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# Can hyperthermic intrathoracic perfusion chemotherapy added to lung sparing surgery be the solution for malignant pleural mesothelioma?

*Akciğer koruyucu cerrahiye eklenen hipertermik toraks içi perfüzyon kemoterapisi malign plevral mezotelyoma için çözüm olabilir mi?*

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***ABSTRACT***

***Background:*** This study aims to investigate whether hyperthermic intrathoracic perfusion chemotherapy added to lung sparing cytoreductive surgery is superior to extrapleural pneumonectomy in patients with malignant pleural mesothelioma in terms of survival.

***Methods:*** We retrospectively reviewed the data of 73 patients (35 males, 38 females; mean age 55.9±12.3 years; range 20 to 80 years) with malignant pleural mesothelioma hospitalized in our clinic between January 2002 and June 2014. Patients were divided into three groups as group 1 (n=20, extrapleural pneumonectomy alone), group 2 (n=17, palliative treatment alone), and group 3 (n=36, lung sparing cytoreductive surgery plus hyperthermic intrathoracic perfusion chemotherapy). Treatment groups were compared for survival and disease free interval.

***Results:*** Median survivals in group 1, 2 and 3 were five, six, and 27 months, respectively. Two-year survival was 56.5% in group 3 while it was 15% in group 1 and 17.6% in group 2 (p=0.01). However, four-year survival rate was significantly higher in group 3 (14.6%) compared to group 1 (0%) and group 2 (11.8%). The survival time in group 3 was not significantly different between epithelial and biphasic histologies (median 28 and 27 months, respectively).

***Conclusion:*** The results of this study suggest that hyperthermic intrathoracic perfusion chemotherapy added to lung sparing cytoreductive surgery provides longer survival with less morbidity compared to extrapleural pneumonectomy or palliative treatment alone in malignant pleural mesothelioma. We also suggest using hyperthermic intrathoracic perfusion chemotherapy added to lung sparing cytoreductive surgery in cases with non-epithelioid cases of malignant pleural mesothelioma.

***Keywords:*** Hyperthermic perfusion chemotherapy; mesothelioma; pleura; surgery.

***ÖZ***

***Amaç:*** Bu çalışmada, malign plevral mezotelyomalı hastalarda akciğer koruyucu sitoredüktüf cerrahiye eklenen hipertermik toraks içi perfüzyon kemoterapisinin sağkalım açısından ekstraplevral pnömonektomiye üstün olup olmadığı araştırıldı.

***Çalışma planı:*** Ocak 2002 - Haziran 2014 tarihleri arasında kliniğimizde yatan malign plevral mezotelyomalı 73 hastanın (35 erkek, 38 kadın; ort yaş 55.9±12.3 yıl; dağılım 20-80 yıl) verileri retrospektif olarak incelendi. Hastalar grup 1 (n=20, yalnız ekstraplevral pnömonektomi), grup 2 (n=17, yalnızca palyatif tedavi) ve grup 3 (n=36, akciğer koruyucu sitoredüktif cerrahi artı hipertermik toraks içi perfüzyon kemoterapisi) olmak üzere üç gruba ayrıldı. Tedavi grupları, sağkalım ve hastalıksız süre açısından karşılaştırıldı.

***Bulgular:*** Medyan sağkalımlar grup 1, 2 ve 3'te sırası ile beş, altı ve 27 ay idi. İki yıllık sağkalım grup 3'te %56.5 iken grup 1'de %15 ve grup 2'de %17.6 idi (p=0.01). Bununla birlikte, dört yıllık sağkalım oranı grup 3'te (%14.6) grup 1 (%0) ve 2 (%11.8) ile karşılaştırıldığında anlamlı olarak daha yüksekti. Sağkalım zamanı grup 3'te epitelyal ve bifazik histolojiler arasında anlamlı olarak farklı değildi (sırası ile medyan 28 ve 27 ay).

