JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1173730
J Contemp Med 2022;12(6):1002-1006

Original Article / Orijinal Araştırma

Prognostic Value of the Clinicopathological Characteristics of Patients With Malign Mesothelioma in the Mediterranean Region of Turkey

Türkiye'nin Akdeniz Bölgesindeki Malign Mezotelyoma Hastalarının Klinikopatolojik Özelliklerinin Prognostik Değeri

Erkan Kayikcioglu[1], Asim Armagan Aydin[2]

[1]Süleyman Demirel University School of Medicine Department of Internal Medicine, Division of Medical Oncology, Isparta, Turkey
[2]Health Sciences University, School of Medicine Department of Internal Medicine, Division of Medical Oncology, Antalya, Turkey

Abstract

Aim: To define the effect of clinicopathological characteristics of patients with malign mesothelioma (MM) on overall survival.

Material and Method: Forty-one patients diagnosed with MM who were treated at the medical oncology clinics between 2008 to 2020 were assessed. Clinicopathological characteristics and overall survival (OS) of patients, and treatment modalities analyzed.

Results: Forty-one patients were included in this study. The median age of patients was 63.5. At a median follow-up of 16.7 (range:0.5-172.6) months, 78%(32) of patients died. Median OS was 17.6 months. 65.9% (27) of patients had stage 3 and 29.3% (12) had stage 4 diseases when they were diagnosed. Most of the patients were diagnosed at the advanced stage (Stages 3-4) (95.2%). The median OS of patients diagnosed with epithelioid histopathologic subtype was 32.4 months, with sarcomatoid subtype was 5.23 months and with biphasic subtype was 4.33 months. This difference was statistically significant (p<0.001). When examined in terms of treatment modalities, there was a statistically significant difference between OS's (p=0.010). The median OS of patients treated with chemotherapy (14.4 months) was shorter than treated with radiotherapy and chemotherapy (42.8 months), and with surgery and chemotherapy (21.4 months). In Cox regression analysis, when sex, location, smoking, histopathological subtype, and sidedness were taken together, the pathological subtype was an independent risk factor on survival. The sarcomatoid subtype increased death risk by 7.2 times compared to epithelioid (p=0.004), biphasic subtype increased death risk by 8.1 times compared to epithelioid (p=0.004).

Conclusion: The etiology of MM is environmental exposure to asbestos or erionite in Turkey. The prognosis of the epitheloid subtype was better than sarcomatid and biphasic subtype. The prognosis of patients treated with surgery or radiotherapy in combination with chemotherapy was more favorable than those treated only with chemotherapy.

Keywords: Malign mesothelioma; overall survival;asbestos

Öz

Amaç: Malign mezoteliyomalı (MM) hastaların klinikopatolojik özelliklerinin genel sağkalıma etkisini tanımlamak.

Gereç ve Yöntem: 2008-2020 yılları arasında medikal onkoloji kliniklerinde tedavi gören MM tanılı 41 hasta değerlendirildi. Hastaların klinikopatolojik özellikleri ve genel sağkalımı (OS) ve tedavi yöntemleri analiz edildi.

Bulgular: Bu çalışmaya 41 hasta dahil edildi. Hastaların ortanca yaşı 63,5 idi. 16.7 (aralık:0.5-172.6) aylık medyan takipte hastaların %78'i (32) hayatını kaybetti. Medyan genel sağkalım 17.6 aydı. Tanı konulduğunda hastaların %65,9'u (27) evre 3 ve %29,3'ü (12) evre 4 hastalığı vardı. Hastaların çoğuna ileri evrede (Evre 3-4) (%95.2) tanı konuldu. Epiteloid histopatolojik alt tip tanısı alan hastaların medyan genel sağkalımı 32.4 ay, sarkomatoid olanların medyan genel sağkalımı 5.23 ay, bifaziklerin medyan genel sağkalımı 4.33 ay idi. Bu fark istatistiksel olarak anlamlıydı (p<0,001). Tedavi açısından bakıldığında genel sağkalımlar arasında istatistiksel olarak anlamlı fark vardı (p=0.010). Kemoterapi ile tedavi edilen hastaların genel sağkalımı 14.4 ay , radyoterapi-kemoterapi (42.8 ay) ve cerrahi-kemoterapiden (21.4 ay) olup daha kötüydü. Cox regresyon analizinde cinsiyet, lokasyon, sigara kullanımı, histopatolojik alt tip ve lateralite birlikte alındığında patolojik alt tip sağkalıma etki eden bağımsız bir risk faktörüydü. Sarkomatoid alt tipi, epiteloide göre ölüm riskini 7,2 kat (p=0,004), bifazik alt tipi ise epiteloide göre 8,1 kat artırdı (p=0,004).

