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Relationship between 18 FDG PET-CT findings and the survival of 177 patients with malignant pleural mesothelioma

A. ABAKAY[1], H. KOMEK[2], O. ABAKAY[3], Y. PALANCI[4], F. EKICI[5], G. TEKBAS[5], A.C. TANRIKULU[1]

[1]Department of Chest Disease, School of Medicine, Dicle University, Diyarbakir, Turkey
[2]Department of Nuclear Medicine, Education and Training Hospital, Diyarbakir, Turkey
[3]Department of Chest Disease, Education and Training Hospital, Diyarbakir, Turkey
[4]Department of Public Health, School of Medicine, Dicle University, Diyarbakir, Turkey
[5]Department of Radiology, School of Medicine, Dicle University, Diyarbakir, Turkey

Abstract. – BACKGROUND AND OBJECTIVES: Malignant pleural mesothelioma (MPM) is a fatal malignancy. Radiological imaging is necessary for the diagnosis, staging, and clinical management of patients with MPM. The 18 fluorodeoxyglucose positron emission tomography (18 FDG-PET) scan has proven useful in preoperative staging and as a prognostic tool in MPM. We aimed to investigate the relationship between the pre-treatment 18 FDG PET/CT results, together with other known clinical parameters, and the survival of patients with MPM in our region.

PATIENTS AND METHODS: A retrospective analysis was performed on the data of 177 patients with MPM between April 2007 and April 2011. Pre-treatment 18 FDG PET/CT scans were done on all patients. Survival time was calculated by the Kaplan-Meier method.

RESULTS: The mean age was 55.40 years. There were 56% male patients and 44% female patients. The mean survival time was 11 months from time of diagnosis. According to multivariate analysis results, being of male gender increased the poor prognosis 5.30 times, a Karnofsky performance score (KPS) < 60 increased a poor prognosis 2.18 times, being on "best supportive care" increased a poor prognosis 25.40 times, the stage III-IV increased a poor prognosis 11.13 times, and a level of maximum standardized uptake value (SUVmax) > 5 increased a poor prognosis 4.34 times.

CONCLUSIONS: MPM remains a fatal prognosis. Significant predictors of survival include KPS, stage of disease, gender, treatment regimen and level of SUVmax. An understanding of the importance of these markers for MPM prognosis should allow targeted treatments to be developed.

Key Words:
Mesothelioma, Poor prognosis, FDG-PET, SUVmax

Introduction

Malignant mesothelioma is a cancer originating from the pleura, although pericardium, peritoneum or tunica vaginalis may also be affected. The strong relationship between asbestos exposure and malignant mesothelioma was first recognized in the early 1960s[1]. The latency period between asbestos exposure and mesothelioma development is 35-40 years. Malignant pleural mesothelioma (MPM) is generally caused by environmental and occupational exposure to asbestos. In addition to asbestos, erionite and the natural fibrous zeolites which can be found in volcanic tuffs have been shown to induce mesothelioma. MPM due to environmental exposure to asbestos and to erionite is a relatively common pleural cancer in some areas of Turkey[2-6].

MPM is a fatal malignancy, resistant to most of the anti-tumor drugs. However, some patients may respond to chemotherapy, radiotherapy or immunotherapy, and a few patients may obtain benefit from radical surgery and multimodality treatments[7,8]. The median survival for MPM has been reported to be about 12 months[9].

Radiological imaging is necessary for the diagnosis, staging, and clinical management of patients with MPM. X-ray imaging techniques (chest radiography and computed tomography (CT)), magnetic resonance (MR) imaging, positron emission tomography (PET), and, most recently, PET/CT all have been employed to evaluate this disease[10].

