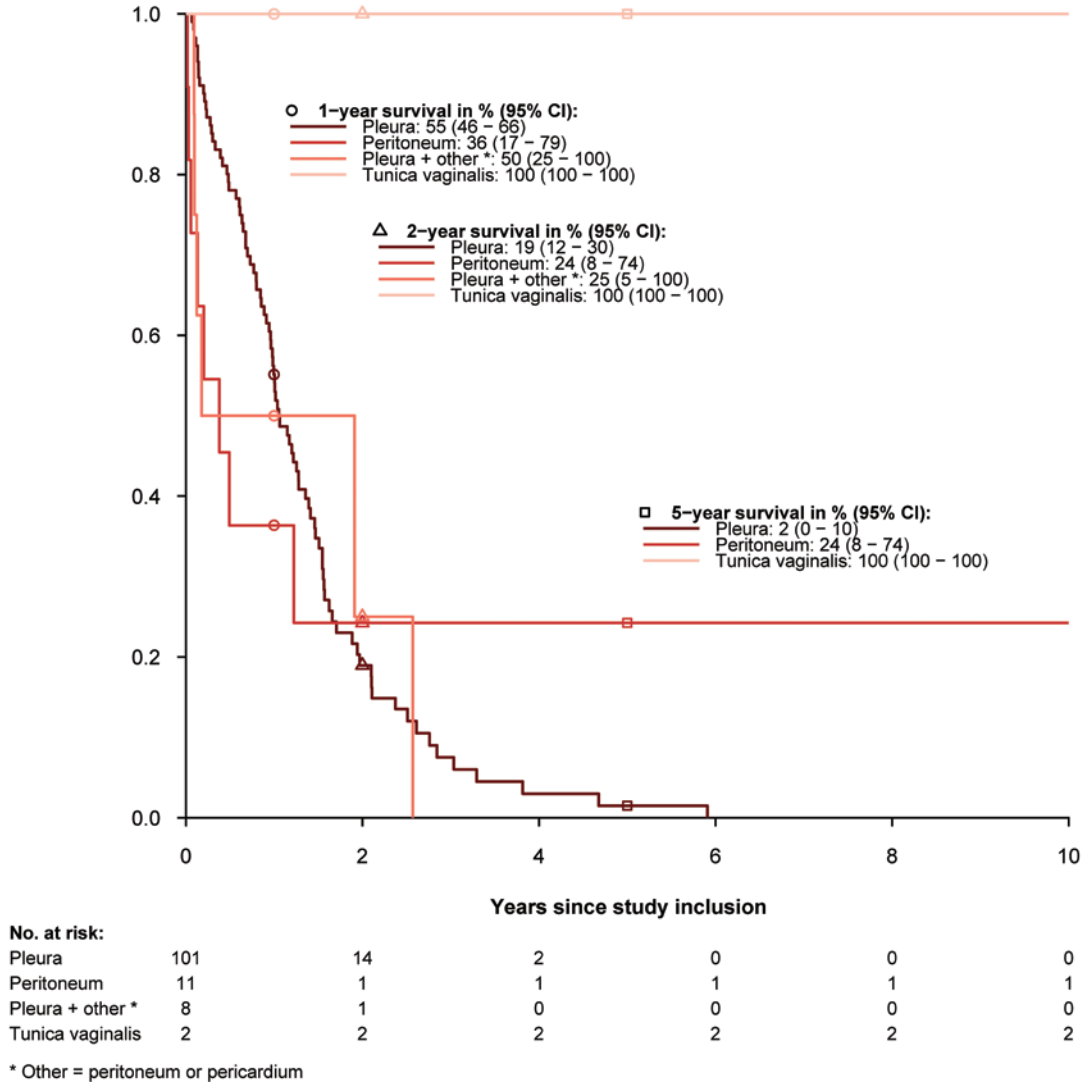

Figure 2: Survival by localization

cases of household/domestic exposure were established.

Mortality and prognostic factors

Of the 122 patients included in the Kaplan-Meier analysis, 102 (83.6%) died during follow-up. The overall median survival was 1.05 (95% CI: 0.96–1.39) years. One-year survival was 54.0% (95% CI: 46.0%–64.0%), two-year survival was 21.0% (95% CI: 15.0%–31.0%), and five-year survival was 5.0% (95% CI: 2.0%–13.0%) years (Fig 1).

Figure 2 shows survival according to localization. Localization of MM to tunica vaginalis testis was associated with a 100% survival, whereas the remaining localizations were associated with a more sinister prognosis with a chance of surviving two years of approximately 20%.

In the three Cox regression models, good PS was consistently associated with

a favorable outcome. Female sex and epithelial histology were also associated with a better prognosis, although not with statistical significance in all models (Table 3). Compared to time before treatment, tri-modal therapy offered some improvement in prognosis, whereas one-/two-modality treatment did not.

Discussion

Male sex and pleural involvement were prevalent among patients with a known exposure to asbestos, which was found in 87.7% of studied patients. The shipbuilding industry was the largest contributor to asbestos exposure, and the median latency time was 42 years. Median overall survival was 359.5 days, and gender, PS, histological subtype, and tri-modal treatment were factors associated with survival.