Sonuç: MM etiyolojisi, Türkiye'de asbest veya erionite çevresel maruziyettir. Epiteloid alt tipin prognozu sarkomatid ve bifazik alt tipten daha iyiydi. Kemoterapi ile kombinasyon halinde cerrahi veya radyoterapi ile tedavi edilen hastaların prognozu, yalnızca kemoterapi ile tedavi edilenlere göre daha olumluydu.

Anahtar Kelimeler: Malig mezotelioma, genel sağkalım, asbestos

Corresponding *(İletişim)*: Erkan Kayikcioglu, Assistant Professor, M.D., Süleyman Demirel University School of Medicine Department of Internal Medicine, Division of Medical Oncology, Isparta, Turkey
E-mail *(E-posta)*: drkayikcioglu@yahoo.com
Received *(Geliş Tarihi)*: 11.09.2022 **Accepted *(Kabul Tarihi)*:** 18.11.2022

INTRODUCTION

Malignant mesothelioma (MM) is a tumor originating from the pleural cavity, peritoneal cavity, tunica vaginalis, and pericardial mesothelial cells; the prognosis is quite poor, and the median overall survival (OS) is approximately 12 months.[1] 85% of MM originates from the pleura, 15% from the peritoneum, and 1% from the tunica albuginea or pericardium. In Turkey, 896 patients were diagnosed in 2020 and 707 people died.[2] MM is histopathologically divided into 3 subgroups with different prognoses: epithelioid, sarcomatoid, and biphasic.[3] Asbestos-related MM is one of the most common occupational diseases in Germany, with an annual incidence of about 1000.[4] MM has different incidences in Turkey according to geographical regions. The most common region in Turkey is Cappadocia, where erionite, a fibrous mineral from the zeolite group, typically can be found in volcanic tuffs is common.[5] Some properties of erionite are similar to asbestos and the International Agency for Research on Cancer has classified erionite as a Group 1 carcinogen since it is known to cause cancer in humans[6] In a study of 93 patients by Mutlu Doğan, the median OS was 22.9 months and 62.3% of MM was originated from the pleura.[5] In Turkey, especially in the eastern and southeastern Anatolia regions, houses with soil containing asbestos are painted white. In a study of 283 patients in Turkey, MM developed in every patient as a result of environmental exposure from birth.[7]

In this study, we aimed to investigate the effects of demographic characteristics, clinicopathological characteristics, and treatment modalities on OS of MM patients in the Antalya, Isparta, and Burdur regions.

MATERIAL AND METHOD

The current study enrolled patients diagnosed with MM at Suleyman Demirel University Hospital, Turkey, and Antalya Hospital of Health Sciences University, Turkey from 2008 to 2020. The ethics committees of Suleyman Demirel University and Antalya Health Sciences University approved the study. Because the investigation was retrospective, there was no need for scientific research funding. Forty-eight patients were identified, but seven were excluded from the study because they dropped out of follow-up. Patients diagnosed with MM who were treated at the medical oncology clinics were assessed. All patients were over the age of 18, had follow-up and treatment in our units, and had records that we could access. Patients' age, clinicopathological characteristics, asbestos exposure and smoking history, treatment modalities, last polyclinic control, and death dates were recorded retrospectively.

Statistical Analysis

Study data were analyzed using SPSS (Statistical Package for the Social Sciences) 23.0 and MedCalc 20.110. Numeric data are expressed as the median and interquartile range (IQR), and frequent data are expressed as rates. A comparison of the two groups with numeric data was performed using the Mann-Whitney U test. Pearson's chi-square and Fischer's exact tests were used to comparing the two groups with categorical variables.