CT plays a role in the detection of diseases involving the pleura, and although it is commonly used to detect intrathoracic nodal disease, its sen-

Corresponding Author: Abdurrahman Abakay, MD; e-mail: arahmanabakay@hotmail.com

sitivity is suboptimal and a biopsy is recommended for definitive diagnosis[11,12]. MRI is used to complement CT, particularly in determining the extent of local invasion. MRI is superior to CT in the evaluation of the local invasion of endothoracic fascia or a single chest wall focus (accuracy 69% vs. 46%) and also with the diaphragm (82% vs. 55%)[13]. Determination of nodal disease is similar, with both modalities at approximately 50% accuracy[13].

In mesothelioma, 18 fluorodeoxyglucose (FDG) PET has been assessed predominantly in diagnosis[14] and preoperative staging[13-15]. 18F-FDG PET has been presented as able to detect metastatic disease in 11-25% of pre-operative patients[15-17] but could not be calculated in the evaluation of loco regional nodal disease[18]. Integrated 18-FDG-PET-CT combines anatomic and metabolic information in a single imaging procedure and has been shown to be a reliable tool in the staging and assessment of patients with MPM who are candidates for radical treatment[19].

A PET scan has proven useful in pre-operative staging and as a prognostic tool in MPM[15,18,20,21]. The most common semi-quantitative parameter used is the maximum standardized uptake value (SUVmax) within a tumor[22]. Mesothelioma is poorly suited to SUVmax measurements as it is often diffused and heterogeneous[23].

Several investigations on MPM epidemiology, with clinical and radiological features, were published. However, there has been no study on the prognostic value of 18 FDG PET/CT parameters in patients with MPM in the southeast region of Turkey. The southeast region of Turkey has a volcano, Mount Karacadag, and due to the emissions, asbestos-related diseases and mesothelioma are common in this region[6].

In several studies, the effects of clinical and laboratory parameters on MPM prognosis have been well investigated, but the contribution of 18 FDG PET/CT parameters to MPM prognosis has not been studied adequately[19,24,25].

In this study, we aimed to investigate the relationship between pre-treatment 18 FDG PET/CT results, together with other clinic parameters, and the survival of patients with MPM in our region.

Patients and Methods

A retrospective analysis was performed on the clinical, laboratory and radiological data of 177 patients with MPM who were registered and followed up in Dicle University Hospital between April 2007 and April 2011. The local Ethical Committee approved the study's protocol according to the Helsinki Declaration.

Histological evaluation was performed on either surgical and/or necropsy material and patients with a histologically proven MPM were included. Histochemical or immunohistochemical stains were used where necessary. Certain laboratory, clinical and radiographic variables were defined as potentially prognostic factors and were measured at the time of diagnosis.

After the histopathological diagnosis, the stage was determined. Because some patients did not allow thoracoscopy, the MPM staging was done according to the Butchart staging system[26]. Thoracic and abdominal computed topographies (CT) were done, and a cranial CT was performed if necessary. These CT scans were evaluated by a specialist radiologist.

Pre-treatment 18 FDG PET/CT scans were done on all patients. The results of all 18 FDG PET/CT scans were calculated by a single nuclear medicine physician who was blinded to all clinical characteristics.

The following clinical characteristics were registered for prognostic evaluation: clinical and laboratory characteristics, such as age (< 60 or ≥ 60 years), gender, asbestos exposure (yes or no), histopathological subtype (epithelial or others), smoking history (yes or no), Karnofsky performance score (KPS, < 60 or ≥ 60), stage (stage I-II or stage III-IV), hemoglobin concentration (< 12.30 g/dl or ≥ 12.30 g/dl), serum alkaline phosphatase (ALP, ≤ 79 or > 79 U/l), C-reactive protein (CRP, ≤ 50 or > 50 mg/l) level, erythrocyte sedimentation rate and pleural thickening as defined by the chest CT (measurement was done of thickest pleural area ≤ 1 or > 1 cm), presence of metastasis (yes or no), talc pleurodesis (yes or no). In this study, median values of laboratory measurements were used for statistical analysis.

Most of our patients had environmental asbestos exposure, were young and only 21 patients were > 70 years of age. Therefore, the cut-off for age was set at 60 years.

