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ORIGINAL ARTICLE

Clinical prognostic factors in pleural mesothelioma: best supportive care and anti-tumor treatments in a real-life setting

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ABSTRACT

Background: This study aims to investigate patient- and disease characteristics associated with survival in malignant pleural mesothelioma (MPM) patients with anti-tumor treatment or with best supportive care (BSC).

Materials and methods: Consecutive MPM cases diagnosed in North Denmark Region from 1972 to 2015 were reevaluated and verified by two pathologists using modern immunohistochemical techniques. Danish registries and hospital records were used to gather patient-, asbestos exposure-, and disease information.

Results: Of the 279 patients, anti-tumor treatment was administered to 184 patients (66.0%). All of those received chemotherapy alone or as part of a multimodal treatment, where pemetrexed was given to 126 (68.5%) patients. Asbestos exposure was documented in 92.5% of all patients. In the treated group, mean age was lower (66 years versus 74 years, $p < 0.01$), rate of occupational asbestos exposure was higher (74.5 versus 54.7%, $p < 0.01$), more patients had better performance score (98.4 versus 60%, $p < 0.01$) and stage was lower (81 versus 63.2%, $p < 0.01$) compared to the BSC group. Multivariate analysis showed that epithelioid subtype was the only common prognostic factor for OS in both groups. In BSC patients, good PS and female gender was associated with improved OS. Median overall survival (OS) was 17 versus 4 months ($p < 0.01$), and independently of the histopathological subtype, the median and 2-year survival was higher in the treated versus the BSC group ($p < 0.02$).

Conclusions: This retrospective study showed that epithelioid subtype is the only independent positive prognostic factor of survival in treated patients with MPM. For BSC patients, the epithelioid subtype, good PS, and female gender were positive prognostic factors, while age and comorbidities were not significant. This study with long-term follow-up of treated and BSC MPM patients can contribute to the clinical stratification of patients. Further validation is appropriate to verify these findings.

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Malignant pleural mesothelioma; prognosis; overall survival; asbestos exposure; chemotherapy; surgery; supportive care

Introduction

Malignant mesothelioma (MM) is a relatively rare and often aggressive tumor arising from mesothelial or submesothelial cells in serosal membranes, most commonly located in the pleura [1].

Median survival in malignant pleural mesothelioma (MPM) patients treated by best supportive care (BSC) has been reported in the range 2–8 months, and in patients treated with pemetrexed-platinum plus bevacizumab the median survival is 18.8 months; however, the 5-year survival is still <5% [2,3]. Currently a combination of nivolumab and ipilimumab has received FDA approval as first line treatment that may change the outcomes more favorably [4].

Multimodal therapy with chemotherapy, surgery and radiotherapy is used in a subset of patients, but even if there are some long-term survivors, there is no definitive cure for this disease [1].

Since the seminal paper by Wagner *et al*. in 1962, asbestos exposure as an etiological factor for MPM has been thoroughly documented [1,5–7]. Asbestos was banned in several countries in the 1980s, but due to latency of 20–70 years and continued asbestos use in several countries the incidence has plateaued or is increasing world-wide [1,8].

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The overall poor prognosis is linked to the biology of this disease, its innate or acquired resistance to therapy, as well as late diagnosis [9,10]. The histological subtypes are prognostic for both response and survival. The epithelioid (50–70% of cases) have a significantly better response and overall survival (OS) versus sarcomatoid (7–20%) and biphasic (20–35%) subtypes [8,11]. However, solid evidence regarding prognostic factors of OS both in treated and BSC patients is rather limited [11,12]. One reason for these discrepancies may be due to the lack of data in treated and BSC patients. Improved knowledge on prognostic factors could aid clinicians in stratification and more personalized approaches to treatment.