Overall comparisons of clinicopathological characteristics and treatment modalities were performed using Kaplan-Meier curves and median survival times. A comparison of the two groups in the Kaplan-Meier analysis was carried out using the log-rank test. Univariate Cox regression analyses were used to establish hazard ratios with 95% confidence intervals for each variable. The hypotheses were constructed as two-tailed, and an alpha value of 0.05 was accepted as significant.

RESULTS

Forty-one patients were included in this study. The median age of patients was 63.5 (range:38-84). The demographic and clinical characteristics are shown in **Table 1**.

Table 1. Demographics and clinical characteristics of patients

% (n)	n	%
Age, years (median, range)	63.5	38-84
Gender		
Male	25	61
Female	16	39
Asbestos Exposure	40	97.6
Histopathology		
Epitheloid	30	73.2
Sarcomatoid	7	17.1
Mixed	4	9.8
Tumor Localization		
Plevna	30	73.2
Periton	10	24.4
Heart	1	2.4
Sidedness (pleural)		
Left	12	40
Right	18	60
Smoking History		
Yes	21	51.2
No	20	48.8
Symptom		
Dyspnea	20	48.8
Chest pain	22	53.7
Cough	10	24.4

At a median follow-up of 16.7 (range:0.5-172.6) months, 78%(32) of patients died. Median overall survival was 17.6 (range: 9.3-25.8) months. 65.9%(27) of patients had stage 3 and 29.3% (12) stage 4 diseases when they were diagnosed. The pathological characteristics of patients are shown in **Table 2**.

Table 2. Pathological characteristics of patients

	n	%
Stage		
2	2	4.9
3	27	65.9
4	12	29.3
Treatment Modality		
Chemotherapy	39	95.1
Radiotherapy	3	7.3
Surgery	8	19.5
Chemotherapy Lines		
1	15	36.6
2	13	31.7
3	7	17.1
4	5	12.2
Chemotherapy		
Platin-Pemetrexed	39	95.1
Platin Gemcitabine	1	2.4
Survival		
Exitus	32	78
Alive	9	22

61% of the patients were male. The most common symptoms at presentation were dyspnea and chest pain (73.2%) in malign pleural mesothelioma, and abdominal pain and distension (100%) in malign peritoneal mesothelioma. In 73.2%, the disease originated from the pleura, 24.4% from the peritoneum, and 2.4% from the heart. The most prevalent histological subtypes were epitheloid (73.2%), sarcomatoid, and biphasic (26.8%). Almost all patients received platin-pemetrexed (95.1%). Most of the patients received one or two lines of chemotherapy (68.3%). 40% of malign pleural mesothelioma originate from the left side and 60% from the right side. About half of the patients (48.8%) were non-smokers. Most of the patients were treated with chemotherapy alone (68.3%). Most of the patients were diagnosed at the advanced stage (Stages 3-4) (95.2%). Most patients had a history of asbestos exposure (97.6%). Median OS was 17.6 months in males and 15.9 months in females but the difference was not statistically significant (p=0.32) (**Figure 1**).