The patients were classified into three groups according to their treatment schedule: the best supportive care (BSC) group, which consisted of patients with low performance status and who were not suitable for other treatment options (87 patients); the chemotherapy group (71 patients); and the multimodality (MM) therapy group (19 patients).

All chemotherapy was given at our chemotherapy unit as cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2).

In the MM group, surgical resection consisted of extrapleural pneumonectomy (EPP) with resection of the lung, parietal pleura, hemipericardium and diaphragm. A systematic hilar and mediastinal lymphadenectomy was conducted. The diaphragm and pericardium were reconstructed using mesh. Adjuvant radiotherapy was delivered to the hemithorax, the thoracotomy incision, and at the sites of chest drains. The chemotherapy protocol for the entire MM group was cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2).

A whole body FDG-PET scan was performed within 4 weeks following consent and registration and before any therapy began. Whole body 18 FDG PET/CT imaging was done on a Siemens Biography 6 PET-CT scanner. Patients fasted for at least 4 h before the 18 FDG PET/CT scan and had blood glucose levels of less than 140 mg/dL at the time of injection. Starting 60 min after the injection of a standard dose of 215 MBq/m^2 FDG was administered intravenously through an indwelling catheter inserted into an antecubital vein. In addition, an oral CT contrast agent was administered during the uptake period. Emission scans were done on multiple bed positions, with 3 min per bed position with a 50% overlap per field of view. The SUVmax were measured. When there was linear increase in the FDG uptake pattern at the pleura, the most active site was found, and the SUVmax was calculated from there.

Statistical Analysis

Mean values and standard deviations were calculated for continuous variables. The normality of the variables was analyzed by the Kolmogorov-Smirnov test. The duration of survival, median and mean event times, with 95% confidence intervals (CIs), were estimated according to the Kaplan-Meier method. The duration of survival was defined as the period between the time of diagnosis and the time of death, or if patients were still alive, survival was defined as the period between the time of diagnosis and April 2011. The proportional hazards regression model, with stratification for the clinical trial, was used for both univariate and multivariate analyses. Univariate analyses examined the prognostic importance of all the factors mentioned above. The Cox proportional hazards model was used to examine the variables. A 2-sided test was used, with a 0.05 level of significance. Comparisons for overall survival were made using 2-tailed log-rank tests. Only variables with p values < 0.05 in univariate analysis were taken into the final model for multivariate analysis. In the Cox regression analysis, the 'backward conditional' method was used. Significance was taken as $p < 0.05$. Of all patients, 54 were alive during this study. Statistical analyses were performed using SPSS statistical program version 12 (SPSS Inc., Chicago, IL, USA).

Results

The mean age of patients (n=177) was 55.40 ± 11.30 (31-79) years. There were 99 male patients (56%) and 78 (44%) female patients. Eighty-five percent of patients had experienced environmental asbestos exposure, and the mean duration of asbestos exposure was found to be 28.71 ± 16.77 years.

The mean KPS was 60.33 (40-90). Of the 177 patients in this study, 128 (72.3%) were diagnosed by non-invasive pleural biopsy and 49 (27.7%) were diagnosed by surgical pleural biopsy. The histological types of MPM were epithelial type in 81.4% of patients with other types (mixed, sarcomatous and undefined) in 18.6% of patients (Table I).

Table I. Demographic characteristics of patients with malignant pleural mesothelioma.

Characteristics	N	%
Total patients	177	100
Age		
< 60 years	111	63
≥ 60 years	66	37
Gender		
Male	99	56
Female	78	44
Presence of asbestos exposure		
Yes	150	85
No	27	15
Smoking history		
Smokers	120	68
Non-smokers	57	32
Histological type		
Epithelial type	144	81
Other types	33	19
Stage of disease		
Stage I and II	90	51
Stage III and IV	87	49

The mean erythrocyte sedimentation rate was 75.7 ± 24.5 mm/h.