***Sonuç:*** Bu çalışmanın sonuçları, malign plevral mezotelyomada akciğer koruyucu sitoredüktif cerrahiye eklenen hipertermik toraks içi perfüzyon kemoterapisinin yalnız ekstraplevral pnömonektomi veya palyatif tedaviye göre daha az morbidite ile daha uzun sağkalım sağladığını göstermektedir. Epitelyal olmayan malign plevral mezotelyoma olgularında da akciğer koruyucu sitoredüktif cerrahiye eklenen hipertermik toraks içi perfüzyon kemoterapisinin kullanılmasını önermekteyiz.

***Anahtar sözcükler:*** Hipertermik perfüzyon kemoterapisi; mezotelyoma; plevra; cerrahi.

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Malignant pleural mesothelioma (MPM) is a rare but unfortunately fatal disease due to limited treatment alternatives. Moreover, its incidence has been increasing since 10 to 15 years due to environmental and occupational asbestosis.[1,2] Particularly in our country, there are areas where asbestos can be found in 54 of 81 provinces and at least 1,000,000 people are living in rural areas just near asbestos locations or using asbestos in their houses for water and cold isolation.[2] Although asbestos trading and usage in industrial branches have been forbidden since 2010 in Turkey, because of asbestos exposure before this date, it is expected that MPM cases will increase in 20 years. So, MPM is a detrimental disease for both health and economy. In addition to this, both pulmonary physicians and thoracic surgeons experience challenges when solving problems arising during treatment or follow-up periods. In the past 35 years, there has been no satisfactory improvement in survival related to MPM.[1,3-7] At least three different treatment modalities are used including surgery, chemotherapy, or radiation therapy to obtain best survival time. Surgery aims to deliver a R0 resection. For this purpose, extrapleural pneumonectomy has been considered as a solution which removes all macroscopic tumors on both visceral and parietal pleura[3,4,8] However, its morbidity and mortality rates due to one sided lung resection are high. Beyond this, expected survival benefit is not satisfactory in addition to the fact that patients have discomfort during the rest of their lives.

Adjuvant treatment modalities have been performed to obtain better comfort and longer survival. One is hyperthermic perfusion chemotherapy (HIPEC) which is performed for eradicating tumor cells after cytoreductive surgery.[9-12] It has been suggested by Giovenella et al.[10] that hyperthermia itself is tumoricidal. In cell culture models, it has been shown that exposure to temperatures of 42.5-43 degrees Celsius for four to eight hours has significantly greater lethal effect on tumor cells compared to non-neoplastic cells. It has also been shown that hyperthermia increases the cytotoxicity of many chemotherapeutic agents on tumor cells.[11,12] Spartt et al.[13] pioneered a system to deliver hyperthermic chemotherapy to the peritoneal cavity in a canine model and in human in 1980. This was followed by several studies using similar systems to perform HIPEC to the peritoneal cavity in subjects with abdominal cancers including malignant peritoneal mesothelioma.[14-16] The optimistic results of these studies lead researchers to investigate whether intrapleural HIPEC is effective in patients with MPM. The results look promising although there are limited data.[17,18]

In this study, we aimed to investigate whether HIPEC added to lung sparing cytoreductive surgery is superior to extrapleural pneumonectomy (EPP) in patients with MPM in terms of survival.

## PATIENTS AND METHODS

For this retrospective study, we investigated the data related to MPM patients who underwent surgical procedures including EPP alone, palliative treatment (PT) alone, and HIPEC added to lung sparing cytoreductive surgery in Medical Faculty of Gaziantep University between January 2002 and June 2014. A total of 73 patients (35 males, 38 females; mean age 55.9±12.3 years; range 20 to 80 years) were included. Patients were divided into three groups as group 1 (n=20, EPP alone), group 2 (n=17, PT alone), and group 3 (n=36, lung sparing cytoreductive surgery plus HIPEC).

This study was approved by Institutional Ethics Committee of Gaziantep University. Written informed consent was obtained from each patient, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Extrapleural pneumonectomies were performed between 2002 and 2009. Histopathological evaluation was performed according to consensus statement of the International Mesothelioma Interest Group updated in 2012.[19] Cases with biphasic and sarcomatoid histology were classified in the same group.

