Original Article

Prognostic factors in malignant pleural mesothelioma: A retrospective study of 60 Turkish patients

ABSTRACT

Aim: Malignant pleural mesothelioma (MPM) is an aggressive tumor with poor prognosis. The study aims to examine the effect of certain clinical, laboratory, radiologic, and pathologic characteristics on survival.

Patients and Methods: Sixty patients who had undergone PET/CT evaluation at initial diagnosis were included. We investigated the effect of certain clinical, laboratory, radiologic characteristics, SUVmax of the tumor, and pathological characteristics such as histological subtype, mitotic activity index (MAI), tumor necrosis, and inflammation on survival. The pathological slides of each patient were re-evaluated for MAI, presence of necrosis, and inflammation. The patients were grouped based on number of mitosis as MAI 1:≤9, MAI 2:10-19, MAI 3: >19 mitosis.

Results: There were 34 male and 26 female patients with a mean age of 53.6 ± 10.6 years. Mean and median survival time was 14.83 ± 10.75 and 11.95 (min 0.43-max 48.10) months, respectively. Using univariate analysis leukocytosis ($P = 0.009$), rind-like pleural thickening ($P = 0.037$), advanced disease stage ($P = 0.004$), best supportive therapy alone ($P = 0.004$), SUVmax higher than 8 ($P = 0.023$), MAI higher than 1 ($P = 0.033$), and presence of tumor necrosis ($P = 0.037$) were found as poor prognostic factors. At multivariate analysis, leukocytosis (P = 0.026, HR: 2.27), advanced disease stage ($P = 0.021$, HR: 2.46), best supportive therapy alone ($P = 0.029$, HR: 5.12), and MAI higher than 1 ($P = 0.01$, HR: 3.01) were independently associated with survival, whereas SUVmax of the tumor failed to enter the model ($P = 0.07$, HR: 1.89).

Conclusion: Presence of leukocytosis, advanced disease stages, supportive therapy alone, and higher MAI were found to be negative prognostic factors in patients with MPM.

KEY WORDS: Malignant pleural mesothelioma, mitotic activity index, prognostic factors, survival

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INTRODUCTION

Malignant pleural mesothelioma (MPM) is an uncommon and aggressive tumor originating from mesothelial cells lining the pleural cavity.[1] It is highly resistant to chemotherapy and radiotherapy, with a median survival less than one year.[2,3] Prognostic information is, therefore, potentially valuable in managing patients. Age, gender, performance status, histology, and treatment intent are the most commonly studied prognostic factors.[4-6]

^{18}F-Fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) is an invaluable imaging technique for the diagnosis, staging, and prognosis of MPM. High maximum standardized uptake values (SUVmax) of the tumor on PET/CT were found as poor prognostic factors in patients with MPM.[7-9]

Mitotic activity index (MAI) is the most commonly used method of assessing the proliferative activity of a tumor. The prognostic effect of MAI in patients with MPM is challenging in the literature. While MAI was not found as a significant prognostic factor in a small series of patients with MPM,[10] it is reported that high mitotic count was independently associated with poor prognosis in a larger series of patients with epithelioid mesothelioma.[11]

In this study, we investigated the prognostic effect of certain clinical, laboratory, radiologic characteristics, and SUVmax of the tumor on PET/CT. Additionally we evaluated the prognostic effect of some pathological characteristics of the tumor such as MAI, tumor necrosis, and inflammation.

PATIENTS AND METHODS

Patients

The study included 60 patients (34 males/26 females) who were diagnosed with MPM and underwent PET/CT for staging purposes between November

1, 2008 and December 31, 2012 at our medical center. With the retrospective design, the study was approved by the Institutional Ethics Committee.

The files of patients were retrieved from the archive, and available study forms were duly filled in. The demographical, clinical, radiological characteristics, basal laboratory parameters, diagnostic methods, pathological findings, and applied treatment modalities were recorded on these forms. The staging of the patients were done based on the clinical and radiological findings according to the staging system proposed by the International Mesothelioma Interest Group (IMIG).[12] Magnetic resonance imaging (MRI) was used to complement PET/CT in the multimodality treatment group, and cranial CT or MRI was performed if necessary.