International incidence of MPM is reported to be around 1–2 per million, but in the Region of North Denmark, the crude incidence from 2010 to 2015 was 6.2/100,000 for men and 1.6/100,000 for women due to a large asbestos cement factory and shipyards that operated in the area for more than six decades [1,13]. The MM cohort of Aalborg University Hospital is one of the largest single-institution cohorts with complete clinical data regarding treatment and asbestos exposure [13].

The primary aim of this study was to investigate which patient- or disease characteristics (i.e. age, gender, asbestos exposure, tumor subtype, stage of disease, Eastern Cooperative Oncology Group performance status (PS), and comorbidities) are associated with survival in MPM patients with or without anti-tumor treatment, and compare survival between these two groups.

Material and methods

Study design

This retrospective study included all patients from the North Denmark Region diagnosed with MM from 1972 to 2015. Data outputs were originally obtained as part of an ongoing research project on MM at Aalborg University Hospital. Approval from the Danish Data Protection Agency and the Ethical Committee (ID# N-20140032) was acquired. The methods regarding pathology evaluation and asbestos exposure data have been published previously [13].

Data collection

Archival data from the Institute of Pathology, Aalborg University Hospital, were retrieved from 1972 to 2015 and patients were followed until September 2018. Pathology data included diagnostic method, (cytology or histology), tumor subtype, (epithelioid, sarcomatoid or biphasic), and certainty of diagnosis, classified in a 5-tier scheme. All cases were reclassified by two pathologists using modern immunohistochemical panels according to the most recent International Mesothelioma Interest Group guidelines, when tissue was available [14]. Tiers included (1) definitely, (2) probably, (3) likely, (4) unlikely, (5) definitely not, of which tier 4 and 5 were excluded.

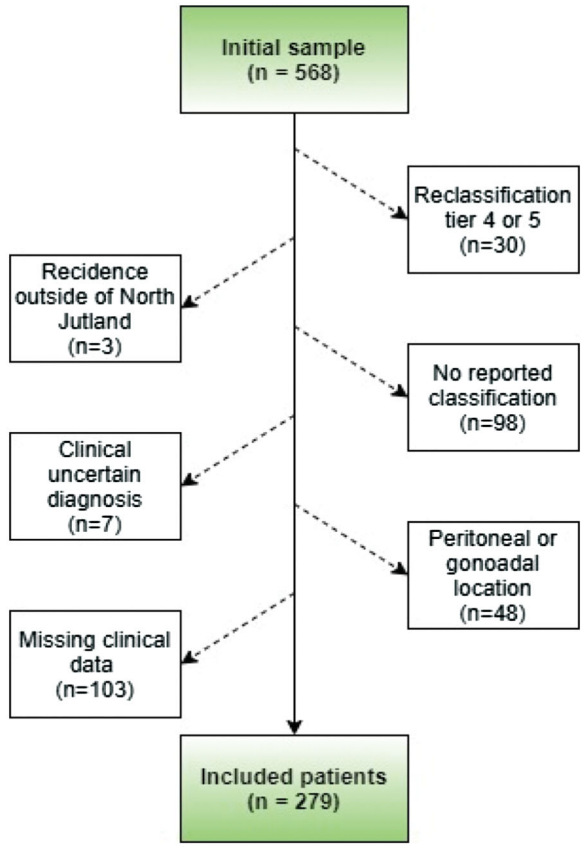

Figure 1. Flow-chart of the inclusion process of the study population.

Clinical and survival data concerning age time of diagnosis, localization, stage, treatment, and OS were obtained from medical records and the Danish Cancer Registry. Age was analyzed as a continuous variable. Tumor localization was divided into pleural and non-pleural, and cases with non-pleural location were excluded (Figure 1). Extent of disease was classified as 'local' or 'metastatic' prior to 2002 and according to Tumor Node Metastasis (TNM) in cases after 2002. Patients were grouped as 'early' (TNM stage 1–3 or 'localized') and 'late' (TNM stage 4 or 'metastatic') stage. Treatments were categorized as BSC, chemotherapy only, chemotherapy and radiation, chemotherapy, and surgery and trimodal treatment (chemotherapy, radiation, and surgery). The OS was defined as time from diagnosis to death. Patient PS was grouped in good (0–2) or poor (3–4). The PS and significant comorbidities (i.e. as heart-, lung-, renal failure, vascular diseases, and other cancers) were obtained from the National Patient Registry, which is a high-quality database established in 1977, comprising patient information registered from all hospital wards in Denmark [15]. It was not possible to achieve PS from registries for patients diagnosed before to 2002 but these were identified by thorough search through hospital records. Medical records were in general used to supplement and validate information.

