

Survival of pleurectomy-decortication and hyperthermic chemotherapy in mesothelioma

Mezotelyoma tedavisinde plörektomi-dekortikasyon ve hipertermik kemoterapinin sağkalımı

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ABSTRACT

Background: This study aims to evaluate overall survival, disease-free survival, and prognostic factors in patients undergoing pleurectomy-decortication and hyperthermic intrathoracic chemotherapy with the diagnosis of malignant pleural mesothelioma.

Methods: Between January 2020 and November 2021, a total of 53 patients (27 males, 26 females; mean age: 58.1±1.3 years; range, 39 to 81 years) who underwent pleurectomy-decortication and hyperthermic intrathoracic chemotherapy with the diagnosis of malignant pleural mesothelioma were retrospectively analyzed. Data including characteristics, comorbidities, postoperative complications, recurrence and mortality status of the patients were recorded. Overall survival and disease-free survival and prognostic factors were evaluated.

Results: The median disease-free survival was 11.67 months and the median overall survival was 24.60 months. The median disease-free survival was 8.80 months in men and 13.17 months in women, indicating a statistically significant difference as it showed that recurrence was detected earlier in male patients (p=0.037). The median disease-free survival and overall survival was 6.13 months and 11.70 in cases diagnosed with biphasic mesothelioma, respectively, while it was 11.67 months and 25.46 months in cases with epithelial mesothelioma, respectively. Pathological subtype was found to be an effective prognostic factor for both survival (p=0.049 and p<0.001, respectively).

Conclusion: Hyperthermic intrathoracic chemotherapy following cytoreductive surgery is a preferable and tolerable method in the treatment of malignant pleural mesothelioma. While evaluating surgical indications, it should be kept in mind that cases with epithelial mesothelioma may benefit more from surgical treatment.

Keywords: Chemotherapy, chest, mesothelioma, pleural disease, survival.

ÖZ

Amaç: Bu çalışmada malign plevral mezotelyoma tanısı ile plörektomi-dekortikasyon ve hipertermik intratorasik kemoterapi uygulanan hastalarda genel sağkalım, hastalıksız sağkalım ve prognostik faktörler incelendi.

Çalışma planı: Ocak 2020 - Kasım 2021 tarihleri arasında malign plevral mezotelyoma tanısı ile plörektomi-dekortikasyon ve hipertermik intratorasik kemoterapi yapılan toplam 53 hasta (27 erkek, 26 kadın; ort. yaş: 58.1±1.3 yıl; dağılım, 39-81 yıl) retrospektif olarak incelendi. Hastaların özellikleri, eşlik eden hastalıkları, ameliyat sonrası komplikasyonları, nüks ve mortalite durumları dahil veriler kaydedildi. Genel sağkalım ve hastalıksız sağkalım ve prognostik faktörler değerlendirildi.

Bulgular: Medyan hastalıksız sağkalım süresi 11.67 ay ve medyan genel sağkalım süresi 24.60 ay idi. Hastalıksız sağkalım süresi erkeklerde 8.80 ay, kadınlarda ise 13.17 ay olup, erkek olgularda nüksün daha erken dönemde saptanması açısından istatistiksel olarak anlamlı bir farklılık idi (p=0.037). Bifazik mezotelyoma olgularında medyan hastalıksız sağkalım ve genel sağkalım süresi sırasıyla 6.13 ay ve 11.70 ay iken, epitelyal tip mezotelyoma olgularında sırasıyla, 11.67 ay ve 25.46 ay idi. Patolojik alt tipin her iki sağkalım için de etkili bir prognostik faktör olduğu bulundu (sırasıyla, p=0.049 ve p<0.001).

Sonuç: Malign plevral mezotelyoma tedavisinde hipertermik intratorasik kemoterapi, sitoreduktif cerrahi sonrası tercih edilebilir ve tolere edilebilir bir yöntemdir. Cerrahi endikasyonlar değerlendirilirken epitelyal mezotelyomalı olguların cerrahi tedaviden daha çok fayda görebileceği akılda tutulmalıdır.

Anahtar sözcükler: Kemoterapi, göğüs, mezotelyoma, plevral hastalık, sağkalım.

