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## **Clinical features in malignant pleural mesothelioma patients with 5-year survival and evaluation of original diagnoses**

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## **Micro Abstract**

We identified within a larger national malignant pleural mesothelioma (MPM) cohort 43 patients with unusually long survival time. This study aimed to evaluate the diagnostic accuracy in this subgroup and the diagnosis was confirmed to be correct in most cases. In addition, we searched for clinical factors related to the prolonged survival time.

## **Abstract**

**Introduction:** Malignant pleural mesothelioma (MPM) is a fatal malignancy strongly associated with previous asbestos exposure. Overall survival remains dismal partly due to poor response to available treatment. Aims of this study were to evaluate diagnostic accuracy in a group of MPM patients with an unusually long survival time and to assess the factors related to this prolonged survival.

**Materials and Methods:** Forty-three patients with overall survival exceeding 5 years were accepted to the long-term survivor (LTS) group, and these patients were compared with 84 epithelial MPM patients. Data were collected from various national registers and electronic medical records. In addition, all available histopathological diagnostic samples and computed tomography studies were re-evaluated by experienced specialists.

**Results:** Our study showed a good diagnostic accuracy, with only one patient (0.5%) having an incorrect MPM diagnosis. Two localized malignant mesotheliomas (0.9%) and two well-differentiated papillary mesotheliomas (0.9%) were also found. LTS patients were younger, more frequently females, had a better performance status at time of diagnosis, and had less evidence of prior asbestos exposure. In multivariate analysis, we showed tumor size, Eastern Cooperative Oncology Group performance status, and first-line treatment (both surgery and chemotherapy) to be associated with survival time.

**Conclusion:** We confirmed the diagnosis of MPM in an overwhelming majority of patients in the LTS group. An epithelial subtype of MPM behaving clinically more indolently seems to exist, but further tumor and genetic characterization is needed. The prolonged survival time is most likely explained by a combination of tumor-, patient-, and treatment-related factors.

*Keywords:* Malignant pleural mesothelioma; Survival time; Diagnostic assessment; Prognostic factors

## Introduction

Malignant pleural mesothelioma (MPM) is a cancer with a poor prognosis; the median survival is 12 months or less.<sup>1,2,3,4,5</sup> The reasons for dismal long-term survival rates include diagnosis at a late stage<sup>4,5</sup> and poor response to conventional treatment modalities<sup>5,6</sup>. However, as some patients achieve prolonged survival after diagnosis, researchers have tried to identify prognostic factors underlying this phenomenon. The European Organization for Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B (CALGB) have proposed scoring systems to predict MPM patients' outcome.<sup>1,6,7</sup> According to their statements, variables associated with poor prognosis include poor performance status, non-epithelioid histology, male gender, high platelet count, high white blood cell count, and a high lactate dehydrogenase (LDH) level.<sup>1,6,7</sup> More recent studies have also found other tumor-related factors affecting prognosis.<sup>2,3,4,8</sup>

Due to the poor prognosis associated with MPM, the impact of treatment modalities on the survival rate is continuously of interest. According to some studies, surgery-based multimodality therapy appears to have superior survival rates, but comparing the results of different studies is challenging as the study settings often vary.<sup>7,9,10,11</sup> However, median survivals associated with trimodality treatment have been reported to exceed 20 months.<sup>7,11</sup>

We established a cohort of 1010 patients diagnosed with MPM in Finland in 2000-2012 from the nationwide Finnish Cancer Registry,<sup>12</sup> and within the cohort, we identified a subpopulation of patients who lived exceptionally long after diagnosis. Our hypothesis was – similar to a study conducted with pancreatic cancer patients<sup>13</sup> – that not all of these patients would represent mesothelioma, but rather had been misdiagnosed.

## Material and methods

### *Study design and population*

In this study, patients exceeding overall survival (OS) of 5 years were classified as long-term survivors (LTS, n=43, 4.3%, Figure 1). The LTS group was compared with a group of patients with epithelial mesothelioma from the Hospital District of Helsinki and Uusimaa in 2007-2012. The epithelial subtype was chosen as a control because of its generally acknowledged better prognosis relative to other subtypes.<sup>5</sup> The study protocol was approved by the local Institutional Review Board (IRB) and the Ethics Committee of the Hospital District of Helsinki and Uusimaa (418/13/03/02/2015).