Asbestos exposure type was determined from data by the Danish Supplementary Fund Register and the Danish Civil Registration System. Asbestos exposure was categorized in occupational, environmental, domestic, combinations of those and no exposure. Occupational exposure was defined

as asbestos-related work i.e. shipbuilding, isolation, mason, carpenter, blacksmith, electrician, joiner, or working at Danish Eternit Factory or Aalborg shipyard. Domestic exposure was defined as sharing residence with an occupationally exposed person. Environmental exposure was defined as living or working within 10,000 meters from asbestos emitting locations, based on previous studies [16]. Exposure type was subdivided in occupational exposure (including patients with any non-occupational exposure), non-occupational exposure (defined as sole environmental, domestic, or mixed exposure with no occupational component), and no exposure.

Statistical methods

Normal distribution was evaluated with Q-Q plots. Descriptive statistics and Fisher's exact tests were used to evaluate the population characteristics. Univariate cox regression analysis was used to determine which independent variables correlated with OS. Variables with $p<0.10$ were considered significant, and included in a multivariate Cox regression analysis, used to determine independent significance, in which $p<0.05$ was considered significant. Kaplan Meier estimate and log rank test were used to investigate survival differences in subtypes among treated and BSC groups. Statistical analysis was performed using SPSS Statistics software version 25.

Results

Study population

Of 568 patients with a MM diagnosis, 279 with verified MPM were eligible for inclusion in the study (Figure 1). At the time of data collection, 10 patients were alive.

A documented asbestos exposure was established in 258 patients (92.5%), the majority with occupational asbestos exposure ($n=189$, 67.7%) (Table 1). The majority of the patients had TNM stage III or IV, good PS, epithelioid subtype and diagnosis was mostly confirmed by histological diagnostic methods (Table 1). Ischemic heart disease was the most frequent significant comorbidity ($n=47$, 15.7%). In the treated group, mean age was lower (66 versus 74 years, $p<0.01$), rate of occupational asbestos exposure was higher (74.5 versus 54.7%, $p<0.01$), more patients had better performance score (PS, 98.4 versus 60%, $p<0.01$) and stage was lower (81 versus 63.2%, $p<0.01$) compared to the BSC group. There was no difference between the groups regarding comorbidities or histological subtypes. Anti-tumor treatment was given to 184 patients (66.0%) where all received chemotherapy alone or as part of multimodal treatment (Table 1). Pemetrexed-based (pemetrexed alone or combined with platinum) chemotherapy was given to 126 (68.5%) patients. Median overall survival (OS) was 17 versus 4 months, $p<0.01$) in the treated versus the BSC group.

Table 1. Characteristics of study population.