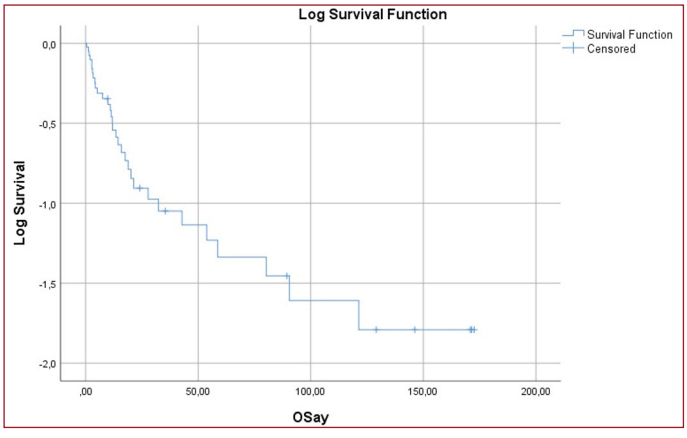

Figure 1. Median OS was 17.6(range: 9.3-25.8) months

Regarding the tumor origin, there was no statistically significant difference in survival for malignant mesothelioma between the lung, peritoneum, and heart (p=0.62). The median overall survival in pleural mesothelioma was 17.57 months, while in peritoneal mesothelioma it was 15.9 months. There was no statistically significant difference between the stages in terms of OS (p=0.27). However, as the stage increases, the OS shortens. While the median OS in stage 2 was 121.3 months, it was 18.9 (range: 5.9-29) months in stage 3; and was 11.8 (range:5.9-17.7) months in stage 4. The Median OS of smokers was longer (18.9 months) than non-smokers (11.9 months) but it was not statistically significant (p=0.70). The median OS of patients diagnosed with epithelioid histopathologic subtype was 32.4 months, while the median OS of those with sarcomatoid subtype was 5.23 months, while the median OS of biphasic subtype was 4.33 months (**Figure 2**). This difference was statistically significant (p<0.001).

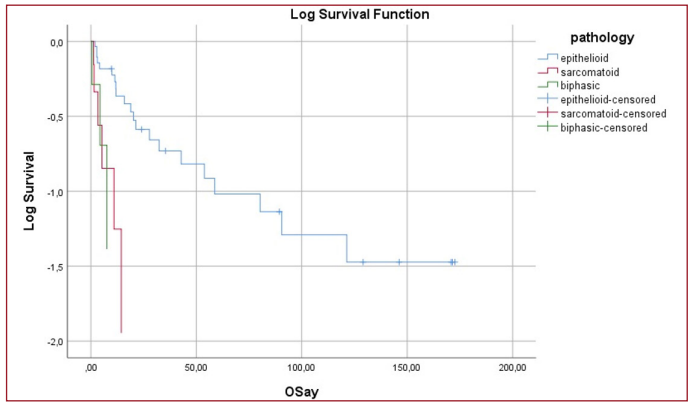

Figure 2. Median OS in patients with epitheloid and sarcomatoid histopathological subtypes was 32.4 and 4.3 months respectively. (p<0.001)

OS of patients with epitheloid subtype was longer than the sarcomatoid and biphasic subtype. When examined in terms of treatment modalities, there was a statistically significant difference between OSs (p=0.010). The Median OS of patients treated with chemotherapy (14.4 months) was worse than with radiotherapy-chemotherapy (42.8 months) and with surgery-chemotherapy (21.4 months) (**Figure 3**)

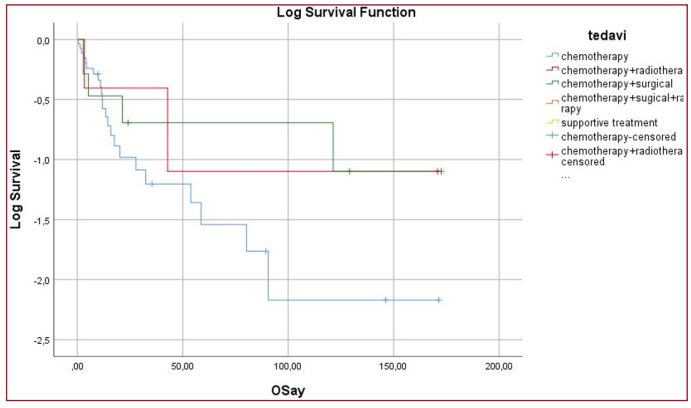

Figure 3. The Median OS of patients who received chemotherapy was 14.4 vs. 21.4 months in patients who had surgery and received chemotherapy.

There was no statistically significant difference in median OS for the right and left sides (14.4 versus 17.6 months) (p=0.736). In Cox regression analysis, when sex, location, smoking, histopathological subtype, and sidedness were taken together, only the pathological subtype was effective on survival (**Table 3**). The sarcomatoid subtype increased death risk by 7.2 times compared to epithelioid (p=0.004), biphasic subtype increased death risk by 8.1 times compared to epithelioid (p=0.004).