Extrapleural pneumonectomy was performed by standard technique. Palliative interventions included biopsy and pleurectomy was performed in order to obtain pleurodesis. Lung sparing cytoreductive surgery included pleurectomy and decortication (P/D) aimed not to leave macroscopic tumor. Parietal pleura was dissected from whole thoracic cavity and even diaphragm if possible. However, in some cases, we had to resect diaphragm partially. Radical systematic lymph node dissection was not preferred. Lymph node dissection was performed in mediastinal sampling manner.

Hyperthermic perfusion chemotherapy was performed through chest tubes inserted for air and liquid drainage using two different perfusators (Rand Performer LRT-Medolla/Italy; Medica Exiper-Medolla/Italy). The temperature was set to 42 degrees Celsius and the perfusion was first started with 0.9% sodium chloride isotonic solution. During intrapleural lavage, affected lung was allowed to be half inflated and the lavage was continued until perfusate came from the exit tube. The volume of perfusate ranged between 1500-3500 mL with 1-1.2 L/minute flow rate.

**Table 1 Adjuvant treatment modalities except hyperthermic intrapleural chemotherapy. Postoperative radiotherapy was performed as chest wall irradiation on incision. Chemotherapy regimens were chosen according to first or second line treatment**

| | Chemotherapy | Radiotherapy | Chemoradiotherapy | Chemotherapy protocols |
|---|---|---|---|---|
| Groups | | | | |
| 1 (n=20) | 14 | 16 | 14 | Cisplatin + vinorelbine |
| 2 (n=17) | 17 | 15 | 15 | Paclitaxel + gemcitabine |
| 3 (n=36) | 36 | 36 | 36 | Carboplatin + gemcitabine |
| | | 2600 cGy | | Cisplatin + pemetrexed |
| | | | | Carboplatin + pemetrexed |

This stage lasted about 1/2 hours. Then, 300 mg/m$^2$ cisplatin was added into perfusate and circulated for 60 minutes additively. In order to protect brain from the side effects of hyperthermia, ice bags were placed around patient's head during the procedure. Hydration with 50 mL/kg/24 hour saline, dextrose solution and fresh frozen plasma intervention was performed in all subjects for renal complications in the postoperative 24-hour period. Oral intake was begun on the first postoperative day.

All patients received adjuvant chemotherapy with cisplatin based regimens. Radiotherapy was given for prevention of recurrences on thoracotomy and tube ports (2600 cGy) (Table 1).

Morbidity was defined as postoperative complications such as arrhythmia, respiratory distress, infection, broncho-pleural fistula, increased urea-creatinine levels and renal failure. Operative mortality was defined as death occurring within first 30 postoperative days due to any cause.

### Statistical analysis

The Kaplan-Meier method was used to estimate the survival curve. Log-rank (Mantel-cox) was used for the comparison of groups. PASW version 18.0 (SPSS Inc., Chicago, IL, USA) software was used for the statistical calculations. P<0.05 was accepted as significant in group comparisons.

## RESULTS

There was no significant difference in terms of demographic data between the groups (Table 2). In group 1, EPP was performed in standard manner including both diaphragm and pericardium resection. Pallative intervention such as partial pleurectomy was performed for pleurodesis in group 2 In group 3, EPP was only performed in two patients because of the lack of dissection cleavage between parietal and visceral pleura. The other 34 patients underwent lung sparing cytoreductive surgery including pleurectomy decortication. In this group, all patients received HIPEC.