For both groups, the medical history and outcome data collected from the Finnish Cancer Registry were complemented retrospectively by electronic medical records (EMRs). The recorded patient baseline characteristics included age at diagnosis, gender, laterality of disease, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status,<sup>14</sup> and treatment information (surgery, chemotherapy, radiation therapy) (Table 1). Additionally, information about previous malignancies was collected from both patients and their family members. Comorbidities were evaluated using the Charlson comorbidity index (CCI) score.<sup>15</sup> Dates and causes of death were collected from the National Registry of Causes of Death at Statistics Finland. Median overall survival (OS) was calculated from the date of the pathologic diagnosis to the time of death from any cause. For the patients alive, the end date used to calculate survival time was January 9, 2018.

The computed tomography (CT) studies available at the time of clinical diagnosis were reviewed by a radiologist (T.V.) with special experience in occupational radiology, and the mesothelioma size was estimated using a method where the maximal tumor thickness on axial images is multiplied by the tumor extent grade.<sup>16</sup> Pleural plaques were searched from both sides separately and then reported overall as

being present or absent. The maximal thickness of pleural effusion was measured on axial planes. Clinical staging was evaluated using the 8<sup>th</sup> edition of the AJCC/UICC staging system. <sup>17</sup>

Possible occupational asbestos exposure was documented from EMRs, if available. In Finland, employees are legally entitled to receive compensation in the case of an occupational disease. The decision regarding worker's compensation benefit was collected from the Finnish Workers' Compensation Center. Pulmonary asbestos fiber counts were measured from lung samples using scanning transmission electron microscopy (STEM) (detection limit ~ < 0.1 million f/g) in the Finnish Institute of Occupational Health (FIOH). <sup>18</sup> For fiber analyses, lung specimens were required to represent a region without tumor or fibrosis, to be at an intermediate distance from the bronchus and pleura, and visually inspected before burning to ashes for STEM.

#### *Histopathological assessment*

For both groups, all available histopathological diagnostic samples were re-evaluated blindly by a senior pathologist (H.W.) with experience in mesothelioma diagnostics. In borderline cases, the diagnosis was made in consensus with another experienced pulmonary pathologist (M.M.). The pathological diagnosis was based on the current standards of morphological and immunohistochemical (IHC) criteria as per the WHO Classification (4<sup>th</sup> edition) for tumors of the pleura. <sup>19</sup> In order for patients to be included in the study, we required at least two positive and two negative mesothelial IHC markers to be available (Table 2).

The diagnostic sample was a surgical biopsy in 88 (69%), a pleural biopsy obtained through medical pleuroscopy in 12 (10%), and a thick needle biopsy performed by interventional radiologists (IRs) in 27 (21%) cases. A larger surgical specimen was evaluated instead of the biopsy if it was obtained within three months. Of all samples, 42 (33%) were considered to be small in the pathological review; seven (6%) of these were evaluated as marginally diagnostic.

### *Statistical analysis*

Statistical analyses were performed using IBM Statistics 25.0 (IBM SPSS Statistics, Chicago, IL, USA). P-value <0.05 was considered significant. Descriptive analyses of qualitative variables are expressed as number of patients and percentage. Quantitative variables are presented as median and interquartile range (IQR). The associations between baseline variables were determined by non-parametric Mann-Whitney U-test for continuous data and Chi-square test for categorical data. Binary logistic regression was used to identify variables predictive of 5-year survival. Crude survival analysis was first used to estimate each factor's impact on survival. The significant variables were then entered into a multivariate Cox Proportional-Hazards model, which was adjusted for age, gender, tumor size (TS), clinical stage, occupational disease, ECOG performance status, and treatment. In line with previous studies, we divided ECOG performance status into two groups (PS 0 versus PS I-III) for survival models.<sup>20</sup> We also combined TNM stage group IA with IB and IIIA with IIIB to increase statistical power.



