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Clinical and Demographic Features in Malignant Peritoneal Mesothelioma: Treatment Approaches and Factors Affecting Survival

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ABSTRACT

Objective: Malignant peritoneal mesothelioma (MPM) is a rare and aggressive malignancy with limited survival, often associated with asbestos exposure. This study aimed to analyze the demographic and clinical characteristics of MPM patients, determine factors influencing survival, and evaluate the effectiveness of current treatment modalities.

Material and Methods: A retrospective, multicenter analysis was conducted on 40 patients diagnosed with MPM between 2009 and 2022. Demographic, histological, and treatment-related data were collected. Survival outcomes, including progression-free survival (PFS) and overall survival (OS), were analyzed using Kaplan-Meier curves and Cox regression models.

Results: The median age of the cohort was 59, and 70% were male. Epithelioid histology was the most common subtype (77.5%) and was associated with significantly better OS (median: 49 months) compared to non-epithelioid subtypes (median: 5 months, p<0.001). Patients who underwent cytoreductive surgery (CRS) demonstrated significantly improved OS. Hyperthermic intraperitoneal chemotherapy (HIPEC) was associated with prolonged PFS (26.18 *vs.* 6.63 months, p=0.013), though its impact on OS was not statistically significant in multivariate analysis.

Conclusion: Histological subtype and treatment strategy significantly influence MPM outcomes. Epithelioid histology correlates with better survival, while aggressive interventions such as CRS and HIPEC offer survival advantages in selected patients. Multidisciplinary approaches and individualized therapeutic strategies are critical to improving prognosis in MPM.

Keywords: Malignant peritoneal mesothelioma; epithelioid histology; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; survival

INTRODUCTION

Malignant mesothelioma (MM) is an aggressive and lethal disease. It affects pleural and peritoneal membranes, often linked to asbestos exposure.[1,2] It is more common in men than in women.[3] Pleural mesothelioma is the most common type, while malignant peritoneal mesothelioma (MPM) is the second most common.[4] Pericardial and tunica vaginalis mesothelioma are very rare. MM usually carries a poor prognosis; the median

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survival of patients with pleural mesothelioma is 9 months; for patients with non-pleural mesothelioma, it is 18 months.[5] Mesothelioma has 3 main subtypes: epithelioid, sarcomatoid and biphasic, with the sarcomatoid subtype having the worst prognosis.[6]

MPM is often diagnosed at an advanced stage due to vague symptoms like abdominal pain, swelling, and weight loss.[7] Due to its rarity, there is no consensus on the optimal treatment. Historically, MPM was managed with chemotherapy, palliative surgery, and occasionally radiation, yielding a median survival of about one year.[8-10] Recent experience with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has demonstrated improved outcomes in selected MPM patients over the past 15 years.[11] CRS and HIPEC are now the preferred treatments for eligible patients, though systemic chemotherapy and immunotherapy remain alternatives.

This study aims to evaluate the impact of current treatment approaches, including CRS and HIPEC, as well as clinicopathologic characteristics, on survival in patients with MPM. Specifically, we hypothesize that patients undergoing CRS and HIPEC will show improved overall survival (OS) and progression-free survival (PFS) compared to those receiving traditional treatments such as chemotherapy alone. By analyzing these factors, this study aims to provide further insights into the effectiveness of current therapies and contribute to refining treatment strategies for MPM.