Demographic data of the patients, diagnostic methods, histopathological diagnosis, stages, and applied therapies are presented in Table 1. The chemotherapy regimen was pemetrexed (500 mg/m^2)/cisplatin (75 mg/m^2) in the entire group receiving chemotherapy. Adjuvant hemithoracal radiotherapy (180 cGy/day, 28 fractions, 5040 cGy totally) was delivered to the patients who had undergone extrapleural pneumonectomy.

Table 1: Patient characteristics

Characteristic	Number of patients (%)
Gender	
Male	34 (56.7)
Female	26 (43.3)
Mean age±SD (min-max) years	53.6±10.6 (27-77)
≤60	41 (68.3)
>60	19 (31.7)
Exposure to asbestos	
Environmental	53 (88.3)
Occupational	-
None	7 (11.7)
Smoking history	
Smokers	26 (43.3)
Non-smokers	34 (56.7)
Diagnostic method	
VATS pleural biopsy	37 (61.7)
Closed pleural biopsy	9 (15)
Transthoracic needle biopsy	9 (15)
Thoracotomy	4 (6.7)
Mediastinoscopy	1 (1.7)
Stage	
I	15 (25)
II	13 (21.7)
III	19 (31.7)
IV	13 (21.7)
Applied therapies	
Best supportive care	15 (25)
Chemotherapy	38 (63.3)
Multimodality therapy	7 (11.7)
Pleuropneumonectomy	4
Pleurectomy/decortication	3
Pleurodesis	
Yes	26 (43.3)
No	34 (56.7)

SD=Standard deviation VATS=Video-assisted thoracic surgery

PET/CT imaging

PET/CT was carried out with an integrated PET/CT scanner *(Siemens, Biograph-6-HI-REZ)* at the time of initial diagnosis in all of the patients. All PET/CT scans were re-evaluated by a single nuclear medicine physician who was blinded to all clinical and pathological data. The SUVmax of the pleura/pleural lesions, which are more evident than the background activity in the visual evaluation and lymph nodes with FDG uptakes more prominent than mediastinal blood pool activity, were recorded.

Pathological evaluations

All prepared hematoxylin-eosin-stained slides of the patients were retrieved from the archive and were re-evaluated by an experienced pulmonary pathologist blinded to clinical data of the patients. Immunohistochemical stains were used in all the patients to confirm the diagnosis of MPM.

All of the slides were evaluated for presence of necrosis, inflammation, and the number of mitosis. Sections were inspected at low power (×40) using light microscopy for the presence of necrosis and inflammation. Mitotic figures were counted in areas selected on the basis of the following criteria: 1) Presence of good cellularity and fields without necrosis, inflammation, or calcification. 2) High density of mitotic figures. Counting was carried out in ten consecutive high power fields of 0.196 mm^2 (x400). Only cells with clear morphological features of metaphase, anaphase, and telophase were considered as a mitotic figure. Apoptotic and hyperchromatic nuclei were not regarded as mitosis. The number of mitosis was graded as "mitotic activity index (MAI) 1" if the number of mitosis is ≤9, "MAI 2" if the number of mitosis is 10-19, "MAI 3" if the number of mitosis is >19.

Statistical analysis

SPSS for windows release 15.0 package program was used to carry out the statistical analysis and construct figures. The descriptive statistics were given as mean ± standard deviation for variables with a normal distribution while median values (minimum-maximum) were used for variables that were not normally distributed and number of cases (%) for nominal variables.

In order to define factors that influence the survival, we calculated the median lifetime using the Kaplan-Meier method and compared it using a log rank test. We also calculated the median estimated lifetime for subgroups of each variable and 95% confidence intervals in relation to this period. In order to determine the independent risk factors that influence the survival, multiple effects of risk factors which have or might have a significant effect on survival were evaluated using the Multiple Cox Regression Analysis following univariate analysis. We also calculated the Hazard Ratio (HR) of independent factors that were found to be significant for mortality as a result of Multiple Cox Regression Analysis as well as its 95% confidence interval (95% CI). Any results with a *P* value less than 0.05 were considered to be statistically significant.

RESULTS

The demographic characteristics of the patients, diagnostic methods, disease stages, and applied therapies are presented in Table 1. The study included 60 patients (34 males, 26 females) with a mean age of 53.6 ± 10.6 years (min: 27 - max: 77). Environmental exposure to asbestos was present in 88.3% of the patients. Smoking history was present in 43.3% of the patients. VATS pleural biopsy was the most common (N = 37, 61.7%) way of diagnosis.