The detailed occupational anamnesis available, has allowed us to compare clinical and demographic features between asbestos- and non-asbestos-related cases. That we found a higher prevalence of women in the group without known exposure is hardly surprising given the work-related etiology of MM. The fact that peritoneal MM is more common among the patients with no known exposure may illustrate that pleural MM is associated with a higher degree of exposure than peritoneal MM, but this has been contradicted in some studies,[16,17] in which peritoneal MM seems to be associated with a very heavy exposure. It may alternatively illustrate that women are more prone to the peritoneal localization for some reason other than exposure level. The fact that peritoneal MM is more common among women is consistent with other studies.[18-20] It has been put forward that ovarian cancer with peritoneal carcinomatosis in women is sometimes misclassified as peritoneal MM.[10,20]

The pronounced dominance of men with pleural involvement corresponds with previous findings that suggest that a man with pleural MM is the most common presentation of this disease.[10,12,17,21] The distribution of histological subtypes, with a predominance of epithelial and a small number of sarcomatoid, is in accordance with other studies.[4,12,22-24]

We were able to obtain an occupational anamnesis for all patients studied. The presence of certain or probable asbestos exposure in 91% of the patients is comparable to other studies.[17,25] The 9% with no known exposure could be idiopathic and unrelated to asbestos exposure, but it is also possible that some of them have been under some level of exposure they were unaware of. It has never been possible to establish a lower threshold for cumulative asbestos exposure in relation to development of MM, despite the fact that a dose-response relationship has been determined,[11,26] and as such it is conceivable that residential/environmental asbestos exposure was the cause of disease for the patients without documented exposure.

The median latency period of 42 years corresponds well with other studies.[18,25] Our observation, that patients with pleural MM had a longer latency compared to patients with MM of the peritoneum, has been investigated elsewhere, and while one study had findings similar to ours,[18] other studies found a longer latency in peritoneal MM compared to pleural MM.[25,27] The fact that we found no significant difference in latency between patients with high, moderate and low exposure, contradicts two other studies,[7,17] where data have suggested an inverse relationship between dose and latency period for MM.

In accordance with previous studies,[17,25] the shipbuilding industry, in which asbestos primarily has been used for insulation purposes, accounted for the largest part of asbestos exposures. The construction industry contributed with a large per-

centage, mainly comprising carpenters, a finding described by others.[17] Dansk Eternit-Fabrik A/S accounted for a very high percentage considering that it is a single factory, not an industry. Previous cohort studies of employees from Dansk Eternit-Fabrik A/S, have found a remarkably high incidence among men for lung carcinoma, MM and non-malignant pulmonary disease.[28]

Among the 12 women included in the study group, seven had no known exposure, three had a low exposure and two had a moderate exposure. This illustrates the known fact that most industries and occupations in which asbestos exposure has taken place are male dominated. As hypothesized in epidemiological studies,[18,19,29] it is possible that women are more susceptible to low exposures (residential/environmental exposure), and that they have a steeper dose-response curve. The explanation for this could be that anatomical and physiological differences between the sexes cause men to clear asbestos fibers more effectively from their lungs than

Table 3: Cox regression survival analyses. Model 1 includes all but patients with localization of MM to tunica vaginalis, whereas models 2 and 3 include patients with a certain histological verification of diagnosis and with localization to pleura. Mortality rate ratios (MRRs) are used as a measure of relative risk of death.

	Model 1	**Model 2**	**Model 3**
Number included in analysis	120	78	78
Number of deaths	102	65	65
	MRR (95% CI)	**MRR (95% CI)**	**MRR (95% CI)**
Age (per year increase)	1.02 (1.00–1.05)	1.01 (0.97–1.04)	1.00 (0.96–1.04)
Gender (male *vs*. female)	2.36 (1.10–5.08)	3.16 (0.71–14.16)	6.95 (1.29–37.38)
Histological subtype			
Epithelial	Reference	Reference	Reference
Sarcomatoid	1.79 (0.58–5.54)	7.80 (2.48–24.53)	6.10 (1.93–19.33)
Biphasic	1.63 (0.96–2.76)	2.25 (1.24–4.10)	1.78 (0.98–3.23)
Unknown	1.30 (0.75–2.26)	NA†	NA
Performance status			
0–1	Reference	Reference	Reference
2	1.39 (0.74–2.59)	2.71 (1.30–5.65)	4.64 (2.08–10.37)
3–4	5.01 (2.66–9.43)	3.33 (1.19–9.32)	4.94 (1.54–15.85)
Treatment			
Time before treatment (incl. best supportive care)	NA	NA	Reference
Time after one-/two-modality treatment	NA	NA	1.76 (0.76–4.10)
Time after tri-modal treatment	NA	NA	0.25 (0.07–0.96)
Localization			
Pleura + others*	Reference	NA	NA
Pleura	1.08 (0.39–3.00)	NA	NA
Peritoneum	2.35 (0.66–8.36)	NA	NA

*Others: Peritoneum and/or pericardium
†Not applicable

women.[29]

The fact that approximately 50% of the patients had a cumulative exposure of <10 fibers/cm^3-year illustrates that a massive exposure to asbestos is not necessary to develop MM. This should be taken into account by all people working with asbestos; in Western countries this primarily includes people working in the construction industry with demolition of old buildings. Proper protection equipment is essential even when working in very low fiber concentrations.