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Malignant pleural mesothelioma (MPM) is an aggressive cancer encountered in pleural surfaces. It is the most common malignant tumor involving the pleura. Asbestos exposure is blamed for most of the cases.^[1,2] Dyspnea and chest pain are the most common symptoms.^[3] After the diagnosis, the main goal of the treatment is to perform macroscopic complete resection.^[4]

The high rate of local recurrence in MPM despite surgical treatment has given rise to the development of new techniques to prevent recurrence. For this purpose, hyperthermic intrathoracic chemotherapy (HITOC) following cytoreduction was developed. It has been reported that the overall survival (OS) rate of MPM is about 12 months with standard chemotherapy and can reach up to 18 to 23 months with this technique.^[5,6]

In the present study, we aimed to evaluate OS, disease-free survival (DFS), and prognostic factors in patients undergoing pleurectomy-decortication (PD) and HITOC with the diagnosis of MPM.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ege University School of Medicine, Department of Thoracic Surgery between January 2020 and November 2021. Among non-metastatic and resectable patients, those who underwent PD and HITOC following thoracotomy were included in the study. Exclusion criteria were as follows: unable to tolerate the HITOC procedure (n=2), receiving neoadjuvant therapy previously (n=3), undergoing anatomical resection, as it may affect complications and survival (n=3), and having incomplete follow-up data (n=3). Finally, a total of 53 patients (27 males, 26 females; mean age: 58.1±1.3 years; range, 39 to 81 years) were included in the study.

Total PD was performed in all cases, and single or multiple wedge resections were performed in patients who were considered to have local invasion of the lung. Lesions on the diaphragm and pericardium were resected, but diaphragmatic or pericardial resection was not performed. Routine lymph node (LN) dissection was not performed, except in required cases. After PD, the cisplatin regimen at a dose of 150 mg/m² was administered for 1 h at 41°C. The vital signs of the patients were monitored.

The patients were staged with the staging system of the International Mesothelioma Interest Group (IMIG). Since all non-metastatic and resectable cases were operated, staging was not performed in our clinic

by preoperative radiological examinations or various minor interventions. Based on the preoperative positron emission tomography (PET)-computed tomography (CT) images of the patients, in the presence of suspected LN involvement, the relevant LN was dissected and pathological examination performed. Evaluations such as pleura, pericardium, and chest wall involvement were based on both PET-CT images and our intraoperative observation. Postoperative stage information was obtained by combining pathological examinations of LN involvement and these data. All patients were followed by the oncology clinic bimonthly and all patients underwent standard adjuvant chemotherapy (pemetrexed-cisplatin) in the postoperative period. Data including age, sex, city of residence, comorbidities, operation sides, complications, length of hospital stay (LOS), pathological diagnoses, disease stages, DFS and OS rates were recorded.

Disease-free survival was defined as the time to recurrence after surgery, while OS was defined as the time from the operation to death.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). The conformity of the numerical data to the normal distribution was checked using the Shapiro-Wilk test and for non-normally distributed variables. Two-group comparisons were made using the Mann-Whitney U test. Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Crosstabs were created for categorical data and chi-square analysis was performed. The Kaplan-Meier analysis was performed for OS and recurrence. Pairwise comparisons were made using the log-rank test for the variables examined categorically in the survival analysis. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Due to the use of asbestos-containing soils at home in some regions of Türkiye, the regions where the cases were born and resided were examined (Table 1). Diyarbakır was the most densely populated province with five (9.4%) cases, followed by Manisa and Sivas with four, and İzmir with three cases.

Twenty-five (47.2%) patients had at least one comorbidity. The most common comorbidity was diabetes mellitus in 14 (26.4%) cases, followed by hypertension and goiter in nine (16.9%) and four (7.5%) cases, respectively.

As standard, PD and HITOC were performed in all operable cases. Wedge resection was performed, if necessary. Since it was also conclusive for disease staging, no additional analyses were performed for the patients who underwent wedge resection. Mesothelioma was located in the right hemithorax in 28 (52.8%) and in the left in 25 (47.2%) cases.

Postoperative one-month surgical complications were recorded. At least one hyperglycemic value was found in 49 of the cases (92.5%); however, the blood glucose levels of the patients, although fluctuating, tended to return to normal. Other complications are

listed in Table 1. The overall complication rate was 71.7%. The median LOS was seven (range, 4 to 18) days (95% CI: 7.38-9.41).