The pathological findings of the patients are presented in Table 2. The histological diagnosis was epithelial in 45 (75%) and biphasic in 14 (23.3%) patients. One patient (1.7%) had unidentified MPM. While MAI varied between 1 and 40, mean MAI was 10.5 ± 7.8. There were 36 (60%) patients with a MAI score 1, 18 (30%) patients MAI 2, and 6 (10%) patients MAI3. Necrosis was observed in 15 (25%) patients. Inflammation was present in 41 (68.3%) patients.

The thoracic CT and PET/CT findings of the patients are summarized in Table 3. In thoracic CT evaluations, right hemithorax was involved in 51.7% (N = 31) of the patients. While 51.7% (N = 31) of the patients had nodular pleural thickening, 16.7% (N = 10) had diffuse pleural thickening and 31.7% (N = 19) had no pleural thickening. There was rind-like pleural thickening in 14 (23.3%) patients. Moderate to massive pleural effusion was present in 73.4% of the patients. In PET/CT imaging, pleural FDG uptake was diffuse in 50%, focal in 16.7%, and mixed in 28.3% of the patients, 5% had no uptake. The mean SUVmax was 8.3 ± 5.5 (min: 0 - max: 27.25).

At the end of the study, 40 patients were dead. The mean and median survival time were 14.83 ± 10.75 and 11.95 (min 0.43- max 48.10) months, respectively. The survival rates at 6-months, 1-year, and 2-years were 90.8%, 58.6%, and 20.4%, respectively. A small number of patients (n = 7, 11.7%) were deemed suitable to undergo multimodality therapy, and median survival was 35.17 months. While 38 patients (63.3%) who received chemotherapy had a median survival of 14.8 months, 15 patients (25%) treated with best supportive therapy had a median survival of 5 months [Table 4]. Pleurodesis was performed in 26 (43.3%) patients. Median survival time was longer in patients with pleurodesis, but pleurodesis was not found to be a prognostic factor both in univariate and multivariate analysis.

In univariate analysis, leukocytosis (P = 0.009), rind-like pleural thickening (P = 0.037), advanced disease stage (P = 0.004), best supportive therapy alone (P = 0.004), SUVmax higher than 8 (P = 0.023), MAI higher than 1 (P = 0.033), and the presence of tumor necrosis (P = 0.037) were negative prognostic factors [Table 4]. In multivariate analysis [Table 5], leukocytosis (P = 0.026, HR: 2.27), advanced disease stages (P = 0.021, HR: 2.46), best supportive therapy alone (P = 0.029, HR: 5.12), and MAI higher than 1 (P = 0.01, HR: 3.01) were independently associated with poor prognosis [Figures 1-4], whereas SUVmax of the tumor failed to enter the model (P = 0.07, HR: 1.89) [Figure 5].

Table 2: Pathological findings of the patients

Characteristic	Number of patients (%)
Histological diagnosis	
Epithelial	45 (75)
Biphasic	14 (23.3)
Undifferentiated	1 (1.7)
Mitotic activity index (mean±SD)	10.5±7.8 (min:1-max:40)
MAI 1	36 (60)
MAI 2	18 (30)
MAI 3	6 (10)
Necrosis	
Present	15 (25)
Absent	45 (75)
Inflammation	
Present	41 (68.3)
Absent	19 (31.7)

SD=Standard deviation MAI=Mitotic activity index

DISCUSSION

MPM is a distinctively aggressive tumor with a relative unresponsiveness to conventional treatments. Owing to its highly aggressive behavior, there have been repeated efforts to identify more accurate prognostic factors. The present study was performed to investigate potential prognostic factors including clinicopathologic characteristics, SUVmax of the tumor, and some pathological characteristic such as MAI, tumor necrosis,

Table 3: Thoracic CT and PET/CT findings of the patients

Characteristics	Number of patients (%)
Thoracic CT	
Involved hemitorax	
Right	31 (51.7)
Left	18 (30)
Bilateral	11 (18.3)
Type of pleural thickening on CT sections	
Diffuse	10 (16.7)
Nodular	31 (51.7)
None	19 (31.7)
Rind-like pleural thickening	
Present	14 (23.3)
Absent	46 (76.7)
Pleural effusion	
Absent	5 (8.3)
Minimal	11 (18.3)
Moderate	28 (46.7)
Massive	16 (26.7)
PET/CT	
Type of pleural FDG uptake	
Diffuse	30 (50)
Focal	10 (16.7)
Mixed	17 (28.3)
None	3 (5)
SUVmax (mean±SD)	8.3±5.5 (0-27.25)
≤8	35 (58.3)
>8	25 (41.7)
Distant metastasis	
Present	5 (8.3)
Absent	55 (91.7)