Table 3. Cox regression analysis of OS

	OS Univariate HR (95% CI for HR)			p
Sex	1.257	0.410	3.858	0.689
Sidedness	0.467	0,160	1.363	0.164
Histopathology	8.396	1.929	36.538	0.004
Smoking History	1.559	0.578	4.207	0.381
Treatment Modality	0,899	0.100	3.447	0.816

DISCUSSION

In Turkey's central Anatolia region, particularly in Cappadocia, MM is an endemic disease. A collection of fibrous, hydrated magnesium silicate crystals is known commercially as asbestos. Long filaments of asbestos can be found in rock and soil. Serpentine and amphibole are the two main types. Chrysotile, a serpentine fiber that is considered less carcinogenic, makes up around 95% of the asbestos produced and used globally.[8] The primary cause of MM in developed countries is occupational asbestos exposure; however, environmental exposure to asbestos-containing soil painted buildings is the leading cause of asbestosis in Turkey. Environmental exposure to erionite in Cappadocia is the other cause in Turkey. Almost all of the patients in the current study were living in the Mediterranean region of Turkey and had been exposed to asbestos through house painting. The median age of the patients was 63.5 and OS was 17.6 months. There was no statistically significant OS variance in males and females. In a study of 367 patients with malign pleural mesothelioma the OS in females was worse.[9] History of asbestos exposure was present in 97.7% of our patients and 62% in CALBG's study including 337 patients. However, in contrast to our patients' environmental exposure, most of this exposure was occupational.[10] The OS of smokers was better than non-smokers (18.9 vs.11.9 months), although it was not statistically significant. This may be evidence that smoking does not induce malignant mesothelioma. There was no statistically significant OS difference for the origin of MM; however, in CALBG's study, pleural MM had worse survival.[10] The stage of MM did not affect OS in the present study, this is consistent with the study including 188 patients with pleural MM.[11] It was statistically significant that the OS in the epitheloid histopathological subtype was better than in the non-epitheloid subtype (32.4 vs. 4.3-5.2 months) consistent with the results of the other studies.[9,11,12] Most of the patients were treated with only chemotherapy because of the higher stages at presentation. The OS of patients treated with radiotherapy-chemotherapy or surgery-chemotherapy was statistically significantly better than those treated with only chemotherapy. In a study that included 367 patients, the OS was better in patients treated with surgery-chemotherapy.[9]

CONCLUSION

The etiology of MM is environmental exposure to asbestos or erionite in Turkey. The prognosis of the epitheloid subtype was better than sarcomatid and biphasic subtype. The prognosis of patients treated with surgery or radiotherapy in combination with chemotherapy was more favorable than those treated only with chemotherapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: Suleyman Demirel School of Medicine ethic commitee approved this study.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21(14):2636-44.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209-49.
3. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10(9):1243-60.
4. Aigner C, Brüning T, Eberhardt WEE, Härter M, Kaelberlah HP, Metzenmacher M, et al. [The Current Therapy of Asbestos-Associated Malignant Pleural Mesothelioma - An Expert Consensus Paper]. Pneumologie 2021;75(10):776-94.
5. Dogan M, Utkan G, Hocazade C, Uncu D, Toptas S, Ozdemir N, et al. The clinicopathological characteristics with long-term outcomes in malignant mesothelioma. Med Oncol 2014;31(10):232.
6. Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. IARC Monogr Eval Carcinog Risks Hum Suppl. 1987;7:1-440.
7. Elkiran ET, Kaplan MA, Sevinc A, Aksoy S, Demirci U, Seker M, et al. Multicentric study on malignant pleural mesothelioma in Turkey: clinicopathologic and survival characteristics of 282 patients. Med Oncol 2012;29(5):3147-54.

8. Hodgson JT, McElvenny DM, Darnton AJ, Price MJ, Peto J. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. Br J Cancer 2005;92(3):587-93.
9. Billè A, Okiror L, Harling L, Pernazza F, Muzio A, Roveta A, et al. Analysis of survival of patients with metastatic malignant pleural mesothelioma. Tumori 2021;107(2):110-8.
10. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest. 1998;113(3):723-31.
11. Boutin C, Rey F, Gouvernet J, Viallat JR, Astoul P, Ledoray V. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 2: Prognosis and staging. Cancer. 1993;72(2):394-404.
12. Dacic S. Pleural mesothelioma classification-update and challenges. Mod Pathol 2022;35(Suppl 1):51-6.