Histopathological types of malignant mesothelioma were epithelial in 60 patients, biphasic or sarcomatoid in 13 patients. Median survival in group 1, 2 and 3 were five, six, and 27 months, respectively (Figure 1). Two-year survival was 56.5% in group 3, 15% in group 1, and 17.6% in group 2 (p=0.00). However, four-year survival was 0% in group 1, 11.8% in group 2, and 14.6% in group 3. Four-year survival was only significant in group 3 (14.6%). There was no living patient in groups 1 and 2, whereas 13 patients were alive in group 3. Among these 13 patients, there were six patients in group 3 who survived more than 36 months (16.1%) and four of them are still alive (range 36 to 52 months). According to histopathological survival data, overall median survival was 15 and 20 months in epithelial and biphasic tumors, respectively. In HIPEC group,

**Table 2. Demographic data of three groups reveals no significant difference**

| Groups | Mean age (Years) | Gender (M/F) | Histology (E/M) | *p* |
|---|---|---|---|---|
| Groups | | | | |
| 1 (n=20) | 51 | 8/12 | 19/1 | >0.05 |
| 2 (n=17) | 60.18 | 9/8 | 12/5 | >0.05 |
| 3 (n=36) | 67.11 | 18/18 | 29/7 | >0.05 |

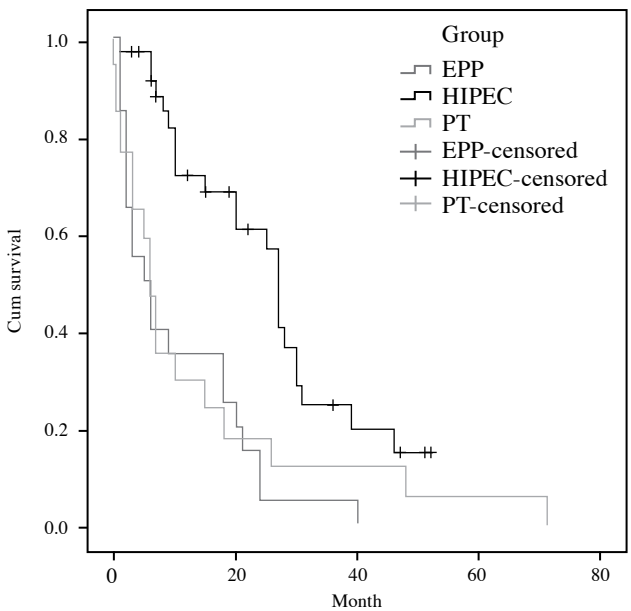
M: Male; F: Female; E: Epitheloid; M: Mesenchymal (this represents both biphasic and sarcomatoid histologies).

there was no significant difference between epithelial and biphasic histologies (median survivals were 28 and 27 months, respectively) (Figure 2).

Postoperative morbidity in groups 1, 2 and 3 were 40%, 11.7%, and 19.4%, respectively. Operative mortality was 3/20 (15%) in group 1 and 1/36 (3.2%) in group 3. There was no operative mortality in group 2 (Table 3).

## DISCUSSION

In this study, we demonstrated that lung sparing surgery followed by hyperthermic intrapleural lavage chemotherapy is a reasonable treatment modality for patients with MPM. Extrapleural pneumonectomy is an aggressive intervention compared to pleurectomy/decortication. Postoperative period may be troublesome for patients who undergo pleuropneumonectomy. However, therapy efforts excluding surgery may not be realistically effective. Most authors agree on trimodality therapy in MPM.[1,3-8] Particularly surgery has an important role in reducing tumor volume. Thus, a treatment modality without surgery does not appear to be effective. Surgical approaches such as EPP and lung sparing pleurectomy plus decortication have been performed to remove tumoral mass in MPM patients.[3-8,20-24]




Pneumonectomy was first described in multiple stages by William Macewen on a patient with tuberculosis and emphysema in 1895. Furthermore, Rudolph Nissen performed two staged pneumonectomy in a patient with crush injury in 1931, and, finally, an acceptable pneumonectomy was performed by Evarts Graham in 1933.[25] Recently, pneumonectomy has been a common procedure performed especially in patients with lung carcinoma. Since most patients with bronchogenic carcinoma who underwent pneumonectomy adapted to the loss of lung tissue in a chronic period, lesser complications due to respiratory dysfunction and cardiac overload have been observed compared to MPM cases. This leads surgeons to search relatively less invasive methods to remove tumor mass in MPM patients. There is no surgical intervention accepted to be as the best method of cytoreduction in MPM. There are few studies suggesting the superiority of adding HIPEC to cytoreductive surgery in MPM.[20] The results of the present study support the findings of such studies although direct comparison of the same surgical approach with or without HIPEC has not been performed.