SD=Standard deviation, PET/CT=Positron emission tomography/computed tomography, FDG=18 F-Fluoro-2-deoxy-d-glucose, SUV=Standardized uptake values

Table 4: Results of univariate analysis for potential prognostic patient characteristics

Variable	6-months survival rate (%)	1-year survival rate (%)	2-year survival rate (%)	Median survival (months)	95% CI	*P*
Age (years)						
≤60	84.3	56.9	34.8	14.0	10.7-17.29	0.161
>60	73.7	49.9	14.5	12.0	8.4-15.49	
Gender						
Male	85.3	55.3	24.8	13.8	10.5-17.03	0.687
Female	72.3	55.3	31.6	14.0	9.7-18.22	
Exposure to asbestos						
Present	84.7	54.1	27.2	13.9	10.7-17.15	0.737
Absent	57.1	42.9	42.9	13.8	36.3	
Leukocyte count						
≤10x10^3/ml	87.8	66.1	36.0	19.6	12.76-26.5	0.009*
>10x10^3/ml	66.7	34.6	10.4	10.1	3.72-16.53	
Platelet count						
≤400x10^3/ml	83.6	57.3	32.0	14.6	5.72-23.41	0.157
>400x10^3/ml	75.0	48.1	20.6	12.2	5.57-18.76	
Hemoglobin (g/dl)						
≤13	72.1	49.2	20.5	12.0	7.74-16.19	0.111
>13	90.1	64.1	36.0	20.1	9.8-30.45	
ESR (mm/hr)						
≤30	88.5	61.7	45.0	22.0	5.93-37.92	0.202
>30	78.4	54.3	23.0	13.7	10.02-17.43	
Rind-like pleural thickening						
Present	71.4	34.3	8.6	9.8	8.54-11.11	0.037*
Absent	82.2	61.7	36.0	19.6	12.69-26.56	
Pleural effusion						
Absent+minimal	81.3	31.0	31.0	11.4	9.32-13.41	0.418
Moderate+massive	81.6	63.3	27.7	14.6	6.63-22.50	
SUVmax						
≤8	94.3	68.9	36.7	19.6	9.52-29.73	0.023*
>8	63.2	34.0	11.3	10.1	5.31-19.94	
Disease stage						
1-2	96.2	78.5	48.6	20.0	3.52-36.33	0.004*
3-4	68.8	40.6	12.6	10.8	8.61-13.04	
Applied therapies						
Best supportive care	40.0	20.0	13.3	5.0	2.56-7.43	0.004*
Chemotherapy	94.7	70.4	27.5	14.8	7.66-21.93	
Multimodality therapy	100	66.7	66.7	35.2	-	
Pleurodesis						
Present	80.4	56.2	30.4	20.1	4.36-35.89	0.593
Absent	82.2	56.9	27.6	13.9	11.15-16.7	
Histological diagnosis						
Epithelial	84.2	60.5	32.6	14.0	7.46-20.54	0.244
Non-epithelial	66.7	46.7	20.0	12.0	8.51-15.42	
Mitotic activity index						
MAI 1	88.9	64.5	37.0	20.0	11.76-28.09	0.033*
MAI 2	71.4	43.7	8.7	12.0	7.61-16.24	
MAI 3	66.7	50.0	33.0	12.0	0-26.97	
Necrosis						
Present	66.7	33.3	13.3	9.4	5.01-13.84	0.037*
Absent	88.8	65.4	31.3	19.6	11.58-27.67	
Inflammation						
Present	82.8	56.0	33.6	13.9	11.14-16.71	0.783
Absent	83.9	58.7	19.6	14.6	4.53-24.60	

ESR= Erythrocyte sedimentation rate, MAI=Mitotic activity index, CI=Confidance interval, SUVmax=Maximum standardized uptake value, *=Statistically significant

and inflammation in a cohort of Turkish patients with MPM. In univariate analysis, leukocytosis, rind-like pleural thickening, advanced disease stage, best supportive therapy alone, SUVmax higher than 8, MAI higher than 1, and presence of tumor necrosis were found as poor prognostic factors. In multivariate analysis, leukocytosis, advanced disease stage, best supportive therapy alone, and MAI higher than 1 were independently associated with survival, whereas SUVmax of the tumor failed to enter the model.

