Prognostic factors influencing survival in 35 patients with malignant peritoneal mesothelioma

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Malignant mesothelioma is a rare but highly lethal form of cancer that affects the serosal membranes. Malignant peritoneal mesothelioma (MPM) is the second most common form of malignant mesothelioma (pleural mesothelioma is the most common). The aim of this study was to evaluate prognostic factors influencing the survival of patients with MPM.

A retrospective analysis was performed on 35 patients who were admitted to our hospital between March 2005 and July 2013. The patients' demographic and clinical data, laboratory results, radiological signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and treatment outcomes were evaluated.

The mean age of the 35 patients was 59.0±14.4 years, the mean survival time was 16.2±12.9 months, and the majority of the histopathological types of MPM were epithelial (68.6%). 82.9% of the patients had been exposed to asbestos, and the mean duration of exposure was 28.3±14.5 years. The most frequent symptoms were abdominal distention/pain, weight loss, dyspnea, and chest pain. The mean interval between the onset of symptoms and the diagnosis was 4.6±3.3 months. Platinum-based combination chemotherapy in combination with supportive care was used in the treatment of 68.6% of the patients, while supportive treatment alone was used in the others. Our results revealed that patients who were >60 years old (p=0.019), who were exposed to asbestos >20 years (p=0.033), who had an ECOG PS of 3 (p=0.000) were more likely to have a poor MPM prognosis.

In conclusion, increased age, duration of environmental asbestos exposure and ECOG PS are important factors that influence the prognosis of MPM patients.

Key words: Malignant peritoneal mesothelioma, prognostic factors, survival

Malignant mesothelioma is a rare but aggressive and fatal type of cancer that develops from the mesothelial cells of serosal membranes (pleura, peritoneum, pericardium or tunica vaginalis testes). Malignant peritoneal mesothelioma (MPM) occurs in the second order among all mesotheliomas. It accounts for about 10 to 15% of all cases diagnosed with mesothelioma in the United States [1]. The inhalation of asbestos fibers is the most frequent and significant etiologic factor in all forms of mesothelioma. Although a strong relationship between asbestos exposure and development of pleural mes-othelioma has been shown, such a strong relationship has not been found with MPM [2]. In addition, although they share asbestos exposure as a common risk factor, MPM and pleural mesothelioma are very different [3]. Most of the published literature examining the prognostic factors of mesothelioma are regarding pleural mesothelioma, but knowledge about MPM is limited [4]. Most patients with MPM have a poor prognosis and survival time ranges between 7 and 13.5 months. Since primary malignancies developing from the peritoneum are very rare, there is no widely and easily applicable prognostic scoring system for MPM (although there is one for pleural mesothelioma) [5].

In the present study, demographic and clinical data, laboratory results, radiological signs, and features of systemic chemotherapy were evaluated in 35 patients who were diagnosed with MPM and questioned regarding their histories of

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Abbreviations: ALP: Alkaline phosphatase, CRP: C-reactive protein, CT: Computed tomography, ECOG: Eastern Cooperative Oncology Group, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin concentration, LDH: Lactate dehydrogenase, MPM: Malignant peritoneal mesothelioma, PS: Performance status, US: Ultrasound, WBC: White blood cell count

environmental asbestos exposure. We also determined which prognostic factors impacted survival.

Patients and methods

A retrospective analysis was performed on 35 patients who were admitted to our hospital between March 2005 and July 2013. The patients' demographic and clinical data, laboratory results, radiological signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and treatment outcomes were defined as potential prognostic factors and were measured at the time of diagnosis. A histopathological evaluation was performed on all surgical (laparotomy/laparoscopy) or percutaneous peritoneal needle biopsies and/or on any paracentesis materials.