	BSC group $N=95$ (100%)	Treated group $N=184$ (100%)	p-Value
Age, mean (SD)	74.18 (8.9)	65.75 (8.6)	<0.01
Survival months, median (IQR)	4.0 (7.0)	17.0 (14.75)	<0.01
Gender, male, *N* (%)	66 (69.5)	157 (85.3)	<0.01
Asbestos exposure			
N (%)			
Occupational	52 (54.7)	137 (74.5)	<0.01
Non-occupational	29 (30.5)	40 (21.7)	
None registered	14 (14.7)	7 (3.8)	
PS			
N (%)			
Good			
0	4 (4.2)	73 (39.7)	<0.01
1	31 (32.6)	92 (50.0)	
2	22 (23.2)	16 (8.7)	
Poor			
3	21 (22.1)	3 (1.6)	
4	17 (17.9)	0	
Comorbidities, yes, *N* (%)	51 (53.7)	84 (45.7)	0.21
Subtype *N* (%)			
Epithelioid			
Epithelioid	61 (64.2)	105 (57.1)	0.30
Non-epithelioid			
Biphasic	16 (16.8)	67 (36.4)	
Sarcomatoid	18 (18.9)	12 (6.5)	
Stage			
N (%)			
Early			
TNM I	3 (3.2)	22 (12.0)	<0.01
TNM II	13 (13.7)	41 (22.3)	
TNM III	18 (18.9)	65 (35.3)	
Local	13 (13.7)	7 (3.8)	
Regional spread	13 (13.7)	14 (7.6)	
Late			
TNM IV	32 (33.7)	35 (19.0)	
Metastatic	3 (3.2)	0	
Treatment			
N (%)			
Chemotherapy	0	94 (51.1)	NA
Chemotherapy + Radiation	0	46 (25.0)	
Chemotherapy + Surgery	0	20 (10.9)	
Chemotherapy + Radiation + Surgery	0	24 (13.0)	

p Value <0.05 indicates significant difference between the BSC and treated group. BSC: best supportive care; SD: standard deviation; IQR: inter quartile range; PS: performance status; HR: hazard ratio; NA: not applicable; TNM: tumor node metastasis.

Prognostic factors for survival

The univariate analyses showed that favorable factors for OS in the BSC group were female gender, epithelioid subtype, early stage, and good PS, while in the treated group only epithelioid subtype was favorable. As no other factors had univariate correlation ($p<0.1$) in treated patients, no multivariate analysis was made in this group. However, even when adjusting for factors with $p<0.2$ (age, stage, and comorbidities), subtype remained the only significant variable ($p<0.019$) (Table 2). As there were only three patients with poor PS in the treated group, this variable was not included in Cox regression analysis. Multivariate analysis in the BSC group revealed female gender, epithelioid subtype, and good PS were associated with higher OS (Table 2. Independently of the histopathological subtype, the median and 2-year survival were higher in the treated versus the BSC group ($p<0.02$) (Table 2, Figure 2).

Median survival for patients with epithelioid and non-epithelioid subtypes in the BSC groups were five and two months ($p<0.001$), respectively. For treated patients with

Table 2. Uni- and multivariate analyses.

	BSC group						Treated group		
	Univariate			Multivariate			Univariate*		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age, years	0.99	0.97–1.02	0.56	NA			1.01	0.99–1.03	0.16
Gender, male	1.64	1.04–2.58	0.03	1.56	0.99–2.47	0.05	1.17	0.77–1.80	0.46
Occupational exposure*	1.05	0.58–1.90	0.88	NA			0.87	0.41–1.87	0.73
Non-occupational exposure*	0.81	0.43–1.55	0.53	NA			0.66	0.29–1.49	0.32
Subtype, epithelioid	0.52	0.34–0.81	<0.01	0.47	0.30–0.74	<0.01	0.7	0.52-0.96	0.02
Stage, early	0.68	0.44–1.04	0.08	0.73	0.47–1.13	0.16	0.78	0.54–1.30	0.19
PS, good	0.59	0.39–0.90	0.03	0.58	0.37–0.90	0.02	NA		
Significant comorbidity	1.18	0.78–1.78	0.43	NA			1.27	0.94–1.71	0.12

Variables with *p* values >0.1 in the univariate analyses were included in the multivariate analysis where $p<0.05$ indicates significant correlation. The PS was not analyzed in the treated group due to small number of patients with PS >2.
*A Cox regression analysis on age, gender, stage, comorbidities and subtype in the treated group correcting for the other variables and again, only subtype was significant ($p=0.019$). BSC: best supportive care; CI: confidence interval; NA: not applicable; PS: performance status; HR: hazard ratio.