MATERIAL AND METHODS

Patients diagnosed with peritoneal mesothelioma between January 2009 and March 2024, and those who were followed up and treated in the oncology clinics, were included in the study. Data were collected from five different centers. Data collection and analysis were conducted according to the ethical standards and the Declaration of Helsinki principles. Ethics committee approval of our study was obtained from Marmara University Faculty of Medicine Ethics Committee on 22.04.2024 with protocol number 09.2024.500. The variables examined in the study included age, gender, Eastern Cooperative Oncology Group performance status, tumor histology, stage at diagnosis, presence of CRS, HIPEC performance, presence of surgery, recurrence status, and treatment regimens used in systemic treatment. Recurrence was defined as radiologically confirmed disease progression during follow-up in patients who had undergone curative surgery. Histopathological classification was based on World Health Organization criteria and included epithelioid, sarcomatoid, and biphasic subtypes. Staging was determined according to the presence of extraperitoneal metastasis: patients without distant spread were classified as stage I–III, while patients with extraperitoneal disease were considered stage IV. Since the study was conducted retrospectively across five different centers, the decision to perform CRS and/or HIPEC was made individually by each institution's multidisciplinary team, taking into account patient performance status, extent of disease, and institutional experience. A standardized eligibility protocol was not applied across all centers. Information about the patients was retrospectively retrieved from their files and the hospital's electronic record database. The relationship between the data obtained, and PFS and OS was analyzed. PFS was calculated as the time between the start of systemic therapy and the date of disease progression. OS was expressed as the time from the date of diagnosis to the date of death from any cause or the date of last follow-up for surviving patients.

Statistical Analysis

Data were analyzed using SPSS software version 26.0. Continuous variables were summarized as medians with interquartile ranges, while categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. The distribution of continuous variables was assessed using the Shapiro-Wilk test. As most variables were not normally distributed, continuous variables were summarized as medians with interquartile ranges and compared using the Mann-Whitney U test. Survival curves were created using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Univariate analysis was conducted to identify prognostic factors, and variables with a p-value of less than 0.05 were included in a multivariate analysis. Hazard ratios (HRs) and their corresponding confidence intervals (CIs) were calculated using a Cox proportional hazards model. Statistical significance was set at $p<0.05$.

RESULTS

The Study Population's Demographic and Clinical Characteristics

The study population consisted of 40 patients, with a median age of 59 years (interquartile range: 55.2-65.7). The majority of patients (70%) were male. The median follow-up time was 25.8 months. Epithelioid histology was the most common subtype, observed in 77.5% of cases, while non-epithelioid subtypes (sarcomatoid and biphasic) accounted for 22.5%. At the time of diagnosis, the majority of patients (67.5%) presented with de novo metastases. Among the therapeutic modalities, 27.5% of patients underwent HIPEC and 30% underwent CRS. No significant differences in baseline characteristics such as age, gender, metastatic status at diagnosis, and first-line treatment were found between patients with epithelioid

and non-epithelioid histology or between those who underwent HIPEC and those who did not (p>0.05). First-line systemic treatment regimens were predominantly cisplatin and pemetrexed (52.5%), and 25% of these regimens were combined with bevacizumab. Only 2 patients (5%) received immunotherapy in the second line or later (Table 1).

Survival Outcomes

Progression-Free Survival

In univariate analysis, non-epithelioid histology (p=0.019) and receiving HIPEC (p=0.013) were significantly associated with improved PFS. In the multivariate Cox regression model, non-epithelioid histology (HR: 2.83; 95% CI: 1.13-7.11; p=0.026) and receiving HIPEC (HR: 0.30; 95% CI: 0.11-0.81; p=0.018) remained independent prognostic factors for PFS (Tables 2, 3).

Overall Survival

Median OS for all groups was 25.5 months. OS analysis revealed significant differences based on histological subtype, metastasis at diagnosis, and treatment modalities. Patients with epithelioid histology demonstrated a markedly better median OS of 49.0 months (95% CI: 37.3-60.7) than 5.0 months (95% CI: 2.0-7.9) for those with non-epithelioid subtypes (HR: 0.09, p<0.001) (Figure 1). Median OS was 17.0 months (95% CI: 1.4-32.6) in patients with metastases at diagnosis and 87.0 months (95% CI: 40.7-133.2) in patients without metastases, with a significant statistical difference between the two (HR=0.31, p=0.039). CRS was a significant predictor of improved OS; patients who underwent surgery had a longer OS (median OS was not reached), while those who did not have a median OS of 17.0 months (HR: 16.65, p=0.001) (Figure 2). The remarkably longer median OS (87.0 months; 95% CI: 37.8-136.2) in patients who received HIPEC showed no statistical significance on multivariate analysis compared to those who did not receive HIPEC (21.0 months; 95% CI: 5.6-36.3).