The optimal surgical intervention for MPM is controversial. Resection margin is an important problem since pleura is a serous membrane. Mainly, R0 resection is aimed; however, it is impossible to prove the negative margins. So, most pleural resections in EPP are accepted as at least R1 resections. For this reason, postoperative adjuvant chemo and radiotherapy are essential. Unfortunately, standard treatment modalities are insufficient to cure MPM.[1,3-8] Therefore, researchers have been striving to find other treatment modalities.[10-13] Hyperthermic perfusion of pleural space is one of these methods. The effect of

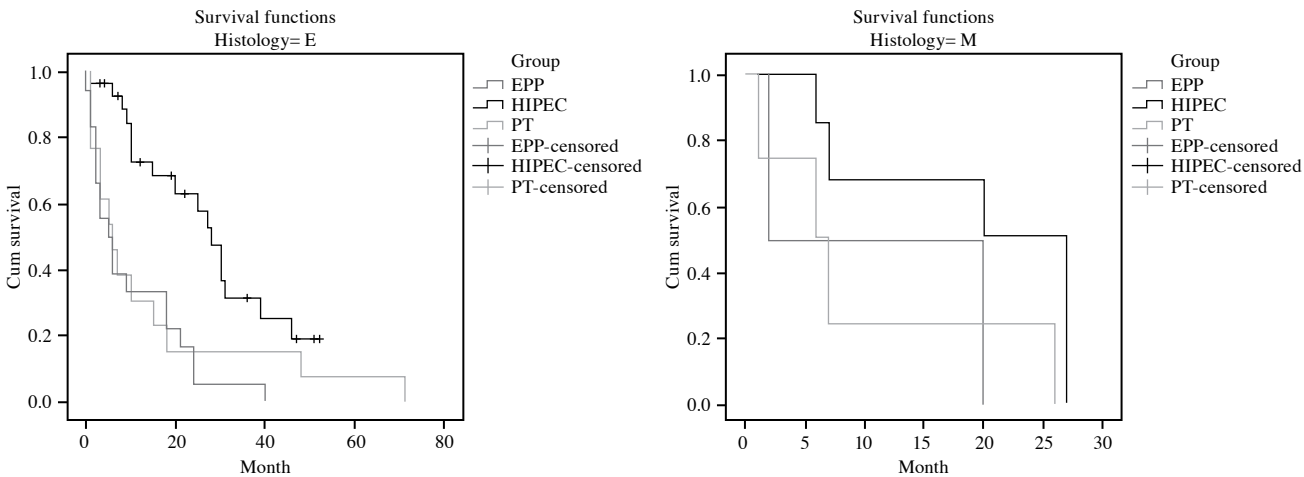
| | Mean* | | | | Median | | Median | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% Confidence interval | | | | 95% Confidence interval | |
| Group | Estimate | SE | Lower bound | Upper bound | Estimate | SE | Lower bound | Upper bound |
| EPP | 10.350 | 2.467 | 0.617 | 9.383 | 5.000 | 2.236 | 0.617 | 9.383 |
| HIPEC | 26.076 | 2.854 | 24.698 | 29.302 | 27.000 | 1.175 | 24.698 | 29.302 |
| PT | 13.471 | 4.619 | 3.983 | 8.017 | 6.000 | 1.029 | 3.983 | 8.017 |
| Overall | 19.659 | 2.440 | 7.389 | 22.611 | 15.000 | 3.883 | 7.389 | 22.611 |

**Figure 1.** Survival data of three groups reveals significant difference in favor of group 3.

* Estimation is limited to the largest survival time if it is censored; SE: Standard error; EPP: Extrapleural pneumonectomy; HIPEC: Hyperthermic perfusion chemotherapy; PT: Palliative treatment.