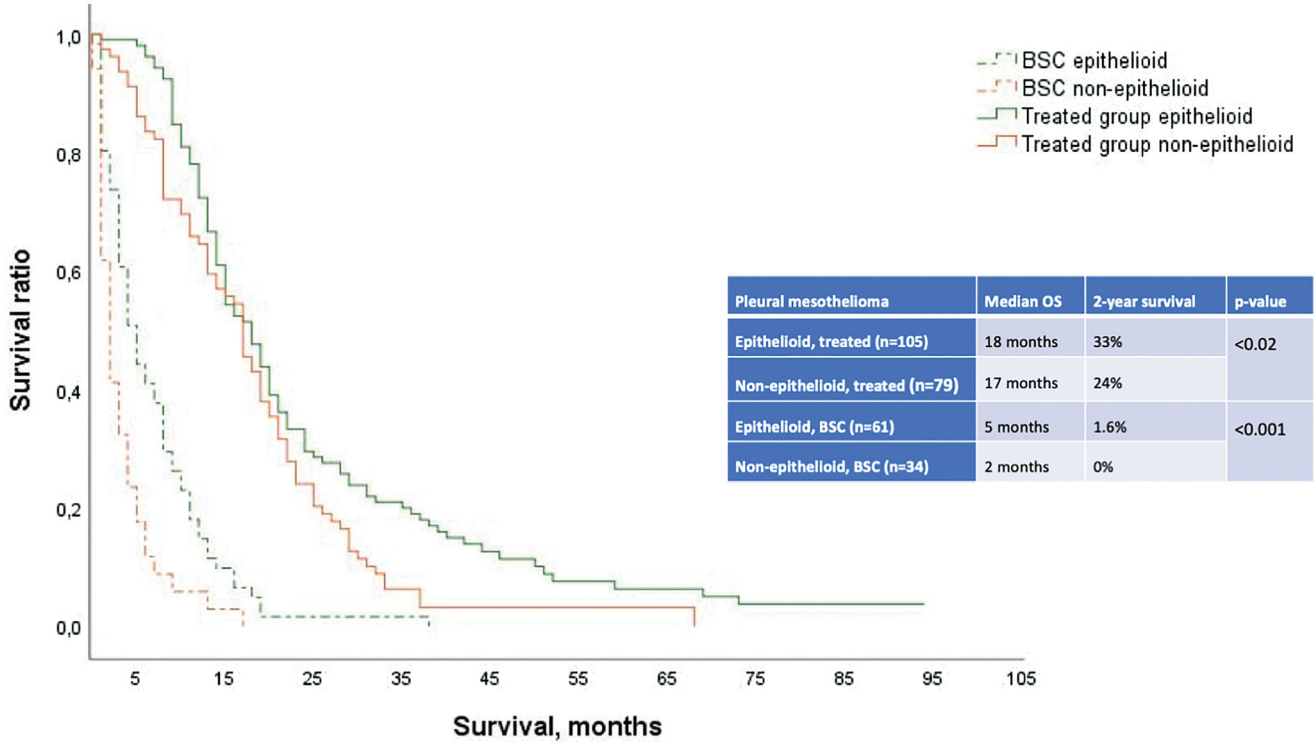

Figure 2. Kaplan–Meier survival curves according to MPM subtypes for the BSC and treated group. Dotted lines indicate BSC group and full lines indicate treated group. *p* Value <0.05 (log-rank test) indicates significant difference in survival between MM subtypes within the groups. BSC: best supportive care; OS: overall survival.

epithelioid and non-epithelioid subtypes the median survival was 18 and 17 months ($p<0.02$), respectively.

The 2-year survival in the BSC group was 1.6% for epithelioid and 0% for non-epithelioid subtypes. Epithelioid subtypes receiving treatment had a 2-year survival of 33.3% ($n=35$), while it was 24.0% ($n=19$) for non-epithelioid subtypes ($p<0.05$).