Forty-five (84.9%) cases were diagnosed with epithelial and eight (15.1%) were diagnosed with biphasic mesothelioma. Based on postoperative staging, five (9.4%) were Stage 1, 27 (50.9%) were Stage 2, and 21 (39.6%) were Stage 3. All patients were followed with standard adjuvant chemotherapy. Recurrences developed in 41 (77.4%) of the cases. The follow-up was terminated due to the death for 33 (62.3%) cases.

Table 1. Characteristics of the study population

Characteristics	n	%	Mean±SD	Median	Range
Count	53	100			
Mean age			58.1±1.3		39-81
Sex					
Male	27	50.9			
Female	26	49.1			
Region					
Aegean	18	34			
Central Anatolia	9	17			
Southeastern Anatolia	8	15.1			
Mediterranean	5	9.4			
Eastern Anatolia	5	9.4			
Marmara	5	9.4			
Others	3	5.7			
Complications					
Hyperglycemia	49	92.5			
Blood transfusion	24	45.3			
Prolonged air drainage	18	34			
Elevated creatinine	5	9.4			
Atrial fibrillation	4	7.5			
Fever	4	7.5			
Elevated aspartate aminotransferase	3	5.7			
Elevated alanine aminotransferase	3	5.7			
Chylothorax	1	1.9			
Median hospital stay (days)				7	4-18
Mesothelioma subtype					
Epithelial	45	84.9			
Biphasis	8	15.1			
Stage					
Stage 1	5	9.4			
Stage 2	27	50.9			
Stage 3	21	39.6			
Median disease-free survival (months)				11.67	2.6-53.2
Median overall survival (months)				24.60	2.6-135.6

SD: Standard deviation.

Table 2. Median survival values and analysis results depending on disease stage

	Disease free survival (month)				Overall survival (month)			
	Median		95% CI		Median		95% CI	
	Estimate	SE	Lower bound	Upper bound	Estimate	SE	Lower bound	Upper bound
Stage 1	11.667	0.796	10.107	13.226	42.500	13.300	16.432	68.568
Stage 2	10.767	1.307	8.205	13.328	22.500	5.830	11.072	33.928
Stage 3	11.667	4.211	3.413	19.921	24.833	5.300	14.445	35.222
Overall	11.667	1.194	9.327	14.007	24.600	4.265	16.241	32.959
<i>p</i> value	0.736				0.653			

CI: Confidence interval; SE: Standard error.

No significant relationship was found between age, sex, pathological subtype, comorbidity, as well as the risk of developing complications related to the operation. Age was found to be an effective factor ($p=0.015$), while sex, pathological subtype, and comorbidity were not found to be effective on the LOS ($p=0.317$, $p=0.195$, and $p=0.067$, respectively).

The median DFS was 11.67 (range, 2.6 to 53.2) months (95% CI: 9.33-14.01). It was 8.80 months (95% CI: 5.77-11.83) for males and 13.17 months for females (95% CI: 9.42-16.91). Male sex was found to be an effective factor on recurrence ($p=0.037$). The median DFS was 6.13 months (95% CI: 4.34-7.93) in cases diagnosed with biphasic mesothelioma and 11.67 months (95% CI: 8.65-14.68) in cases with

epithelial type. Although the pathological subtype was statistically significant, it showed a weak relationship ($p=0.049$) (Figure 1). Comorbidities and stage were not effective on DFS ($p=0.32$ and $p=0.74$, respectively).

The median OS was 24.60 (range, 2.6 to 135.6) months (95% CI: 16.24-32.96). Sex, which was found to be a prognostic factor on DFS, was not effective on OS ($p=0.14$). Comorbidity and stage were not prognostic factors for OS, similar to DFS ($p=0.38$ and $p=0.66$, respectively). Although there was a difference in the median survival between Stages 1 and 2, stage was not a significant prognostic factor for either DFS or OS (Table 2).