DISCUSSION

Our results show that patients with epithelioid histology experience significantly longer PFS and OS than those with non-epithelioid subtypes. This finding is important as it highlights the prognostic value of histologic subtype in MPM. Furthermore, our study highlights the importance of specialized surgical interventions such as HIPEC and CRS, which were found to have a positive impact on survival rates. These therapies are most effective in patients without extraperitoneal spread and favorable histology. In addition to these results, the presence of metastatic disease negatively impacted prognosis, resulting in shorter survival for metastatic patients. These findings provide important clues

TABLE 1: Demographic and clinical characteristics of the study patients.

Age, year	
Median (IQR)	59 (55.2-65.7)
Age group, n (%)	
<60 years	21 (52.5)
≥60 years	19 (47.5)
Gender, n (%)	
Female	12 (30.0)
Male	28 (70.0)
ECOG-PS, n (%)	
0-1	33 (82.5)
≥2	7 (17.5)
Histology, n (%)	
Epiteloid	31 (77.5)
Sarcomatoid	5 (12.5)
Biphasic	4 (10.0)
Asbestos exposure, n (%)	
Yes	19 (47.5)
No	21 (52.5)
Tobacco exposure, n (%)	
Yes	21 (52.5)
No	19 (47.5)
Most common symptom at presentation, n (%)	
Abdominal pain	19 (47.5)
Stage group at diagnosis, n (%)	
Stage I-II-III	13 (32.5)
Stage IV	27 (67.5)
Surgery (CRS), n (%)	
Yes	12 (30)
No	28 (70)
HIPEC, n (%)	
Yes	11 (27.5)
No	29 (72.5)
Recurrence in operated patients, n (%)	
Yes	8 (66.7)
No	4 (33.3)
Systemic treatment, n (%)	
Cisplatin+pemetrexed	21 (52.5)
Carboplatin+pemetrexed	9 (22.5)
Cisplatin+pemetrexed+bevasizumab	10 (25.0)
Use of immunotherapy in any line, n (%)	
Yes	36 (16.6)
No	181 (83.4)

IQR: Interquartile range; ECOG: Eastern cooperative oncology group; HIPEC: Hyperthermic intraperitoneal chemotherapy; CRS: Cytoreductive surgery; PS: Performance status.

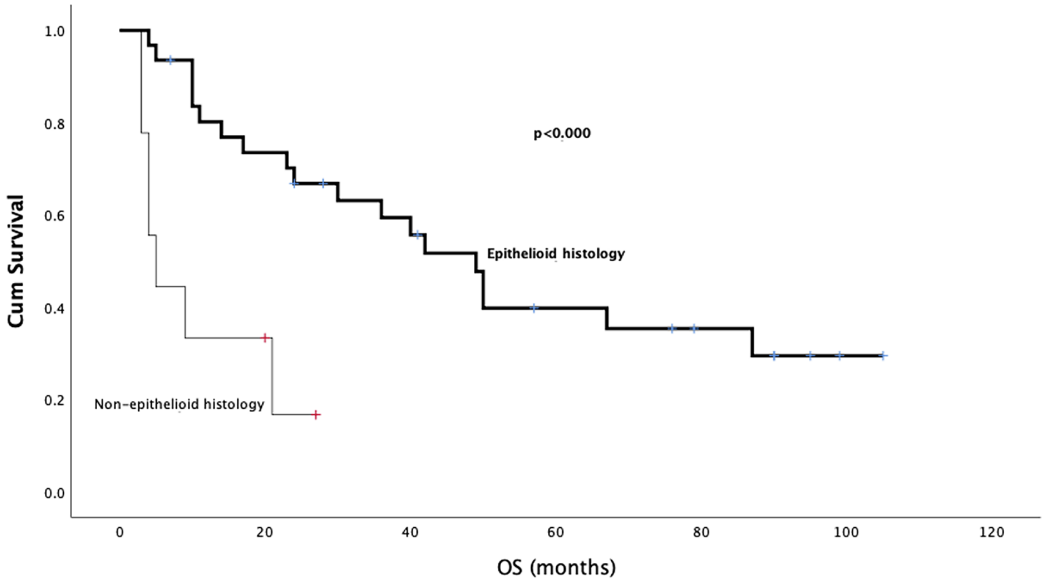

FIGURE 1: Association of histologic subtype with survival.