Discussion

Prognostic information may help in stratification of MPM treatment. This retrospective study reiterated that epithelioid subtype is the most important independent prognostic factor of survival in patients with anti-tumor treatment, but age, stage and female gender were not significant. In the BSC patients, the epithelioid subtype, good PS, and female gender were positive prognostic factors, while age and comorbidities were not associated with OS in either group.

Prognostic factors of survival

Prior literature on prognostic factors of MPM often analyze treated patients alone or pool them with untreated patients. In this study, the patients in the BSC group consisted of patients from the era prior to active treatment (1972–2000) as well as patients that were not regarded as fit for treatment from the era of active treatment. This relatively large cohort of untreated patients made it possible to assess differences in prognostic factors among the treated and the BSC groups separately.

Epithelioid tumors were found to be independently associated with better OS than non-epithelioid, both in the

patients that received active treatment and in the BSC group. These findings support results of prior studies suggesting that sarcomatoid and biphasic tumors are more aggressive and more resistant, with lower OS, regardless of treatment [11,12,17–20]. However, any type of treatment seemed to have a positive impact on OS versus the BSC group. Interestingly, patients with the non-epithelioid subtype had a median survival of 17 months in contrast to the epithelioid in the BSC group that had five months median OS, indicating a good effect of treatment also in this unfavorable subgroup.

All treated patients received some form of chemotherapy but only a minor subgroup received chemotherapy plus surgery or tri-modal treatment. The survival difference between treated and untreated is more than one year, and this may reflect the positive effect of treatment. However, there was also a significantly higher number of patients with PS 3–4 and more advanced disease in the BSC group. So, the true difference and impact of treatment is probably more modest.

Good PS (PS 0–2) was independent positive factor of OS in BSC patients. Patients with poor PS are immobilized and affected by symptoms, hence more unlikely to receive treatment according to modern treatment indications [21]. This further explains why very few patients in the treated group had poor PS. One study did not find a significant influence of PS on OS, however, that study pooled BSC and treated patients, and split groups into PS=0 and PS=1–5, hence potentially confounding the poor PS group with patients with relatively good clinical status 11. Three other studies that differentiated groups similar to this one found significant impact of good PS on OS [17,20,22]. Our findings confirm that PS is important for OS as part of the natural history of the disease [17,20,22].

Female gender was a significant favorable factor in BSC patients. While no significance was found in the treated group, only 14.7% were women, hence they were potentially underrepresented. Some previous studies have suggested that female gender is associated with improved OS in MM patients, while others did not [11,12,23]. This study indicates that female gender is a significant protective factor in BSC patients, although the mechanisms responsible for this are unclear [24].

Early stage appeared to be positive prognostic for OS in BSC patients, as expected. When adjusted to subtype and PS, it was no longer a significant factor, indicating that the non-epithelioid subtype and PS probably overshadows the prognostic effect of stage. Tumor stage was not a significant factor in the treated patients. In the treated group, late stage disease comprised only 19%, hence potentially underrepresented. However, the high rate of non-epithelioid type (46%) may confound the outcome. Prior literature, where both treated and BSC groups were pooled, have found contradicting results [12,19]. Advanced tumor stage may not be as important for prognosis if a patient has a good PS and responds to chemotherapy. There are, however, several questions regarding staging. In MPM, staging is difficult due to several challenges, such as the radiological evaluation of tumor burden in pleura and lymph nodes [25]. Death from mesothelioma is often unrelated to tumor burden, even locally advanced tumors can be lethal [26]. Moreover, the staging system has evolved over the last decades and it is difficult to compare staging in 1990 and 2015. Therefore, the staging information in this population spanning over 40 years may not be that reliable.

There is limited literature investigating significant comorbidities as a prognostic factor. Comorbidities can theoretically alter the clinical progress with potential limitations to treatment options and ultimately lead to death. However, this study found no independent effect of comorbidities on OS in neither BSC nor treated patients. A potential explanation is that quantitative data on comorbidity does not detail how or if a patient is clinically affected. Hence, some comorbidities may be correlated with PS, while asymptomatic comorbidities may not alter the clinical process significantly. However, the accuracy of the comorbidity data may be hampered by the retrospective nature of the study.