Clinical features. The following pretreatment characteristics were analyzed for their impact on survival: age at the time of diagnosis (≤60 or >60 years), gender, environmental asbestos exposure (yes or no), duration of exposure (≤20

Table 1. Demographic, clinical, and laboratory features of the malignant peritoneal mesothelioma patients

Age (mean±sd, years)	59.0±14.4
Age group (≤60/>60 years)	22/13
Gender (female/male)	19/16
Asbestos exposure (n,%)	29 (82.9)
Duration of asbestos exposure (mean±sd, years)	28.3±14.5
History of smoking (n,%)	13 (37.1)
Symptoms at diagnosis (n,%)	
Abdominal distention/pain	34 (97.1)
Weight loss	17 (48.6)
Dyspnea	15 (42.9)
Chest pain	8 (22.9)
Laboratory results (mean±sd)	
Hemoglobin concentration (g/dl)	11.4±1.8
White blood cell count (x10³/μl)	9.8±4.0
Platelet count (x10³/μl)	404.7±160.4
Serum albumin level (g/dl)	2.7±0.7
Lactate dehydrogenase (U/l)	325.4±317.4
Alkaline phosphatase (U/l)	128.8±95.6
C-reactive protein (mg/l)	58.8±39.6
Erythrocyte sedimentation rate (mm/h)	59.8±25.5
Histopathological type (n,%)	
Epithelial	24 (68.6)
Others	11 (31.4)
Performance status (ECOG) (n,%)	
1	17 (48.6)
2	12 (34.3)
3	6 (17.1)
Systemic chemotherapy (n,%)	24 (68.6)
Status (n, %)	
Alive	3 (8.6)
Dead	32 (91.4)

ECOG: Eastern Cooperative Oncology Group.

or >20 years), history of smoking (yes or no), pack-years of smoking (≤20 or >20), symptoms at the time of diagnosis [presence of abdominal distention/pain, weight loss (>5% in the last 3 months), chest pain, dyspnea], the interval between the onset of symptoms until the diagnosis (≤6 or >6 months), diagnostic procedures, and histopathological types [epithelioid or others (biphasic, sarcomatous and unspecified)]. Performance status was assessed using an ECOG score from 0 to 5, with 0 indicating asymptomatic, 1 indicating symptomatic but completely ambulatory, 2 indicating symptomatic with <50% of time spent in bed during the day, 3 indicating symptomatic with >50% of time spent in bed but not bedridden, 4 indicating bedridden and 5 indicating death [6]. The patients who received systemic chemotherapy were further split into two groups, with the first group receiving pemetrexed and cisplatin and the second group receiving gemcitabine and cisplatin. The interval between the diagnosis and death or the last visit (months) was recorded.

Laboratory results. The following laboratory parameters were determined and recorded: hemoglobin concentration (Hb, <12.30 or ≥12.30 g/dl), white blood cell count (WBC, ≤11,300 or >11,300/μl), platelet count (≤420,000 or >420,000/μl), levels of serum albumin (≤3.0 or >3.0 g/dl), lactate dehydrogenase (LDH, ≤500 or >500 U/l), alkaline phosphatase (ALP, ≤79 or >79 U/l), C-reactive protein (CRP, ≤50 or >50 mg/l), and erythrocyte sedimentation rate (ESR, ≤50 or >50 mm/h).

Radiological signs. All radiological imaging recorded in our database, including abdominal and/or transthoracic ultrasound (US) and computed tomography (CT) was evaluated. Initial CT results (abdominal and thoracic changes) of MPM patients were classified as follows: the presence of ascites, peritoneal, omental and mesenteric involvement, abdominal organ involvement (liver, spleen), abdominal adenopathy, pleural fluid, pleural calcification/plaques and pleural thickening.

Statistical analysis. The data collected were analyzed using SPSS® for Windows version 15.0. The patient characteristics were reported using frequency and descriptive analysis. Survival analysis was performed using the Kaplan-Meier method and confounding factors related to survival were analysed using the stratified Log Rank test. Duration of survival was defined as the period between diagnosis and death, and for patients who did not die, this duration was defined as the period between the time of diagnosis and July 2013. P values <0.05 were considered statistically significant.