Peritoneal invasion was detected in 24 and pericardial invasion in 6 patients.

The mean survival time from diagnosis was 11.02 ± 6.38 months (range 1-16).

A total of 16 parameters that we expected to find associated with the prognosis were used in the univariate analysis. Significant poor prognostic factors were male gender, non-epithelial histological type, KPS < 60, stage of disease III-IV, level of hemoglobin < 12.30 g/dl, level of serum ALP > 79 U/l, presence of pleural thickening > 1 cm, BSC treatment regimen and level of SUVmax > 5 ($p < 0.05$ for each variable). Variables with $p < 0.05$ in the univariate analysis were taken into the final model for the multivariate analysis (Table II).

According to multivariate analysis results, male gender increased poor prognosis 5.30 times, a KPS < 60 increased poor prognosis 2.18 times, BSC treatment regimen increased poor prognosis 25.40 times, stage of disease III-IV increased poor prognosis 11.13 times, and level of SUVmax > 5 increased poor prognosis 4.34 times (Table III).

Our data and those of previous studies that investigated the prognostic factors of PET findings in MPM are shown in Table IV.

The survival curves of patients for the SUVmax, stage of disease, treatment regimens and gender are presented in Figures 1 to 4.

Discussion

In spite of improvement in treatment regimens, malignant pleural mesothelioma (MPM) still has a poor prognosis: anticipated survival time of patients is 6-12 months[6,27-31]. In our study, mean survival time was 11 months.

In our region, asbestos exposure is mostly environmental[6,32,33], and begins at birth. Therefore, MPM is detected at earlier ages. The mean age of MPM patients in our study was relatively low, probably as a result of regional environmental asbestos exposure.

The Cancer and Leukemia Group B and the European Organization for Research and Treatment of Cancer have analyzed large numbers of patients enrolled in MPM trials and have identified the following poor prognostic factors for MPM[34]: non-epithelioid histology, poor performance status, chest pain, age > 75 years, male gender, WBC ≥ 8.3 × 10 9/l, platelet number > 400,000/μl, and LDH > 500 IU/l. In several studies, poor prognostic factors associated with MPM were detected to be older age[28,34] male gender[27,28,35], advanced stage[32,36], non-epithelioid histology[27-30,34,35], thrombocytosis[27,34], higher serum LDH level[32,34], lower hemoglobin level[8], lower pleural fluid glucose level[6] and poor performance status[6,27,30,32,34,35]. In our study, worse survival rates were observed in patients with lower KPS and male gender.

The prognostic parameters of 18 FDG PET-CT findings determined to be significant or insignificant, as well as their comparison with other MPM studies, are shown in Table IV. Flores et al[20] incorporated SUVmax into a prognostic model with histology and stage in a series of 137 patients with untreated proven MPM, showing that SUVmax > 10 was associated with poor prognosis. Gerbaudo et al[37] have found that a lesion SUVmax > 10.7 was the independent predictor of survival. This finding is consistent with those of Ceresoli et al[38], as well as Flores et al[39], reported that a high SUVmax, mixed histology, and advanced anatomic stage were poor risk factors in MPM. Nowak et al[40] showed that tumor volume and its glycolytic metabolism, may be better predictors of disease aggressiveness in mesothelioma. Bernard et al[14] observed that increased tumor metabolic activity as assessed by the uptake of FDG in tumor tissue is associated with a poor prognosis in MPM.

Francis et al[41] found total lesion glycolysis to be superior to SUVmax in mesothelioma response assessment. However, SUVmax has also been found to be a potent predictor of outcomes in other studies of mesothelioma[38,42]. Lee et al[25] reported that volume-based parameters of 18 FDGPET-CT have the potential to provide prognostic information in MPM patients who are receiving surgery or palliative chemotherapy. Tan et al[19] referred that 18 FDGPET-CT is useful in diagnosing disease recurrence after multimodality therapy for MPM.