OS: Overall survival

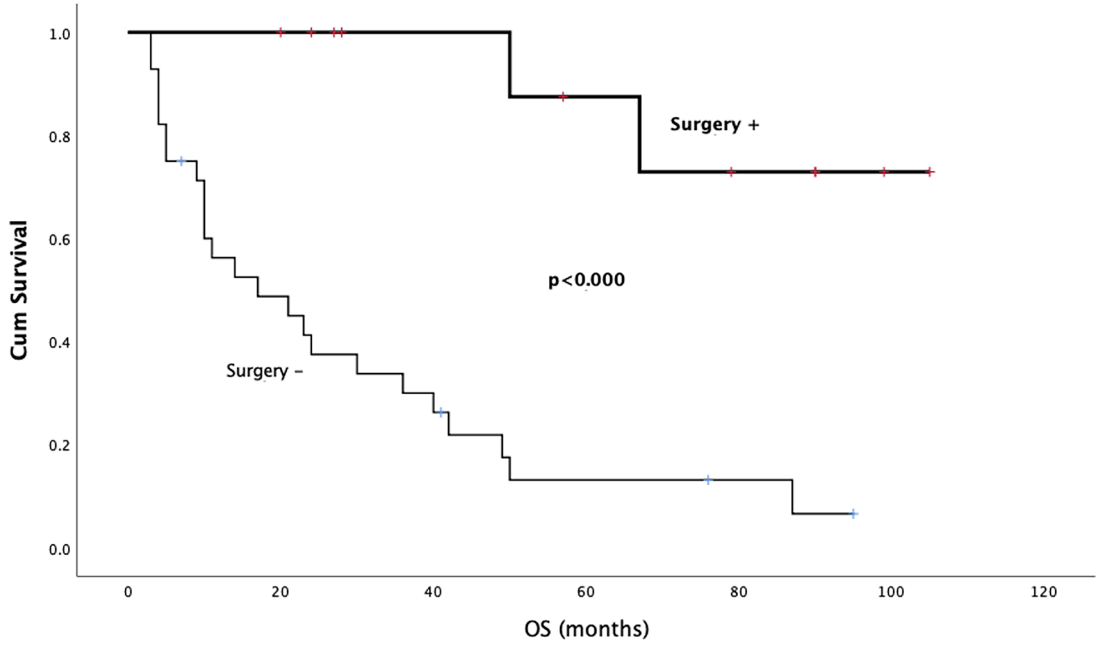

FIGURE 2: Relationship between CRS and survival.

CRS: Cytoreductive surgery, OS: Overall survival

for determining optimal treatment strategies to improve survival in MPM patients.

Regional treatment using CRS and HIPEC is recommended for selected patients with good performance status, absence of extraperitoneal disease spread, and a likelihood of achieving complete surgical cytoreduction. A study conducted in Australia demonstrated a significant prolongation of OS, with CRS and HIPEC in patients with MPM.[12] In the study by Elias et al.[13], the median OS was over 100 months and the 5-year OS was 63%. Another multi-center study reported a median OS of 53 months and a 5-year survival rate of 47%.[14] Survival prolongation by surgery was confirmed in both univariate and multivariate analyses in our study, and seems to be consistent with the literature. Notably, the fact that the median OS has not yet been reached in patients who