MPM is generally caused by occupational or environmental exposure to asbestos.[1] The latency period is 25-40 years. In Turkey, it is mainly due to environmental exposure to asbestos and erionite that begins at birth.[13-16] Therefore, MPM is diagnosed at earlier ages and both gender affected equally as in the present study.

The best-known clinical prognostic scoring systems for MPM have originated from *European Organization for Research and Treatment of Cancer (EORTC)* and *Cancer and Leukemia Group B (CALGB)* and

use a combination of some biological and clinical factors. Poor performance status, non-epithelioid histology, male gender, low hemoglobin level, and high white blood cell count were found independent poor prognostic factors in MPM.[5] Recently, in a retrospective registry of 3101 patients undergoing surgical resection, disease stage, histological subtype, gender, age, and treatment intent (curative/palliative) were core prognostic variables.[6] In the current literature, age, gender, performance status, hemoglobin levels, leukocyte and thrombocyte counts, lactate dehidrogenase, and C-reactive protein (CRP) levels are the most commonly studied patient-related prognostic factors in MPM. There are conflicting data about the impact of these prognostic factors, probably due to limited number of patients or retrospective nature of the data.[4,17-22] The present study is also a retrospective study with limited number patients. While age, gender, and thrombocyte counts were not found as prognostic factors, leukocytosis was associated with poor prognosis. Higher levels of CRP, an acute phase reactant, were reported as a poor prognostic factor in patients with MPM.[16,23] In this study, we examined the prognostic effect of erythrocyte sedimentation rate, which is another acute phase reactant, but failed to demonstrate it.

Table 5: Results of multivariate analysis

Variable	Hazard ratio	95% CI	*P*
Leukocyte count			
≤10x10^3/ml	1	1.101-4.699	0.026*
>10x10^3/ml	2.27		
Disease stage			
1-2	1	1.143-5.315	0.021*
3-4	2.46		
Applied therapies			
Multimodality therapy	1	0.476-7.555	0.036*
Chemotherapy	1.89	1.112-23.57	0.029*
Best supportive care	5.12		
Mitotic activity index			
MAI 1	1	1.305-6.953	0.010*
MAI 2-3	3.012		
SUVmax			
≤8	1	0.95-3.762	0.07
>8	1.89		

CI=Confidance interval

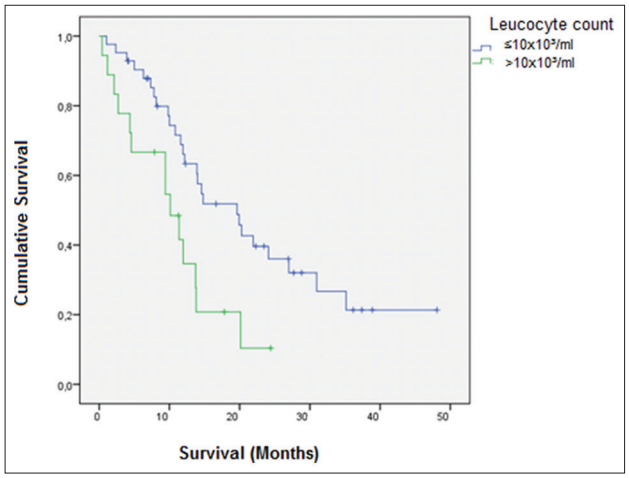

Figure 1: Kaplan-Meier survival curves according to leucocyte count (*P*=0.009)

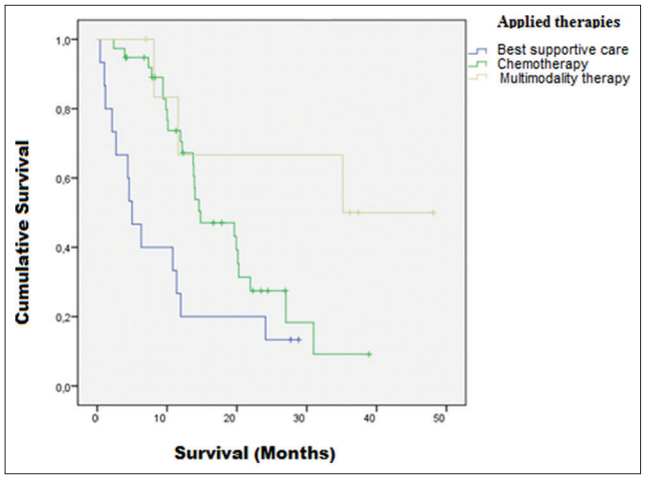

Figure 3: Kaplan-Meier survival curves according to applied treatment strategies (*P*=0.004)