the modality can be attributable to the apoptotic effect of high temperature on tumor cells.[18] Also, some authors approved its potentiating effect on penetration of chemotherapeutic agents.[11-13,17,18] Sugarbaker et al.[20] published their results on the effect of HIPEC among low-risk patients. They found longer survival time in patients treated with HIPEC (35.3 versus 22.8 months). Disease free interval was also longer than patients who were not treated by HIPEC (27.1 versus 12.8 months). However, they performed both EPP and P/D procedures in groups and comparison has been made according to adjuvant or neoadjuvant chemotherapy, radiotherapy and N status, excluding surgical procedure. Demographic data equation of groups revealed the positive influence of HIPEC.

Flores et al.[22] reported better survival in patients who underwent P/D compared to EPP, although selection criteria of the study may have affected the results in favor of P/D. There were 663 patients who underwent EPP or P/D at three institutions. Mortality rate of both groups were similar (7% in EPP versus 4% in P/D). Median survival was 16 months and 12 months in P/D and EPP groups, respectively. In a meta-analysis by Cao et al.,[21] it was mentioned that P/D is superior to EPP with lower morbidity (27.9% versus 62%) and mortality (2.9% versus 6.8%) although overall survival data is not significantly different. There are several other reports showing higher morbidity rates in subjects who underwent EPP for the treatment of MPM.[4,21,22,24,26] These findings support the superiority of less invasive cytoreductive surgery in subjects with MPM. Based on these data, one might consider less invasive methods such as P/D as the preferred method for cytoreduction prior




Mean and medians for survival time

| | Mean* | | | | Median | | Median | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% Confidence interval | | | | 95% Confidence interval | |
| Group | Estimate | SE | Lower bound | Upper bound | Estimate | SE | Lower bound | Upper bound |
| E | | | | | | | | |
| EPP | 10.278 | 2.650 | 5.083 | 15.473 | 5.000 | 2.121 | 0.842 | 9.158 |
| HIPEC | 28.088 | 3.402 | 21.420 | 34.756 | 28.000 | 2.564 | 22.975 | 33.025 |
| PT | 14.538 | 5.871 | 3.031 | 26.046 | 6.000 | 2.397 | 1.303 | 10.697 |
| Overall | 20.839 | 2.928 | 15.100 | 26.577 | 15.000 | 3.516 | 8.109 | 21.891 |
| M | | | | | | | | |
| EPP | 11.000 | 9.000 | 0.000 | 28.640 | 2.000 | – | – | – |
| HIPEC | 19.371 | 3.975 | 11.580 | 27.162 | 27.000 | 0.000 | – | – |
| PT | 10.000 | 5.492 | 0.000 | 20.765 | 6.000 | 3.000 | 0.120 | 11.880 |
| Overall | 15.087 | 3.030 | 9.147 | 21.026 | 20.000 | 5.586 | 9.052 | 30.948 |
| Overall Overall | 19.659 | 2.440 | 14.878 | 24.441 | 15.000 | 3.883 | 7.389 | 22.611 |

**Figure 2.** Detailed analysis of survival data according to histopathological results were surprising compared with literature although number of cases was low.

* Estimation is limited to the largest survival time if it is censored; SE: Standard error; EPP: Extrapleural pneumonectomy; HIPEC: Hyperthermic perfusion chemotherapy; PT: Palliative treatment; E: Epithelioid mesothelioma; M: Biphasic and sarcomatoid mesothelioma.