## Results

### *Validity of MPM classification*

For the purpose of re-evaluation, a median of 3 (IQR 1 - 5) hematoxylin and eosin saffron-stained slides were reviewed from each tumor, and additional IHC stains were conducted for 19 patients (15%) to supplement the original diagnosis. Only one patient (0.5%) was noted to have an incorrect MPM diagnosis (Figure 1). Furthermore, two localized malignant mesotheliomas (LMMs) (0.9%) and two well-differentiated papillary mesotheliomas (WDPMs) (0.9%) were found, and the diagnosis of 15 patients (7%) could not be confirmed due to, for instance, incomplete immunohistochemical (IHC) profile. Five patients (2%) were also excluded since the diagnostic sample was missing and 10 patients (5%) due to a non-representative sample. Forty-three patients were accepted to the LTS group and the histological re-evaluation confirmed the group to solely consist of epithelial subtype. The control group comprised 84 patients.

### *Clinical factors related to long-term survival*

The clinical characteristics are summarized in Table 1. Compared with the control group, the long-term survivors were younger, more frequently females, and their performance status was better at the time of diagnosis. The proportion of patients having another malignancy was roughly similar in both study groups (LTS group n=7, 16% versus control group n=14, 17%, p=0.213). In the LTS group, two patients' (5%) first-degree relative was noted to have a previous history of mesothelioma and two patients (5%) had received lymphoma-related radiation therapy over 15 years before MPM diagnosis in comparison with the control group, in which none of the patients had prior therapeutic intrathoracic radiation.

No difference was observed between the study groups in the reported first-line treatment modality given to the patient (p=0.054, Table 1). Excluding the diagnostic procedures, a trend in the long-term survivors being more likely to undergo surgery for mesothelioma was noted (44.2% versus 27.4%, p=0.057), albeit

the difference in extensive surgery was insignificant (n=12, 28% versus n=19, 23%, p=0.511). Palliative local radiotherapy was also more common in the LTS group (n=12, 28% versus n=9, 11%, p=0.014).

Eighteen patients (42%) in the LTS group were determined to have an occupational asbestos disease compared with 63 patients (75%) in the control group (p<0.001). Similarly, 19 LTS patients (44%) had self-reported asbestos exposure compared with 64 patients (76%) in the control group (p<0.001). Asbestos fiber analysis was performed for 13 LTS patients (30%) and 60 controls (71%). The median pulmonary fiber content was significantly lower in the LTS group than in the control group (p=0.019). The median concentrations of fiber counts are presented as million fibers per dry lung gram (mf/g) (Table 1).

#### *Prognostic factors*

The median overall survival (OS) was 19.5 months, but OS clearly differed between the study groups (Table 1). Ten LTS patients (5%) were still alive at the end of the study period on January 9, 2018. Three patients (2%) died of causes other than MPM. The clinical factors with prognostic significance in survival analysis are summarized in Table 3. Adjusted Cox Regression model showed surgery (HR 0.39, 95% CI 0.21-0.73) and chemotherapy (HR 0.47, 95% CI 0.27-0.83) to be independent predictors for better OS, while ECOG performance status I-III (HR 2.97, 95% CI 1.82-4.82) was associated with worse survival. Tumor size (TS) was also noted to have an impact on survival time (HR 1.01, 95% CI 1.00-1.01).

## Discussion

In this study, we presented a unique group of MPM patients with an overall survival exceeding 5 years. Several studies have reported 5-year survival rates of around 5%, which is similar to the proportion in our larger cohort.<sup>21</sup> However, this is to our knowledge the first study with a thorough validation of histopathological diagnostics, and contrary to our original hypothesis, the re-evaluation confirmed good diagnostic accuracy in the LTS group, suggesting the existence of an indolent MPM subtype with a better prognosis. *Carpelan-Holmström et al.*<sup>13</sup> previously performed a similar re-evaluation for pancreatic ductal adenocarcinoma patients with the opposite result, showing increased survival explained mostly by false diagnosis. Additionally, we recognized differences between the study groups in baseline characteristics and identified clinical factors associated with survival time in these patients, and our results to some extent resemble the findings of previous publications.<sup>22, 23</sup>