Results

Patient characteristics. Baseline characteristics for the 35 patients are summarized in Table 1. Their mean age was 59.0±14.4 years (range 36 – 92), and 13 were older than 60 years. The mean duration of asbestos exposure was 28.3±14.5 years (range 5 – 70). The most frequent initial symptom (97% of the patients) was abdominal distention/pain. The mean interval between the onset of symptoms and the diagnosis

was 4.6±3.3 months (range 1-12). Seventeen (48.6%) patients underwent surgical diagnostic procedures, 18 (51.4%) underwent percutaneous peritoneal needle biopsy, and 21 patients (60%) were diagnosed by paracentesis materials. ECOG PS of the patients scored 1, 2 or 3 at the time of diagnosis (48.6%, 34.3%, 17.1%, respectively). A combination of platinum-based combination chemotherapy and supportive care was used in the treatment of 68.6% of the patients.

Laboratory results. There was no significant prognostic relationship between survival and the pretreatment levels of complete blood count (Hb, WBC and platelets), serum albumin, LDH, ALP, CRP, and ESR (p>0.05).

Radiological signs. The radiological signs of the 35 patients are summarized in Table 2. The most common signs were ascites, pleural calcification/plaques, and omental and peritoneal involvement (100%, 51.4%, 37.2%, 31.4%, respectively). During the follow-up, the direct invasion of adjacent abdominal organs and/or distant metastases were diagnosed in 16 patients as follows: liver (nine), liver and spleen (two), lung (one), liver and lung (three) or liver, spleen, lung and bone (one).

Prognostic factors affecting survival. The mean survival time was 16.2±12.9 (range 3–52) months. During the follow-up, 32 of the patients died. Results of survival analyses revealed that age>60 years (p=0.019), duration of asbestos exposure >20 years (p=0.033), and ECOG PS of 3 (p=0.000) were associated with poor MPM prognosis (Table 3).

Discussion

Prognostic factors are important for the management of MPM as they can help clinicians with both the prognosis of the disease and the treatment plan [4]. In this study, the relationship between survival and demographic data, duration of environmental asbestos exposure, histopathological type, ECOG PS and systemic chemotherapy was determined in patients with MPM. Poor MPM prognosis was found to be associated with the following factors: being older than 60, having been exposed to environmental asbestos for more than 20 years and having a poor PS (ECOG 3).

There are conflicting results regarding the relationship between survival and age in patients with MPM. While some studies have rejected the existence of any relationship between age and survival in MPM patients, others have suggested that patients younger than 60 had a longer survival time [4,5,7]. Contrary to these earlier studies, one study reported that younger patients had a poorer survival than their older counterparts. This contradiction has been attributed to the fact that malignant histopathological type (nonepithelioid) mesothelioma occurs more frequently in younger patients [8]. In the present study, patients who were 60 years of age or younger had a longer survival than did patients over the age of 60. This may be because there were a greater number of patients less than 60 years of age than those over the age of 60 in our study, and younger patients were able to receive systemic chemotherapy since they often had a better PS.

Table 2. Initial radiological findings of the 35 patients with malignant peritoneal mesothelioma

Findings		n	%
Pleural calcification/plaques	yes	18	51.4
	no	4	11.4
	unknown	13	37.1
Pleural fluid (US or CT)	yes	12	34.3
	no	23	65.7
Pleural thickening	yes	7	20.0
	no	15	42.9
	unknown	13	37.1
Ascites (US)	slight	4	11.4
	moderate	18	51.5
	extensive	13	37.1
Ascites (CT)	yes	24	68.6
	unknown	11	31.4
Omental involvement	yes	13	37.2
	no	11	31.4
	unknown	11	31.4
Peritoneal involvement	yes	12	34.3
	no	12	34.3
	unknown	11	31.4
Omental caking	yes	9	25.7
	no	15	42.9
	unknown	11	31.4
Mesentery involvement	yes	7	20.0
	no	17	48.6
	unknown	11	31.4
Abdominal adenopathy	yes	6	17.1
	no	18	51.5
	unknown	11	31.4

US: Ultrasound, CT: Computed tomography.