Standard uptake values in normal tissue are not stable with time, because blood-pool and liver uptake fall with increasing delays from time of injection, whereas uptake in tumor typically rises. Thus, normalization is difficult if the scan uptake times vary. However, a threshold for post-treatment PET is an attractive concept, and may be more important in the future as standardiza-

Table II. Results of univariate analysis for potential prognostic patient characteristics.

Variable	O/N*	%	Median survival time (months)	95% CIs	p
Age (years)					
< 60	60/111	54.05	11.00	7.88-14.12	0.713
≥ 60	33/66	50.00	12.50	10.47-14.53	
Gender					
Male	57/99	57.57	13.00	11.40-14.60	0.000
Female	36/78	46.15	9.00	8.44-9.56	
Asbestos exposure					
Present	81/150	54.44	11.00	8.45-13.55	0.240
Absent	12/27	44.44	13.00	9.83-14.18	
Smoking					
Nonsmokers	24/57	42.10	9.00	4.99-13.01	0.128
Smokers	69/120	57.50	12.50	10.75-14.25	
Stage of disease					
Stage I-II	18/90	20.00	15.00	12.88-17.12	0.001
Stage III-IV	75/87	86.20	9.00	7.92-10.09	
Karnofsky performance score					
< 60	24/99	24.24	9.00	8.34-9.66	0.002
≥ 60	69/78	88.46	13.00	11.61-14.39	
Histologic type					
Epithelial type	60/144	41.66	13.00	10.94-15.06	0.000
Non-epitelyal types	33/33	100	9.00	6.49-11.51	
Haemoglobin					
> 12.30 g/dl	30/99	30.30	9.00	8.38-9.62	0.001
≤ 12.30 g/dl	63/78	80.76	15.00	13.65-16.35	
Alkaline phosphatase					
≤ 79 U/l	15/57	26.32	15.00	11.48-17.90	0.047
> 79 U/l	78/120	65.00	10.00	7.72-12.28	
C reactive protein					
≤ 50 mg/l	33/93	35.48	12.00	7.72-13.99	0.939
> 50 mg/l	60/84	71.42	12.50	9.92-15.08	
SUVmax					
≤ 5	42/60	70.00	14.00	11.39-16.61	0.013
> 5	51/117	43.58	10.00	8.14-11.86	
Pleural thickening					
≤ 1 cm	24/66	36.36	15.00	13.91-16.09	0.000
> 1 cm	69/111	62.16	9.00	7.98-10.02	
Metastasis					
Present	45/108	41.66	11.00	7.73-14.27	0.766
Absent	48/69	69.56	12.00	8.45-15.55	
Pleurodesis					
Yes	36/60	60.00	10.00	10.91-14.09	0.544
No	57/117	48.72	12.50	8.55-11.45	
Treatment regimen					
Best supportive care	57/87	65.52	9.00	9.63-13.25	0.002
Chemotherapy	23/71	32.39	13.00	6.32-11.00	
Multimodality treatment	13/19	68.42	15.50	9.47-15.73	

CIs: Confidence intervals; O: Observed death number; N: Total patient number.

tion for PET performance improves[44]. In our work, the SUVmax level > 5 was established as a poor prognostic factor. Our study of the literature on this subject is one of the most extensive series researches yet conducted.

As expected, patients who had BSC treatment had the shortest survival times, as they were generally older, and had advanced-stage MPM and low KPS. We determined that the median survival time was 9, 13, and 15.5 months in

Table III. Multivariate stepwise model.

Variable	Hazard ratio	95% CIs	p
Gender			
Female	1	1.227-22.971	0.025
Male	5.30		
Stage of disease			
Stage I-II	1	1.680-73.850	0.013
Stage III-IV	11.13		
Karnofsky performance score			
< 60	1	1.002-154.47	0.049
≥ 60	2.18		
SUVmax			
≤ 5	1	1.028-18.346	0.046
> 5	4.34		
Treatment regimen			
Other regimens (chemotherapy, multimodality)	1	2.154-99.695	0.010
Best supportive care	25.40		

CIs: Confidence intervals.