Earlier studies have reported increased risk for mesothelioma after thoracic radiation therapy.<sup>24</sup> However, *Chirieac et al.*<sup>25</sup> found that lymphoma radiation-associated MPM had different histologic features and longer overall survival than asbestos-associated disease. In concordance with these results, we found two LTS patients with post-radiation mesothelioma with no reported asbestos exposure. Another etiological explanation for long-term survival could be germline BAP1 mutation, which has been linked to a 7-fold increased survival.<sup>3</sup> Patients with somatic BAP1 mutation have also been studied and interestingly, somatic BAP1 mutation does not seem to associate with a similar kind of survival benefit.<sup>26</sup> *Panou et al.*<sup>27</sup> recently found BAP1 to be the most prevalent germline cancer susceptibility mutation in malignant mesothelioma, and they also showed any germline mutations to be associated with minimal-to-no asbestos exposure, younger age, and another malignancy. In our cohort, there was no difference in the frequency of other malignancies between the study groups, and only one patient had a malignancy linked to a known BAP1-related cancer syndrome.<sup>28</sup> However, otherwise the clinical characterization of our LTS group suggests that germline mutations could be a factor in the

improved long-term survival and in addition to BAP1, other cancer susceptibility genes harboring germline mutations seem to exist in malignant mesothelioma. <sup>29</sup> *Hassan et al.* <sup>30</sup> showed that tumor mutation status is also of clinical significance since germline mutations might be associated with a better response to certain chemotherapy regimens.

Asbestos exposure is a well-known risk factor for mesothelioma, and over 80% of pleural mesotheliomas are reported to be derived from a prior asbestos exposure. <sup>31</sup> However, its prognostic significance has been reported with mixed results. Some studies have described a worse outcome in those with a prior asbestos exposure, <sup>9,32</sup> while others have found no association <sup>21,33,34</sup> . Interestingly, a study on the association between asbestos fiber burden and survival noted that MPM patients with a low asbestos burden had a 3-fold increased risk of death relative to those with a moderate fiber burden, while for patients with a high burden the risk of death was 4.8-fold. <sup>35</sup> We found that LTS patients were less likely to have a known asbestos exposure and similarly their asbestos fiber burden was significantly smaller. Furthermore, the CT analysis showed less pleural plaques in the LTS group, indicating a lower level of asbestos exposure. However, asbestos-related occupational disease was only a significant variable in crude survival analyses. Non-asbestos related MPM could partly explain why the LTS patients, compared with controls, were younger and more often female; asbestos-exposure work has historically mainly been done by men, and the latency period has been reported to be up to 30-60 years. <sup>36</sup>

In the revised WHO classification of pleural tumors, well-differentiated papillary mesotheliomas (WDPMs) and localized malignant mesotheliomas (LMMs) are recognized as distinct pleural tumors with a better prognosis than diffuse MPM. <sup>19</sup> We were able to identify two WDPMs and two LMMs with over a 5-year survival. All of them were originally diagnosed as diffuse MPM and subsequently excluded from our analysis.

Unsurprisingly, performance status was a powerful prognostic factor in our study since this has been observed in many diseases and guides the treatment options for individual patients.<sup>37</sup> We confirmed our previous finding that tumor size approximation with tumor thickness and extension was a better prognostic factor than CT stage.<sup>16</sup> The optimal treatment regimen remains controversial in MPM since only the benefit from combination chemotherapy has been established in prospective controlled clinical trials.<sup>38</sup> Although we found that surgery and chemotherapy were associated with longer survival, the effects of these treatment modalities on survival could be confounded by patient-driven factors in a non-randomized setting. Also, different treatment regimens could be flawed by regional and time-dependent differences. Thus, the role for treatment in survival of the LTS group cannot be isolated due to heterogeneity of the population and clinical practices. A comprehensive national MPM treatment program could facilitate more coherent clinical practices. Of note, none of the patients received multimodality treatment and the role of radical-intent surgery was insignificant.

### **Limitations of the study**

The main limitation of this study lies in its retrospective design. However, this is still a large MPM cohort with a thorough diagnostic assessment and clinical evaluation of the 5-year survivors. Missing BAP1 information is acknowledged to be a possible confounding factor in the survival analyses due to its strong association with age, but, unfortunately, this information was unavailable for the purposes of this study and remains to be assessed in future studies. One-third of our tumor samples are categorized as small, which can complicate histopathological diagnostics, but in our study diagnostic assessment was performed by pathologists with special experience in mesotheliomas using sufficient immunohistochemistry to reduce the error. The possible effect of lead-time bias for superior survival of the LTS group cannot be ruled out, but given the dismal prognosis associated with disseminated MPM, we feel that it does not significantly contribute to the findings of our study. Another limitation lies in the disproportion of asbestos fiber analyses between the study groups.