Tumor stage and histology are the most commonly studied tumor-related prognostic factors. In the literature, there

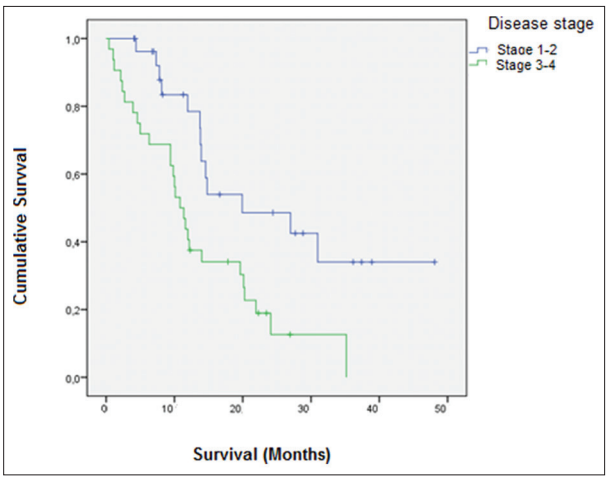

Figure 2: Kaplan-Meier survival curves according to disease stages (*P*=0.004)

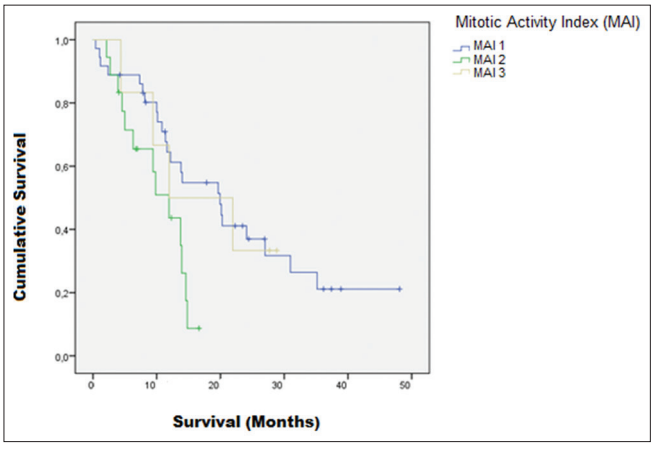

Figure 4: Kaplan-Meier survival curves according to MAI (*P*=0.033)

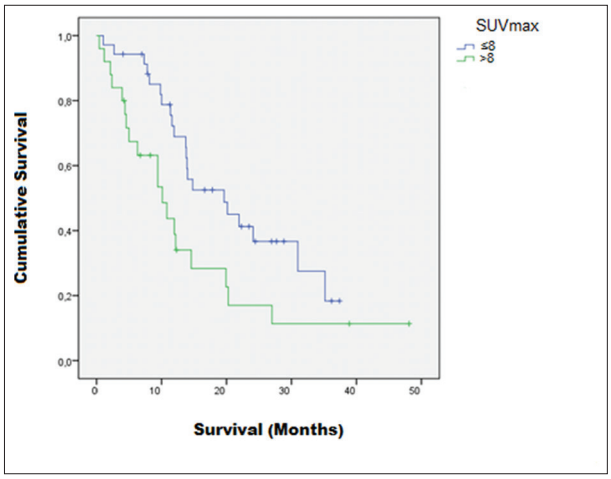

Figure 5: Kaplan-Meier survival curves according to SUVmax on PET/ CT (*P*=0.023)

is conflicting data about the prognostic effect of disease stage that can be probably due to different staging systems. This condition provided the rationale for a revised staging system. In 1994, MPM investigators analyzed existing surgical databases to develop a TNM-based staging system known as IMIG staging system.[12] This proposed staging system was accepted by UICC (International Union Against Cancer) and the AJCC (American Joint Commission on Cancer) as the international MPM staging system in their last staging manuals.[24] In the present study, we clinically staged patients based on IMIG staging system and found that advanced tumor stage is an independent poor prognostic factor. Non-epithelioid histology is widely known as a poor prognostic factor.[4,19,20,23,25] In this study, tumor histology was not found as a significant prognostic factor. This can be due to lower number of cases in non-epitheloid histology group. In fact, median survival time was longer in epithelioid histology group (14 months) compared to non-epithelioid histology group (12 months).