**Table 3. Operative morbidity (defined as death occurring within 30 days postoperatively) and mortality according to groups. Elevation of blood urea and creatinine levels was mostly solved with hydration. However, renal failure required hemodialysis in one patient who died**

| | Morbidity | Morbidity causes | Operative mortality | | Operative mortality cause |
|---|---|---|---|---|---|
| | % | | n | % | |
| Groups | | | | | |
| 1 | 40.0 | Right heart failure<br>Bronchopleural fistula<br>Pneumonia<br>Arrhythmia/dysrhythmia | 3 | 15 | Right heart failure<br>Bronchopleural fistula<br>Pneumonia |
| 2 | 11.7 | Prolonged drainage | - | - | |
| 3 | 19.4 | | | | |
| | | Prolonged air leakage<br>Elevation of blood creatinine and urea levels<br>Renal failure | 1 | 3.2 | Severe renal failure |

to HIPEC in subjects with MPM. The latter was also supported with the results of this study indicating a significantly higher mean survival in the group of P/D plus HIPEC compared to EPP or PP alone in cases with MPM. We found that five-year survival in EPP group was 0% while mean survival time was five months. Additionally, none of the subjects who underwent P/D plus HIPEC suffered from dyspnea or fatigue in the postoperative period except for one patient who had serious dyspnea and cough due to radiation pneumonitis.

A reason for EPP to be advocated as a treatment option in MPM is probably related to the idea of leaving no tumor residue in the resection margin. Resection margin is considered to be an important issue for an effective treatment of cancer. Although surgeons aim R0 resection, it is nearly impossible to perform R0 resection in patients with MPM. Thus majority of pleural resections including EPP are accepted as at least R1 resection and adjuvant radiotherapy and postoperative chemotherapy are needed.[1,3-8] Therefore, it is reasonable to accept that adjuvant therapy would provide better survival in MPM subjects who undergo cytoreductive surgery plus HIPEC.

The survival benefit of lung sparing surgery plus HIPEC was significant. In EPP group, five-year survival was 0% and median and mean survival rates were six and five months, respectively. This is not an encouraging result for clinicians and surgeons. According to some authors, EPP is a feasible intervention in selected patients. However, it should not be forgotten that MPM cases are mostly diagnosed at stage 3 or higher stages. Consequently, most authors agree that EPP is useful in early stages of MPM.[8,22,24]

Hyperthermic perfusion of pleural space with a chemotherapeutic agent has been considered beneficial in cases with peritoneal carcinomatosis.[12-16] These studies led researchers to seek the effectiveness of HIPEC in cases with MPM. It is suggested that hyperthermia may cause apoptotic effect on tumor cells.[18] It has also been showed that hyperthermia increases penetration of chemotherapeutic agents to tumor cells.[11-13,17,18] Sugarbaker et al.[20] investigated the effect of HIPEC in low-risk patients with MPM undergoing surgical macroscopic complete resection. They performed both EPP and P/D procedures in all study subjects. Then, they divided the subjects into two groups according to whether they applied HIPEC or not following the surgery. They found that HIPEC significantly prolonged the survival of HIPEC group compared to non-HIPEC group (35.3 versus 22.8 months). Disease free interval was also longer in HIPEC group compared to non-HIPEC group (27.1 versus 12.8 months). Our study showed that P/D plus HIPEC provides significantly longer survival in subjects with malignant pleural effusion compared to conventional treatment modalities. Supporting the previous studies, the overall survival time and rate of morbidity were significantly in favor of P/D plus HIPEC group compared to EPP or PP alone groups.

Histological differentiation may determine the treatment procedures, since, for example, non-epithelial MPM has shorter median survival;[4,6,8,20-22,24] therefore, surgery is usually not recommended in this group. Although the number of non-epithelial MPM cases was

limited in our series, we observed that lung sparing surgery and HIPEC had a remarkable contribution on survival (median survival 25 months). We believe it is worthwhile to test this hypothesis with further studies.

In conclusion, we showed that pleurectomy and decortication plus hyperthermic perfusion chemotherapy provides better survival with less morbidity compared to extrapleural pneumonectomy or pleural pneumonectomy alone in cases with malignant pleural mesothelioma. The results of this study also support the idea of using pleurectomy and decortication plus hyperthermic perfusion chemotherapy in cases with non-epithelioid cases of malignant pleural mesothelioma.

**Declaration of conflicting interests**

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