## **Conclusions**

Prolonged MPM survival is not explained by a diagnostic error, but rather by tumor-, patient-, or treatment-related factors. We found tumor size, ECOG performance status, and first-line treatment (both surgery and chemotherapy) to be associated with survival time.

## Clinical Practice Points

- Malignant pleural mesothelioma (MPM) is a malignancy strongly associated with previous occupational asbestos exposure.
- The expected outcome after MPM diagnosis is usually poor.
- We showed that clinically more indolently behaving MPM subtype with prolonged survival time might exist.
- The baseline characteristics differed between our two study groups (long-term survivor group versus control group).
- In addition, we found tumor size, Eastern Cooperative Oncology Group (ECOG) performance status, and first-line treatment (both surgery and chemotherapy) to be associated with survival time.

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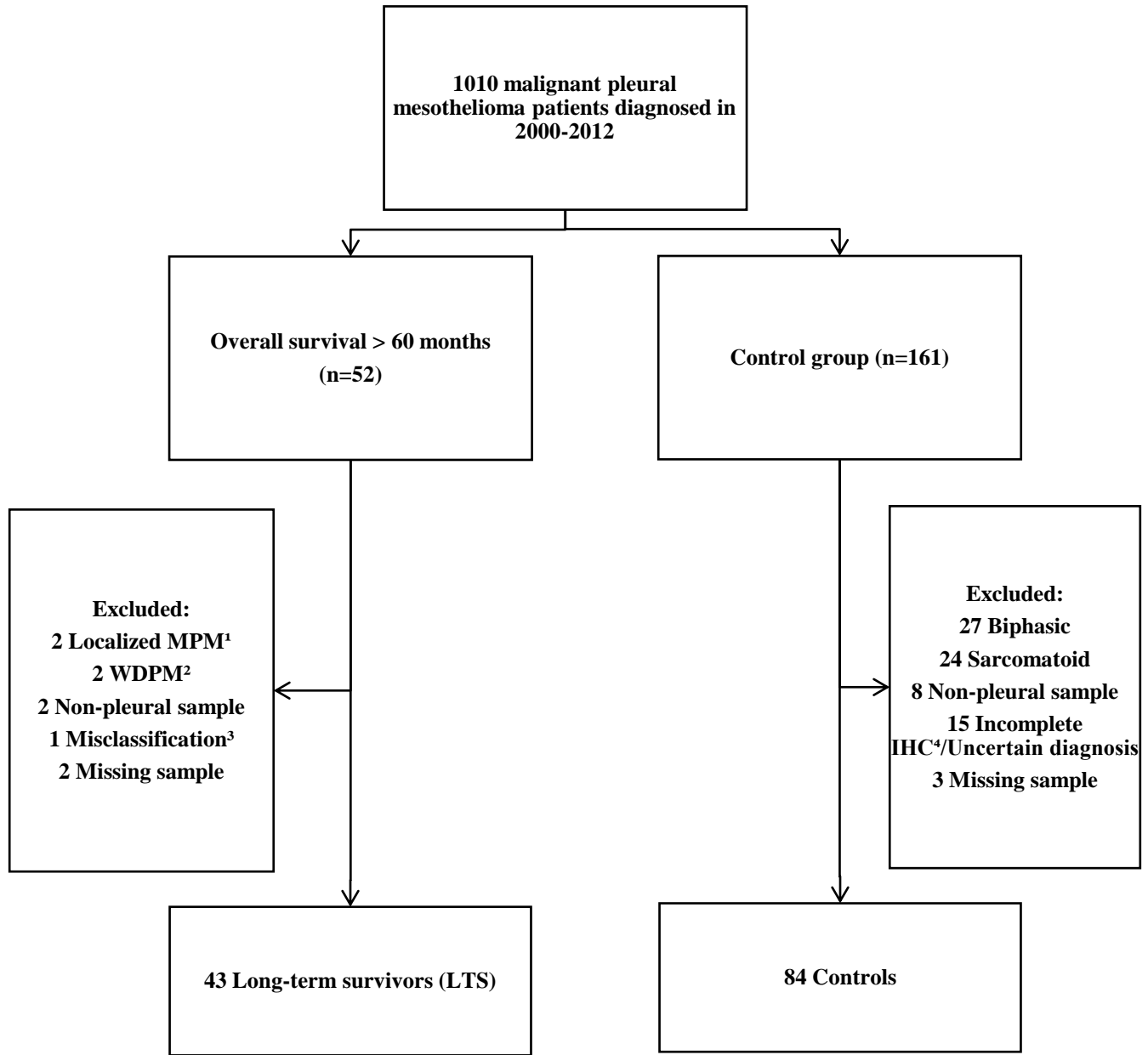
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**Figure 1.** Study flow chart. <sup>1</sup> MPM, malignant pleural mesothelioma; <sup>2</sup> WDPM, well-differentiated papillary mesothelioma; <sup>3</sup> Adenocarcinoma misclassified as MPM; <sup>4</sup> IHC, immunohistochemistry.