Table 3. Analysis of the prognostic factors influencing the survival of malignant peritoneal mesothelioma patients

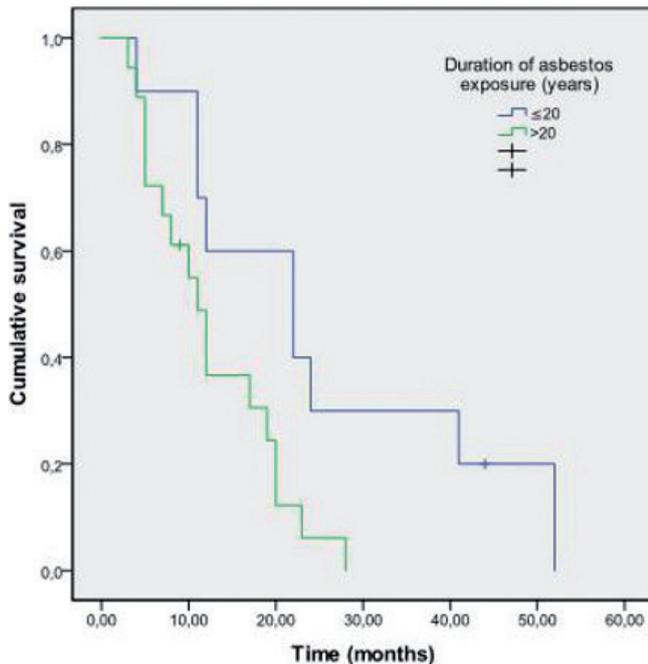| Variables	Median survival (months)	p*
Age group (years)		
≤60	19.6	0.019
>60	10.3	
Sex difference		
Female	13	NS
Male	20	
Duration of asbestos exposure (years)		
≤20	24.3	0.033
>20	12.1	
Histopathological type		
Epithelial	15.7	NS
Others	11	
Performance status		
ECOG 1	17.6	<0.001
ECOG 2	19.5	
ECOG 3	5.5	
Systemic chemotherapy		
Yes	19	NS
No	8.4	

*Stratified Log Rank test, NS: Not significant.

Figure 1. Survival curves according to the duration of environmental asbestos exposure the patients with peritoneal mesothelioma.

The strong relationship between asbestos exposure and the development of mesothelioma at any location is well known, and the latency period is on average 30 years. In industrialized countries, occupational asbestos exposure has been shown to play a significant role in the development of MPM [9]. However, some studies have indicated an increased risk of MPM with non-occupational exposure (i.e. household or residential exposure), especially in developing countries [10,11]. Most researchers agree that asbestos fibers reach the peritoneal cavity in the pathogenesis of MPM by travelling to membrane by means of the lymphatic system following inhalation [12]. High cumulative asbestos exposure is a major risk factor for both pleural and peritoneal mesothelioma [3]. However, asbestos-induced MPM usually requires a higher cumulative dose than its pleural counterpart [13]. It is well known that people have been exposed to environmental asbestos in some rural areas of the Southeast Anatolia Region of Turkey due to its geographical structure [14]. In the present study, the rate of asbestos exposure was much higher (82.9%) than that reported in the literature, and survival was worse in those with more than 20 years of exposure (Figure 1).

While pleural mesothelioma mainly affects men (male to female ratio: 4-5 to 1), the male/female ratio is much smaller in MPM [1]. In studies of pleural and peritoneal mesothelioma conducted in developed countries, the male gender was found to be associated with a worse survival [4,15]. One of the plausible epidemiologic differences between men and women is the probability of asbestos exposure. Direct

exposure to asbestos, which was less obvious in women, was a causative factor in men. A study conducted in a country with high rates of asbestos exposure revealed that the rate of asbestos exposure among men was 88% for pleural mesothelioma and 58% for peritoneal mesothelioma. These rates were 23% for both types of mesothelioma in women [9]. In contrast to studies conducted in developed countries, no significant difference was found between sex and survival in the presented study. This may be because both sexes are exposed to asbestos long-term, since it is typically used for domestic purposes such as painting, plastering and ceiling coating [16]. This study suggests that sex is not the sole influential factor in the development and prognosis of MPM, and that the duration of exposure and cumulative dose are more important factors.

Common complaints of patients with MPM include abdominal distension, abdominal pain, nausea, anorexia and weight loss. Abdominal distension is the most common initial symptom, and it is present at diagnosis in 30-80% of the cases. Abdominal pain is the second most frequent initial symptom, and it occurs in 27-58% of the cases. Many patients with an advanced disease burden due to the nonspecific nature of the symptoms [17]. In the presented study, the most frequent symptoms were abdominal distension and/or pain (97%) and weight loss (48%).