In this study, we additionally evaluated the prognostic effect of some pathological characteristics of the tumor such as MAI, tumor necrosis, and inflammation. MAI is a well-known and most commonly method of assessing the proliferative activity of a tumor. It is frequently used for classification, grading, and prognosis of solid tumors. It has been shown as a prognostic factor in node-negative breast cancer.[26] Demirag *et al.* investigated the effect of MAI on prognosis in 40 patients with MPM and reported that MAI was not a significant prognostic factor.[10] Recently, Kadota *et al*. evaluated the slides of 232 patients with epithelioid MPM and reported that high mitotic count was independently associated with poor prognosis.[11] In our study, MAI was found to be a significant prognostic factor both in univariate and multivariate analysis. Tumor necrosis is a common feature of solid tumors and has been reported as an indicator of poor prognosis. It has also been reported as an indicator of poor prognosis in MPM.[27] Demirag *et al.* reported that the presence of tumor necrosis was significantly associated with poor prognosis in univariate analysis.[10] Similarly, in our study, tumor necrosis was significantly associated with poor prognosis in univariate analysis, but was not found as an independent prognostic factor in multivariate analysis. Suzuki *et al*. were the first who investigated the inflammatory response in tumor and stroma and reported that chronic inflammation in stroma was an independent predictor of survival and associated with good prognosis.[28] In our study, the presence of inflammation was not found as a prognostic factor.

After widespread usage of PET/CT in the area of oncology, it has also become an invaluable imaging technique for the diagnosis, staging, and prognosis of MPM.[7-9,29,30] PET/CT accurately diagnoses MPM, predicts survival and diseases recurrences. It can guide further management by predicting the response to chemotherapy and excluding surgery in patients with extrathoracic disease.[9] Higher SUVmax levels (>10) were found to be associated with lower survival.[9] In the present study, univariate analysis revealed that patients live longer if SUVmax values are lower than 8. However, SUVmax was not identified as an independent prognostic factor in multivariate analysis, probably in part due to small number of patients.

The treatment of MPM remains substantially disappointing, and there are limited therapeutic options. Despite advances in surgery and chemotherapy, median survival is approximately 1 year.[2,3] Multimodality therapy, a combination of surgery, chemotherapy, and radiotherapy that was introduced in 1990s has improved survival in selected patients.[31] However, inter-individual variability of response to multimodality therapy remains a challenge, and generally MPM prognosis continues to be poor.[32] In our study, median survival time was 12.0 months compatible with the literature. In both univariate and multivariate analysis, patients treated with multimodality therapy (median survival: 35.2 months) or chemotherapy (median survival: 14.8 months) showed a significant survival advantage compared to patients treated with best supportive therapy (median survival: 5 months). The presence of pleurodesis was not associated with survival. Again compatible with the literature, the median survival time was shorter in patients treated with best supportive therapy. We attributed this condition to the fact that best supportive therapy is preferred in disabled patients with advanced disease who cannot tolerate treatment with chemotherapy and/or surgery. Likewise, multimodality therapy is selected for patients particularly with good performance status and at early stage disease. Although the reported median survival of these selected groups of patients treated with multimodality therapies appears to be superior to that of untreated patients, prospective trials are justified to clarify the role of these approaches.

The limitations of this study are its retrospective design and small sample size. But, the study group is homogeneous based on diagnostic methods, radiologic and nuclear imaging techniques, and applied therapies. Due to retrospective nature of the current study, we did not investigate some factors such as performance status and chest pain.

In conclusion, high leukocyte count, advanced disease stage, best supportive therapy alone, and higher MAI were found independent predictors of poor survival in patients with MPM. Overall, the prognosis is dismal with a median survival of 12 months. MAI can be an important tumor-related prognostic factor in MPM. The main advantage of MAI over other prognostic factors is that MAI is both an easy and inexpensive technique. Prospective studies are required to validate the significance of MAI as a prognostic factor.

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