**Table 1. Baseline characteristics and crude analysis for long-term survival.**

Characteristic	LTS <sup>1</sup> (n=43)	Controls (n=84)	p-value <sup>9</sup>	OR (95% CI) <sup>2</sup>
Age, years, median (IQR) <sup>3</sup>	61.0 (57 – 70)	67.30 (62 – 74)	0.003	0.93 (0.89-0.98)
Overall survival, months, median (IQR)	79.3 (69.3 – 99.3)	11.3 (5.6 – 19.2)	<0.001	NA
Gender, n (%)			0.011	
Female	13 (30.2%)	10 (11.9%)		3.21 (1.27-8.10)
Male	30 (69.8%)	74 (88.1%)		1.00
Occupational asbestos disease, n (%)			<0.001	
Yes	18 (42%)	63 (75%)		1.00
No	25 (58%)	21 (25%)		4.17 (1.91-9.10)
Pulmonary fiber content, mf/g <sup>4</sup> , median (IQR)	0.4 (0.2 – 5.4)	9.0 (0.6 – 132.5)	0.019	0.99 (0.97-1.00)
ECOG <sup>8</sup> performance status, n (%)			<0.001	
PS 0	39 (90.7%)	33 (39.3%)		15.07 (4.93-46.10)
PS 1-3	4 (9.3%)	51 (60.7%)		1.00
CCI <sup>5</sup> , 0 point, n (%)	24 (55.8%)	50 (59.5%)	0.995	0.86 (0.41-1.81)
CCI over 1 point, n (%)	19 (44.2%)	34 (40.5%)		1.00
Smokers, n (%)			0.621	
Never	19 (44.2%)	41 (48.8%)		1.00
Former/Current	24 (55.8%)	43 (51.2%)		1.20 (0.58-2.52)
Pack-years, median (IQR)	9.5 (0 – 27.8)	0 (0 – 37.5)	0.907	1.00 (0.98-1.02)
Laterality, right, n (%)	22 (51.2%)	44 (52.4%)	0.897	0.95 (0.46-1.99)
Tumor size, mm, median (IQR)	17.0 (2.3 – 45.3)	30.0 (10 – 62.3)	0.035	0.99 (0.97-0.99)
Bilateral pleural plaques, yes, n (%)	16 (42.1%)	52 (62.7%)	0.034	0.43 (0.20-0.95)
Clinical stage, n (%) <sup>7</sup>			0.029	
No measurable tumor	7 (17.9%)	4 (4.8%)		11.38 (1.65-78.4)
Stage I	16 (41.0%)	27 (32.1%)		3.85 (0.77-19.31)
Stage II	3 (7.7%)	3 (3.6%)		6.50 (0.73-57.83)
Stage III	11 (28.2%)	37 (44.0%)		1.93 (0.38-9.90)
Stage IV	2 (5.1%)	13 (15.5%)		1.00
First-line treatment, yes, n (%)			0.054	
Only BSC <sup>6</sup>	4 (9.3%)	21 (25.0%)		1.00
Chemotherapy	20 (46.5%)	40 (47.6%)		2.63 (0.79-8.68)
Surgical	19 (44.2%)	23 (27.4%)		4.38 (1.27-14.84)

<sup>1</sup> LTS, long-term survivors (over 5 years); <sup>2</sup> OR, odds ratio (95% confidence interval); <sup>3</sup> IQR, interquartile range; <sup>4</sup> mf/g, million fibers per gram of dry lung tissue; <sup>5</sup> CCI, Charlson comorbidity index score; <sup>6</sup> BSC, best supportive care; <sup>7</sup> Clinical stage unknown for four LTS patients due to unavailable CT results; <sup>8</sup> ECOG, eastern cooperative oncology group.