The only parameter effective on OS was the mesothelioma subtype. Accordingly, the median OS in

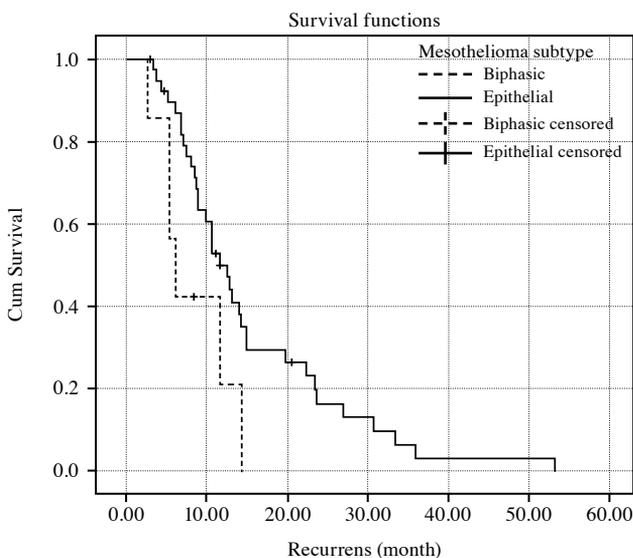


Figure 1. Relationship between mesothelioma subtype and disease-free survival.

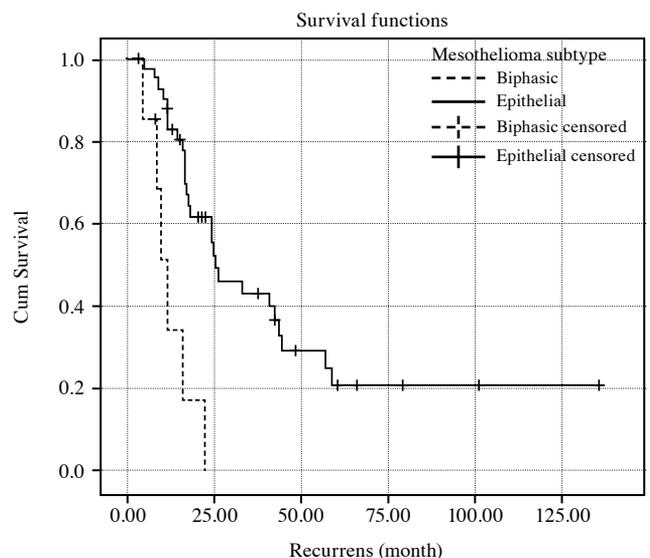


Figure 2. Relationship between mesothelioma subtype and overall survival.

biphasic cases was 11.70 months (95% CI: 8.65-14.75), while it was 25.46 months (95% CI: 14.15-36.78) in epithelial cases, indicating a statistically significant difference ($p < 0.001$) (Figure 2).

DISCUSSION

In the present study, we evaluated OS, DFS, and prognostic factors in patients undergoing PD and HITOC with the diagnosis of MPM. In a similar study including MPM patients, 77.4% of the cases were men with an average age of 58.05 years.^[7] In our study, the mean age was 58.1 ± 1.3 years, consistent with the literature. The fact that the rate of female cases is close to males in our study brings to mind the question whether the susceptibility of female cases to mesothelioma has increased over time. Current studies also support this idea.^[8,9]

Due to the high mortality of extrapleural pneumonectomy, PD has been investigated whether it can provide similar cytoreduction. However, it brings about such complications as hemorrhage and prolonged air drainage.^[10] Due to the limited efficacy of chemotherapy alone and its severe side effects, the application of HITOC in MPM has come to the fore.^[11,12] The HITOC is a technique based on circulating the heated chemotherapy drug in the thoracic cavity for 1 h. In this way, tumor cells contact with the high-dose chemotherapeutic agent. Since it is a local procedure, the patient is not exposed to the systemic side effects of chemotherapy. During the procedure, the drug is heated up to 41 to 43°C. This makes cytotoxicity more effective by denaturing tumor proteins. While normal tissues are not damaged at this temperature, tumor cells become more sensitive to chemotherapy.^[13] de Bree *et al.*^[12] excised the affected parietal and visceral pleura and applied coagulation to small diaphragmatic nodules. They reported that this technique had an acceptable morbidity and could provide locoregional disease control. We also applied the coagulation in residual nodules similar to de Bree *et al.*'s^[12] study. Markowiak *et al.*^[14] reported the complication rate following PD and HITOC as 31% and median LOS as 18 days.^[14] The nephrotoxic effect of cisplatin is known. In another study, patients who received amifostine and sodium thiosulfate infusion and those who did not in the perioperative period were compared, and no significant difference was found in the creatinine values in the early period.^[15] In our study, pre- and postoperative hydration were preferred, and the nephrotoxicity rate was found to be 9.4%. All patients returned to normal creatinine

values until discharge. No factor had any effect on complications following PD and HITOC. The median LOS in our study was seven days and it increased in correlation with age ($p = 0.015$).