Age was not a significant prognostic factor in either group. Other studies found that age was a significant factor [11,23]. However, they did not adjust for PS, and PS does not necessarily to correlate to age, as seen in other patient populations with cancer [27]. While this study did find a higher mean age in the BSC group, low age did not seem to predict a better OS, regardless of treatment, after adjustment to important patient and disease characteristics.

Asbestos exposure had no correlation with OS after multivariate adjustment, as has been already by suggested by other studies [11,17,18,20]. Domestic exposures for men were only available after 2001, and considering three male patients were registered with no exposure prior to this, they may potentially have been exposed non-occupationally. However, our study had uniquely detailed data regarding occupation, household, and addresses for the sample population. This provided a more reliable analysis of asbestos exposure types compared to other studies, and potential low-scale misclassification would not alter the conclusions. Interestingly there were significantly more patients with occupational exposure in the treated group. This may be due to the fact that individuals that have been exposed knowingly will be more alert if they get symptoms and seek medical attention while they are in good PS, and therefore be fit to receive treatment.

Study population characterization

This study found that 92.5% of the MPM patients had been exposed to asbestos, which is much higher than studies from other countries, while similar to other Danish studies [17–20]. Potential reasons are that most studies defined asbestos exposure as prior occupation with asbestos material, hence excluding non-occupational exposure. Further, information needed to classify exposure type (i.e. household, address, and occupational history) are uniquely and readily accessible in the high quality The Supplementary Fund Register and the Civil Registration System databases for each Danish citizen [28,29]. This study suggests that environmental asbestos plays an even more prominent role in MPM than originally thought.

Mean age and median OS were very similar to demographics of other countries, further validating that prognosis for MPM patients is poor [11,12,17–19]. In the literature, median OS for all included patients ranges from 10 to 15 months, which corresponds to our findings [11,12,17–20,30]. Two studies reported OS in BSC and treated groups [20,30]. Both report higher OS for BSC patients (7.0 and 8.0 months), and lower OS for treated patients (11.0 and 11.5 months) compared to this study. The reason could be due to differences in patient selection and treatments available at a certain time point [20,30]. Epithelioid subtype was the most frequent histopathological subtype, followed by biphasic and sarcomatoid, respectively. Frequencies of epithelioid subtypes are consistent with the literature from other countries, however, distribution of biphasic and sarcomatoid subtypes are more diverse. One reason could be that the diagnosis relies on a semiquantitative method of estimating sarcomatoid components [14]. Regarding stage of disease, TNM stage III and IV were the most common, recapitulating the results of four other studies [11,12,17,19].

The strengths of this study is the long period over where this material has been collected, the completeness of the material, the relatively large group of non-treated cases, the comprehensive reevaluation of histology, the detailed clinical data on asbestos exposure and outcomes. The main limitations are the retrospective design and the lack of response-data. Further investigation into the treatment details regarding chemotherapy type, number of cycles etc. could add to the quality of results. Our data show that the characteristics of Danish MPM patients are similar with those reported in other countries, although asbestos exposure was more prevalent, probably due to the access to complete and detailed databases.

Conclusions

This retrospective study reiterate that the epithelioid subtype is a strong independent prognostic factor both in BSC and treated MPM patients, while age and comorbidities do not seem to be significant factors. Patients with non-epithelioid MPM treated with anti-neoplastic treatment had significantly better survival than BSC patients of any subtype, which reinforces the rationale to treat this patient group. Among BSC patients, the epithelioid subtype, good PS, and female gender were positive prognostic factors but all patients with BSC had a very low life expectancy. This long-term study can contribute to the clinical stratification of MPM patients and validation in other cohorts is appropriate to verify these findings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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