- <sup>9</sup> P-values are for the comparison of LTS and controls and were calculated by the Mann-Whitney U-test or Chi-square test as appropriate
- <sup>2</sup> Odds ratios with corresponding 95 percent confidence intervals were calculated by univariate binary logistic regression

**Table 2. Performed immunohistochemistry (IHC).**

<b>Positive IHC markers<sup>2</sup></b>	<b>LTS group</b>	<b>Control group</b>	<b>Total</b>
Calretinin	43/43 (100%)	84/84 (100%)	127/127 (100%)
Keratin 5/6	40/41 (98%)	81/81 (100%)	121/122 (99%)
Podoplanin (D2-40)	6/6 (100%)	3/4 (75%)	9/10 (90%)
WT-1	11/11 (100%)	32/34 (94%)	43/45 (96%)
Vimentin	7/9 (78%)	13/14 (93%)	20/23 (87%)
EMA	6/6 (100%)	2/2 (100%)	8/8 (100%)
<b>Negative IHC markers<sup>3</sup></b>			
CEA	29/29 (100%)	11/11 (100%)	40/40 (100%)
TTF-1	35/35 (100%)	80/80 (100%)	115/115 (100%)
CD15/Leu-M-1	17/17 (100%)	16/16 (100%)	33/33 (100%)
Ber-EP4	25/26 (96%) <sup>1</sup>	65/67 (97%)	90/93 (97%)
MOC-31	1/1 (100%)	-	1/1 (100%)

<sup>1</sup>EP4 immunohistochemistry is performed on metastasis for one patient; <sup>2</sup>Positive IHC staining supports MPM diagnosis;

<sup>3</sup>Negative IHC staining supports MPM diagnosis.

**Table 3. Clinical factors associated with survival.**

<b>Variable</b>	<b>Unadjusted HR (95% CI)<sup>2</sup></b>	<b>p-value</b>	<b>Adjusted<sup>1</sup> HR (95% CI)</b>	<b>p-value</b>
Age (continuous)	1.03 (1.01-1.06)	0.002	1.02 (0.99-1.04)	0.179
Gender, male	1.48 (0.92-2.39)	0.104	1.06 (0.57-1.96)	0.861
TS <sup>3</sup> (continuous)	1.01 (1.00-1.01)	0.002	1.01 (1.00-1.01)	0.022
Clinical stage		0.103		0.903
No measurable tumor	1.00		1.00	
Stage I	1.34 (0.67-2.70)	0.409	1.16 (0.55-2.45)	0.694
Stage II	1.63 (0.59-4.51)	0.345	1.76 (0.56-5.57)	0.334
Stage III	1.90 (0.95-3.80)	0.070	1.27 (0.57-2.81)	0.562
Stage IV	2.57 (1.14-5.77)	0.022	1.27 (0.48-3.36)	0.631
Occupational disease, yes	1.70 (1.15-2.50)	0.008	1.29 (0.78-2.16)	0.314
ECOG <sup>5</sup> performance status		<0.001		<0.001
PS 0	1.00		1.00	
PS I-III	4.09 (2.69-6.22)		2.97 (1.82-4.82)	
First-line treatment		<0.001		0.009
BSC <sup>4</sup>	1.00		1.00	
Surgery	0.30 (0.17-0.50)		0.39 (0.21-0.73)	
Chemotherapy	0.45 (0.28-0.73)		0.47 (0.27-0.83)	
Charlson comorbidity score		0.755		
CCI 0	1.00			
CCI >1	1.06 (0.73-1.54)			

<sup>1</sup> Cox regression model adjusted for age, gender, TS, clinical stage, occupational disease, ECOG performance status, and treatment; <sup>2</sup> HR, hazard ratio (95% confidence interval); <sup>3</sup> TS, tumor size, mm; <sup>4</sup> BSC, best supportive care; <sup>5</sup> ECOG, eastern cooperative oncology group.