Malignant pleural mesothelioma is a disease with a poor prognosis, which is diagnosed late due to non-specific symptoms. Tumor cells are resistant to chemotherapy. Only a limited number of patients are candidates for surgical treatment due to delayed diagnosis. Currently, it is recommended that surgery should be a part of multimodal treatment. Radiotherapy is often used for pain control. Of note, radiotherapy applied to the operation site to prevent recurrence after surgery is highly controversial. Postoperative prophylactic radiotherapy has not been recommended as a standard procedure, since 2018.^[16] However, in case of recurrence in the operation site, radiotherapy can be applied after resection.^[17] First-line treatments such as chemotherapy regimens are pemetrexed-cisplatin or pemetrexed-carboplatin combinations. No second-line therapy has been approved in terms of contribution to quality of life or survival. Repeat pemetrexed is applied in cases with long survival time.^[16,18] We did not apply prophylactic radiotherapy to patients. The pemetrexed-cisplatin combination was adopted as the first-line treatment. In patients who completed first-line treatment and had a longer-than-expected survival, treatment continuity was provided with pemetrexed as standard.

In a study sharing the results of PD and HITOC, the authors reported a survival of 17.9 months for epithelial subtype, 10.9 months for biphasic, and 9.2 months for sarcomatoid type.^[19] They concluded that epithelial subtype had a better prognosis in terms of survival. The cases were staged according to the 8th American Joint Committee (AJC) on Cancer Staging Manual. They reported that the survival of T1 cases was 17.9 months, T2 cases was 18.5 months, T3 cases was 15.1 months, and T4 cases was 8.3 months. The authors concluded that the stage was not effective on survival whether they included T4 cases in the analysis or not. In our study, we found that the stage was independent of OS and DFS, epithelial mesothelioma was a good prognostic factor for both OS and DFS, and male patients had a higher risk for recurrence.

Sugarbaker *et al.*^[20] reported that epithelial subtype had a better prognosis in patients who underwent HITOC. In the epithelial group, they found longer median DFS (27.1 months) and OS (35.3 months). This study appears to be an important step in predicting

the patients who may benefit from treatment. In our epithelial mesothelioma cases, the median DFS and OS was 11.67 and 25.46 months, respectively.

Nonetheless, there are some limitations to this study. First, it has a single-center, retrospective design. Second, although PD and HITOC are applied in a limited number of centers in our country, the fact that our center is located in the Western Türkiye restricts admission to our hospital from regions where the prevalence of the disease is high, affecting our epidemiological data. In addition, in this study in which we performed a survival analysis for HITOC, we compared our survival rates with the literature, since the study has no control group. On the other hand, we believe that a case series of 53 cases on mesothelioma and this specific surgery provides satisfactory data to the literature.

In conclusion, pleurectomy-decortication and hyperthermic intrathoracic chemotherapy combination is a preferable and tolerable treatment method in malignant pleural mesothelioma as long as pre- and postoperative management is appropriate. In the light of the literature, its effect on the survival of the patients has been revealed. The fact that postoperative survival times are not affected by the disease stage supports that it is possible to be more courageous in the selection of patients who are candidates for the operation, particularly in cases without distant metastasis and in patients with epithelial type mesothelioma. Considering that the length of stay in elderly patients may be prolonged and male sex is a poor prognostic factor for recurrence, postoperative surgical and oncological follow-up should be performed. However, we believe that further well-designed, comprehensive studies are needed to better understand the effect of the technique on increasing the survival time.

Ethics Committee Approval: The study protocol was approved by the Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee (date: 27.04.2022, no: 2022/04-80). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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