Table IV. 18 FDG PET-CT findings with MPM patients in our and several investigations.

Studies	N	SUVmax	TGV	TTP	TLG	PETvol	SUVavg	MTV
This study	177	+ (> 5)	Ø	Ø	Ø	Ø	Ø	Ø
Nowak et al.[40]	89	Ø	+	Ø	Ø	Ø	Ø	Ø
Flores et al.[20]	137	+ (> 10)	Ø	Ø	Ø	Ø	Ø	Ø
Ceresoli et al.[42]	22	– (> 5.96)	Ø	+	Ø	Ø	Ø	Ø
Schaefer et al.[45]	41	–	Ø	Ø	–	–	Ø	Ø
Lee et al.[25]	13	– (> 9.5)	Ø	Ø	+	Ø	– (> 4.4)	+
Tan et al.[19]	42	+ (> 8.9)	Ø	Ø	Ø	Ø	Ø	Ø
Gerbaudo et al.[37]	50	+ (≥ 10.7)	Ø	Ø	Ø	Ø	Ø	Ø
Bernard et al.[14]	28	+ (> 4.03)	Ø	Ø	Ø	Ø	Ø	Ø

N: number of patients; SUVmax: Standardized uptake value; TGV: Total glycolytic volume; TTP: Time to tumour progression; TLG: Total lesion glycolysis; PETvol: Fluorodeoxyglucose volume; SUVavg: Average standardized uptake value; MTV: Metabolic tumour volume; +: Significant; –: Not significant; Ø: Not studied.

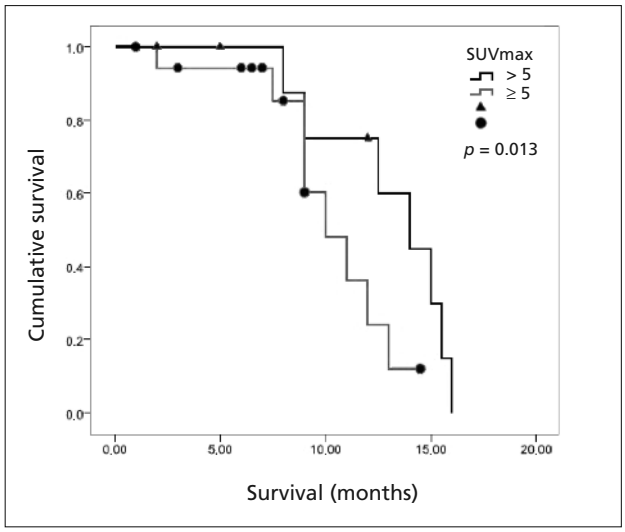

Figure 1. Kaplan-Meier survival curves according to the SUVmax level.

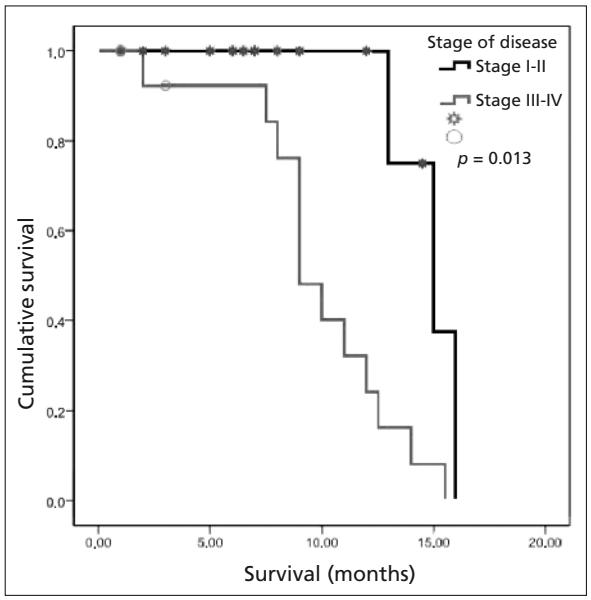

Figure 2. Kaplan-Meier survival curves according to the stage of disease.