In studies regarding pleural mesothelioma, high platelet and WBC count, high levels of serum LDH and CRP, and low levels of hemoglobin have been associated with poor prognosis [4,18]. To our knowledge, there is no study in the literature exploring biochemical prognostic markers in patients with MPM. However, we did not find any significant relationship between survival and the laboratory parameters that were evaluated in our study. This may be because there was a lower number of patients in this study as compared to those regarding pleural mesothelioma.

Computed tomography is the most useful initial diagnostic tool for mesothelioma. Moderate to extensive (or rarely, massive) ascites is present in 60-100% of the newly diagnosed patients. The majority of patients with MPM present with diffuse peritoneal involvement. Other findings include omental caking/thickening, scalloping, or direct invasion of intraabdominal organs, such as the liver [19]. In the present study, ascites was detected at moderate levels by abdominal ultrasound in all of the patients. The most common finding in patients who had abdominal CT was omental involvement, and the second most common finding was peritoneal involvement. Half of the patients who had thoracic CT showed evidence of pleural calcification/plaques. Direct invasion of adjacent abdominal organs and/or distant metastasis occurred in 16 patients, which was observed during follow-up.

Pleural plaque is the most common radiological manifestation of asbestos exposure. The presence of calcification suggests a benign process. Calcified plaques rarely occur in patients with MPM, and because of this, there are a limited number of published studies investigating thoracic changes

(pleural changes and effusion) in MPM. Calcified plaques are less frequent in MPM than in pleural mesothelioma, but calcified pleural plaques and other signs associated with asbestos exposure may exist in the chest in up to 50% of patients with MPM [20]. In a previously published study, pleural changes, such as calcification or thickening, were found in a high proportion (65%) of patients with MPM [21]. In the present study, radiological evaluation revealed evidence of pleural calcification/plaques in 51% of the patients and pleural thickening in 20%, which is in accordance with the literature. The presence of pleural plaques may be a guide in the differential diagnosis of MPM (to differentiate from such diseases as peritonitis carcinomatosa and ovarian carcinoma) and may facilitate the establishment of a specific diagnosis.

Eastern Cooperative Oncology Group scoring is a widely used system for the assessment of functional status in mesothelioma patients [7]. Poor prognosis is associated with poor PS, and ECOG PS is one of the most significant predictors of poor prognosis [4]. One study found that patients who scored between 2-4 on the ECOG scale had shorter survival times when compared to those with score between 0-1 [5]. According to the records, our patients with score 1, 2 or 3 at the time of diagnosis, and their median survival was 17.6, 19.5 and 5.5 months, respectively. Survival was obviously shorter in those who had an ECOG score of 3.

There is still no consensus on what the optimal MPM treatment should be. For many years, systemic chemotherapy was an important treatment option. Today, platinum-based combination chemotherapy regimens, particularly the combination of cisplatin and pemetrexed, are recommended because of their positive impact on the survival of mesothelioma patients [22,23]. In the present study, receiving systemic chemotherapy treatment had no effect on survival. Although patients who received combination chemotherapy seemed to have a relatively longer survival than those who received only supportive care, this result was not significant when age was included as a confounding factor using the stratified Log Rank test. Younger patients may have received chemotherapy due to their better ECOG PS than the older patients.

The limitations in this study arise from its retrospective nature. For example, we could not find imaging results in some files for patients who were referred to our hospital by some other centers following examination.

In conclusion, we determined that age, duration of asbestos exposure and ECOG PS were associated with MPM prognosis. Since the latency period of asbestos exposure is very long, and since asbestos exposure is the most important risk factor for this disease, MPM will continue to appear in the coming years. Therefore, effective measures should be taken to protect those who are still at risk, and criteria should be developed for an early diagnosis and optimal treatment for those who develop the disease. Lastly, prospective studies are needed to determine the factors related to the prognosis of this disease that exhibit a heterogeneous clinical behavior.

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