We found that the median survival was just over a year (1.05 years), which is comparable to other studies.[3,22,30,31] Several studies present a shorter survival time in the range of 4 to 10 months,[2,4,20,32,33] while some studies demonstrate a somewhat longer survival time in the range of 13 to 15 months.[25,34,35] We have chosen to include MM of all localizations, including the tunica vaginalis testis which has a favorable prognosis compared to the other localizations. However, this has no real effect on the median survival, which changes by only one day when estimated without the two patients with localization to the tunica vaginalis testis. In the literature, there is a difference in the definition of "survival" with some studies using the date of entry into their study rather than the date of diagnosis as the starting point, which could account for part of the difference in median survival between some of the studies.

In our study, three patients survived more than 10 years. Among these three patients, two were men with localization to tunica vaginalis testis, and one was a woman with localization to the peritoneal cavity. All three patients had a histological verification of MM, which makes pathological misclassification a minuscule possibility. They all had epithelial histological subtype, PS of 0–1, and received the one-/two-modality treatment. The patients with localization to tunica vaginalis testis were still alive at the end of data collection, whereas the woman with peritoneal MM had died during the follow-up period.

Our Cox regression analysis included age, gender, PS, histological subtype, localization, and treatment modality. We were unable to control for TNM-stage, although it has been verified as a prognostic factor,[4,20,23,24,30,33] due to absence of reliable information in the medical journal, and due to the fact that complete staging of MM of the pleura is only possible when an EPP is performed.[36] Our findings, that male sex, nonepithelial histology and a poor PS were significantly associated with a decreased survival, are analogous to other studies.[2,3,20-24,30-32,34,37]

The importance of histological subtype has been discussed in many studies, and there is good consensus that epithelial histology is associated with a better prognosis than the biphasic or sarcomatoid subtype. We found, in contrast to others,[20,21,24,31-34] that age at diagnosis did not have a significant effect on prognosis, whereas PS did. PS might, better than age, be a proxy for the general health condition, as an underlying significant factor for survival. The modulation effect of gender on the prognosis is, however, not immediately obvious. A possible explanation of the decreased survival in men might be that males often have a greater cumulative exposure and consequently a larger lung fiber burden than women, increasing the risk of nonepithelial histology and thus decreased survival.[36] It has been suggested that women seek medical attention earlier than men, resulting in earlier diagnosis and medical intervention and therefore a better survival.[38]

In patients with pleural MM, tri-modal treatment was significantly associated with an increased survival, whereas one-/two-modality treatment was not (Table 3). Comparison between the different treatment modalities in this study is problem-

atic given the retrospective design and the lack of randomization in a controlled clinical setting. An improvement of survival among patients receiving aggressive therapy illustrates both the possible benefit of treatment, but also the selection criteria for treatment modalities, which includes people with good PS, epithelial histology, and a low TNM-stage being chosen for aggressive treatments. Although we did try to adjust for these potential confounders, we can, nevertheless, not exclude the possibility of residual and unknown confounding, and therefore caution should be taken when interpreting these results.

Results are conflicting in regard to survival in patients treated with combinations of therapies compared to patients receiving only palliative treatment. In some studies an effect on prognosis of combinations of therapies compared to only palliative treatment, has been observed,[23,34,37,39] while others reported no effect.[3,22]

Although the present study is small and based on retrospectively collected information of clinical data not designed for scientific purposes, the study population serves well for a clinicopathological and demographic description. However, the data might have inborn errors due to skewed distributions and misclassification introducing a risk for misinterpretation in analysis. Diagnostic procedures and treatment have changed during the observation period indicating a possible differentiation to the diagnostic criteria and to the effectiveness of the treatment. MM is a challenging pathological diagnosis to make,[40] and there is therefore a risk of misclassification. Ninety-eight (80.3%) patients had a certain histological diagnosis obtained by biopsy or necropsy; among these patients the risk of misclassification should be negligible. Immunohistochemistry tests were performed in 95% of all cases further reducing the risk of a wrong diagnosis. There is a risk of recall bias when exploring the history of asbestos exposure, due to an economic benefit for the patient if exposure can be proven. However, the occupational physician must verify to the Danish Board of Industrial Injuries that the patient has had a relevant exposure to asbestos, which ensures an occupational anamnesis of high accuracy.

In conclusion, our findings do emphasize that MM is a serious health issue in Denmark. Identifying previous asbestos exposure, diagnosing the disease correctly and promptly, as well as instituting adequate treatment is still a challenge to physicians.

Conflicts of Interest: None declared.

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