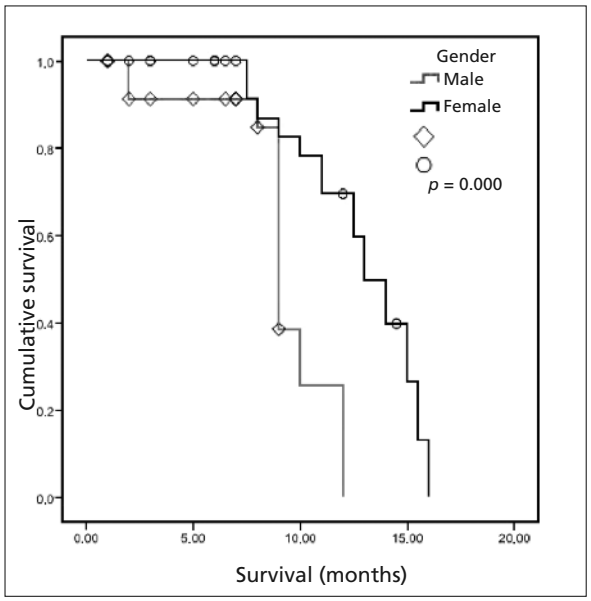

Figure 4. Kaplan-Meier survival curves according to the gender.

BSC, chemotherapy, and multimodality treatment groups respectively. Patients who received multimodality treatment were younger, their KPS was higher, and they were at earlier stages in the disease as compared with the other treatment groups. Patients in the multimodality treatment group also had better survival times than other treatment groups, probably due to lower patient age, better performance status and earlier clinical stage. In an earlier study conducted in Turkey, MPM patients receiving multimodality therapy, who had stage I-II, epithelial types and earlier ages, had better survival rates than other groups[45]. Thus, age, the histopathological type of MPM, KPS and disease stage are very important prognostic factors for planning the treatment after diagnosis.

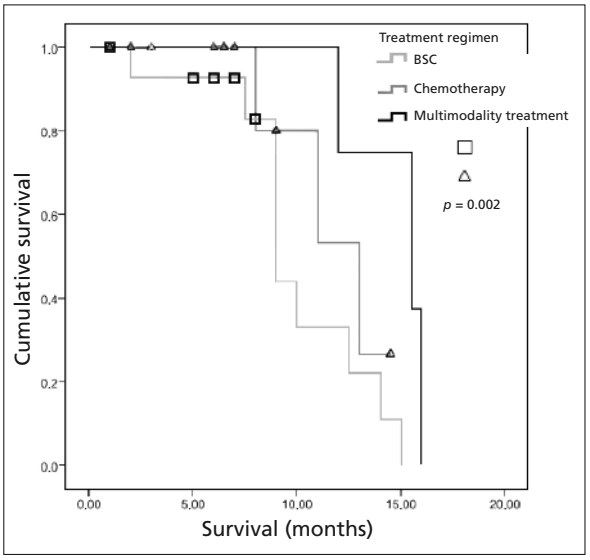

Figure 3. Kaplan-Meier survival curves according to the treatment regimens.

Conclusions

Malignant pleural mesothelioma remains a fatal prognosis. We investigated the pretreatment 18 FDG PET-CT results and other various clinical and laboratory characteristics affecting the survival of patients with MPM. Their treatment schedules were also taken into account. Significant predictors of survival included KPS, stage of disease, gender, treatment regimen and level of SUVmax. Understanding the importance of these markers for MPM prognosis should allow targeted treatments to be developed. Therefore, we believe that studies of large series are needed to investigate the relationship between prognostic markers and treatment regimens.

Conflict of Interest

None declared.

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