TABLE 2: Clinical and pathological factors related to PFS based on univariate and multivariate Cox regression analysis.				
	Univarite		Multivariate	
	Median PFS	p	HR (95% CI)	p
Age				
<60 years	8.24 (6.32-10.21)	0.495		
≥60 years	6.72 (1.03-18.91)			
Gender				
Male	7.26 (1.13-14.70)	0.967		
Female	8.28 (8.12-8.43)			
Asbestos exposure				
No	7.26 (2.62-11.91)	0.074		
Yes	12.81 (0.92-29.43)			
Histology				
Epiteloid	8.28 (1.14-21.71)	**0.019**	Ref	**0.026**
Non-epiteloid	3.54 (1.92-5.23)		2.83 (1.13-7.11)	
Metastases at diagnosis				
Yes	6.73 (2.12-11.31)	0.156		
No	26.18 (10.91-41.42)			
HIPEC				
No	6.63 (3.04-10.21)	**0.013**	Ref	**0.018**
Yes	26.18 (1.22-66.43)		0.30 (0.11-0.81)	
Surgery (CRS)				
Yes	26.18 (1.12-59.01)	0.104		
No	6.73 (2.02-11.53)			
Systemic treatment				
Carboplatin+pemetrexed	6.73 (2.53-10.91)	0.293		
Cisplatin+pemetrexed	19.08 (18.82-19.31)			
CT regimen with bevacizumab				
Yes	6.63 (2.53-10.72)	0.355		
No	8.28 (1.62-14.93)			

PFS: Progression free survival; HR: Hazard ratio; CI: Confidence interval; CT: Chemotherapy; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy.
Note: In Cox regression analysis, the first listed group was used as the reference category for each variable.

underwent surgery indicates that this treatment significantly improves prognosis. Additionally, the substantially longer PFS observed in patients treated with HIPEC suggests that this modality, when combined with CRS, offers a valuable option in the treatment of MPM. However, the fact that the effect of HIPEC on OS did not reach statistical significance in multivariate analyses suggests that patient selection criteria and factors affecting response to treatment should be better defined. As is well established, the success of HIPEC is closely linked to the surgeon's skill and experience.[15] The absence of significance in the multivariate analysis may be attributable to factors such as a limited sample size, patient selection, or variations in the experience of surgeons across the participating centers. Nevertheless, the results suggest that the combination of HIPEC and surgery may provide a long-term control and survival advantage in appropriate patient groups.

The prognosis of MPM differs in relation to histological subtype.[16] The epithelioid subtype is associated with the most favorable biological behavior, whereas the sarcomatoid subtype is linked to the worst prognosis.[17] Moreover, the sarcomatoid subtype is the rarest among the MPM subtypes.[18] Our study supports these findings, as we observed that epithelioid histology was significantly associated with improved survival, consistent with existing literature. The significantly longer median OS observed in patients with the epithelioid subtype, compared to those with other histological subtypes, further supports the less aggressive biological

TABLE 3: Clinical and pathological factors related to OS based on univariate and multivariate Cox regression analysis.				
	Univarite		Multivariate	
	Median OS	p	HR (95% CI)	p
Age				
<60 years	30.00 (1.02-64.71)	0.400		
≥60 years	40.00 (14.91-65.02)			
Gender				
Male	49.00 (22.12-75.91)	0.792		
Female	36.00 (13.42-58.61)			
Asbestos exposure				
Yes	50.00 (1.22-100.51)	0.693		
No	30.00 (13.71-46.22)			
Histology				
Epithelioid	49.00 (37.32-60.71)	**<0.001**	Ref	**<0.001**
Non-epithelioid	5.00 (2.01-7.92)		0.09 (0.02-0.31)	
Metastases at diagnosis				
Yes	87.00 (40.71-133.22)	**0.001**	Ref	**0.039**
No	17.00 (1.40-32.61)		0.31 (0.09-1.04)	
HIPEC				
Yes	87.00 (37.82-136.20)	**0.006**	Ref	0.198
No	21.00 (5.61-36.32)		2.52 (0.61-10.30)	
Surgery (CRS)				
Yes	NR	**<0.001**	Ref	**<0.001**
No	17.00 (0.26-33.70)		16.65 (2.13-130.09)	
Systemic treatment				
Cisplatin+pemetrexed	21.00 (5.91-36.42)	0.852		
Carboplatin+pemetrexed	42.00 (11.60-72.41)			
CT regimen with bevacizumab				
Yes	21.00 (1.00-52.31)	0.384		
No	42.00 (13.91-70.00)			

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; CT: Chemotherapy; CRS: Cytoreductive surgery; NR: Not reached.

behavior of this subtype and its heightened sensitivity to treatment. These findings underline the importance of the epithelioid subtype as a key prognostic factor and support the use of more intensive treatment approaches in affected patients.

In our study, advanced disease was identified as an important unfavorable prognostic factor. Metastatic patients were not eligible for CRS and/or HIPEC and were treated only with systemic palliative chemotherapy. In contrast, locally advanced cancer patients without extraperitoneal spread may be candidates for CRS and/or HIPEC, and we believe this approach improves survival outcomes. Studies in the literature suggest that maximal CRS and HIPEC may slow disease progression by reducing tumor burden, and that they significantly improve OS. Systemic chemotherapy remains the primary treatment approach for patients with inoperable MPM, typically using regimens adapted from pleural mesothelioma treatment protocols. In a phase 3 trial involving patients from different centers, it was shown that some regimens, such as cisplatin + pemetrexed, can significantly prolong OS.[19] In a study of inoperable MPM patients, survival times are limited in general, but appropriate treatment combinations may improve the prognosis for some patients.[20] In our study, all patients received dual systemic therapy (platinum and pemetrexed) with or without bevacizumab. However, OS was significantly reduced in patients with metastasis. This finding suggests that systemic therapy alone has a limited impact on survival in patients with metastatic disease and that CRS and HIPEC are potential treatment options that may provide a survival advantage. Therefore, a multidisciplinary approach

should be adopted in determining optimal treatment strategies and ensuring careful patient selection.

Study Limitations

Although the results of our study are consistent with the literature, there are some limitations. First, in this retrospective analysis, there is no clear information about the selection criteria and standardization of the procedures. The study included patients from multiple institutions, so the criteria for selecting candidates for CRS and HIPEC could not be standardized. In particular, the impact of the surgeon's experience and skill level on outcomes was not considered, and these factors can significantly influence a complex procedure such as HIPEC. This heterogeneity may have affected treatment outcomes and should be taken into account when interpreting the results. Second, treatment differences were observed between the study groups. Some patients received bevacizumab in combination with platinum therapy, and we do not have information on patient selection criteria. This may limit the comparability of responses to treatment and introduce a potential bias into the results. We also did not have access to patient files on the presence of ascites or why patients were considered inoperable, which may weaken the comparability of results and introduce potential bias. Finally, the retrospective nature of the data precludes full information on patient selection criteria, treatment decisions, and treatment duration details. These limitations underscore the need for cautious interpretation and future prospective studies.

CONCLUSION

MPM is a rare malignancy that can be managed with proper patient selection and multidisciplinary treatment strategies. The data from our study suggest that epithelioid histologic subtype is associated with better survival, and aggressive treatment strategies such as CRS and HIPEC may provide long-term control in appropriate patients. Especially when complete cytoreduction is achieved, this combination has been shown to offer a significant benefit in long-term tumor control and PFS. The limited survival with systemic therapy in inoperable MPM necessitates more careful evaluation of this patient group and customization of treatment approaches. In the future, individualizing treatments and performing surgical procedures in specialized centers will contribute to more effective outcomes in MPM management.

Ethics

Ethics Committee Approval: Ethics committee approval of our study was obtained from Marmara University Faculty of Medicine Ethics Committee on 22.04.2024 with protocol number 09.2024.500.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.S., S.Y., E.Z., E.K., A.Ç., M.A., İ.V.B., Concept: N.S., S.Y., A.F.G., D.K.K., A.K.G., B.D.Ç., B.P., R.A., M.S., Design: N.S., A.F.G., P.E., E.K., A.Ç., R.A., İ.V.B., Data Collection or Processing: N.S., E.Z., Y.A., B.P., N.M., M.S., Analysis or Interpretation: N.S., Y.E.A., P.E., M.A.T., S.I., M.A., O.K., Literature Search: N.S., Y.E.A., Y.A., M.A.T., S.I., R.A., O.K., Writing: N.S., A.K.G., S.K.

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