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# Intrapleural hyperthermic perfusion chemotherapy in subjects with metastatic pleural malignancies

Ahmet Feridun Işık [a,*], Maruf Şanlı [a], Miray Yılmaz [a], Fatih Meteroğlu [b], Öner Dikensoy [c], Alper Sevinç [d], Celaletdin Camcı [d], Bülent Tunçözgür [a], Levent Elbeyli [a]

[a] Gaziantep University, Medical School, Thoracic Surgery Department, Üniversite Bulvarı, Şehitkamil-Gaziantep, Turkey
[b] Dicle University, Medical School, Thoracic Surgery Department, Turkey
[c] Gaziantep University, Medical School, Chest Disease Department, Turkey
[d] Gaziantep University, Medical School, Medical Oncology Department, Turkey

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**KEYWORDS**
Malignant pleural effusion;
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**Summary**
*Objectives:* Malignant pleural effusion (MPE) means poor prognosis in the majority of cases. Intrapleural Hyperthermic perfusion chemotherapy (HIPEC) looks promising approach for these patients. We aimed to investigate whether cytoreductive surgery followed by HIPEC provides any survival benefit in cases with metastatic MPEs.
*Methods:* Between January 2009 and December 2011, 19 patients with metastatic MPEs were treated with HIPEC following surgical interventions such as pleurectomy/decortication and/or lung resection (Group 1). Comparison was done with historical control groups consisted of patients who received either talc pleurodesis or pleurectomy/decortication followed by systemic treatment for the management of metastatic MPEs between June 2007 and June 2008 (group 2 and 3). Statistical analyses including overall survival, disease free interval were done for the group comparisons.
*Results:* Median survival in group 1, 2 and 3 were 15.4, 6, 8 months, respectively. One year survival was 54.7% in group 1 where it was 0.6% and 0.8% in group 2 and 3, respectively. There was no operative mortality. Morbidity was occurred in 1 patient in group 1 (5.3%).
*Conclusions:* HIPEC combined with cytoreductive surgery seems to be a promising treatment option for subjects with metastatic MPEs. Further studies are needed for the optimization of HIPEC method, drug of choice, and the best combination therapy for the multimodal treatment.


* Corresponding author. Tel.: +905323643767.
*E-mail address:* abaybora@msn.com (A.F. Işık).

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## Introduction

Malignant pleural effusion (MPE) is not a rare entity faced by pulmonary clinicians and thoracic surgeons.[1,2] The metastatic malignancies of pleura are more common than its primary tumors. Lung cancer is the most common primary neoplasm metastasizes to pleura followed by breast cancer and lymphoma.[3] Current treatment options of malignant pleural effusions are limited to supportive care in the majority of patients. MPE related to lung carcinoma means a median survival of 4–6 months despite using multimodal treatments including surgery, chemotherapy and radiotherapy.[4] Therefore, new therapeutic options are needed.

It has been suggested by Giovanella and colleagues that hyperthermia itself is tumoricidal.[5] Exposure to temperatures of 42.5–43 °C for 4–8 h has been shown to have significantly greater lethal effect on the tumor cells compared to non-neoplastic cells in cell culture models. It has also been shown that hyperthermia increase the cytotoxicity of many chemotherapeutic agents in human cell culture models and animal models.[6,7]

Spratt and colleagues pioneered a system to deliver hyperthermic chemotherapy to the peritoneal cavity in a canine model and in human in 1980.[8] This was followed by several studies using similar systems to perform hyperthermic perfusion chemotherapy (HIPEC) to the peritoneal cavity in subjects with abdominal cancers including malignant peritoneal mesothelioma.[9–11] These studies reported significant survival advantage of intraperitoneal HIPEC compared to standard of care. These optimistic results lead researchers to investigate whether intrapleural (IP) HIPEC works in subjects with malignant pleural effusion. Although there are limited data, IP HIPEC in malignant pleural effusions looks promising.[12,13]

In this study, we aimed to investigate the survival and disease free interval in subjects with metastatic pleural malignancies who underwent IP HIPEC in addition to cytoreduction.

## Materials and methods

The hospital records of the subjects with malignant pleural effusion who admitted to Department of Thoracic Surgery of Gaziantep University Hospital between January 2009 and December 2011 were reviewed in a retrospective manner. The patients who underwent IP HIPEC in addition to cytoreduction for the management of metastatic MPE were included in group 1. Another two groups of patients with secondary MPE who have been investigated in our previous study were included as the historical control groups and defined as group 2 and 3.[14] Subjects in group 2 received talc pleurodesis and subjects in group 3 received pleurectomy/decortication by video assisted thoracic surgery (VATS) for the management of metastatic MPE. All of the subjects in groups received systemic chemotherapy following pleural interventions. Selection criteria were as follows: subjects with metastatic pleural malignancies proved by pleural cytology and/or biopsy, subjects with good performance status, subjects with lung cancer and no distant metastasis except pleura, subjects with lung cancer and nodal status of N1 or less. Informed consent forms were signed by all subjects. The study protocol was approved by institutional Ethics Committee.

Overall survival defined as the period from the date of the first therapeutic intervention as cytoreduction plus HIPEC and pleurodesis to the date of death. Disease free interval was accepted as recurrence of malignant pleural effusion proved by cytological or histopathological examination.

Cytoreduction in group 1 was performed as pleurectomy and decortication in all subjects. Additionally lung and adjacent structures were resected if possible. Parietal, mediastinal and diaphragmatic pleura were resected. Only in one patient, diaphragma had to be resected in order to provide maximum cytoreduction. Large bore (28–32 F) chest tubes were inserted at the end of surgery before the thoracic cavity was closed. HIPEC was performed through these chest tubes. HIPEC was applied intraoperatively using a perfusator (Rand Performer LRT-Medolla/Italy). The temperature was set to 42 °C, and the intrapleural perfusion was first started with 0.9% sodium chloride isotonic solution. During the IP lavage, the effected lung was allowed to be half inflated and the lavage was continued until perfusate (0.9% sodium chloride isotonic solution) comes from the exit tube. The volume of saline used was ranged between 1500 and 3200 mL with 1–1.2 L/min flow rate. This stage took about 1 h. Then IP HIPEC was performed by using 300 mg/m$^2$ of Cisplatin for 60 min. In order to protect brain from the side effects of hyperthermia, ice bags were placed around patient's head during intrapleural perfusion. Hydration with 50 mL/kg/24 h saline, dextrose solution and fresh frozen plasma was performed in all subjects in order to prevent renal complications in the postoperative 24 h. Oral intake was begun on the first postoperative day.

Selection criteria were as follows: subjects with metastatic pleural malignancies proved by pleural cytology and/or biopsy, subjects with good performance status, subjects with lung cancer and no distant metastasis except pleura, subjects with lung cancer and nodal status of N1 or less. All subjects over 20 years old diagnosed to have metastatic MPE during the study period were included. Malignant pleural effusion was defined as exudative pleural effusion associated with one of the followings: positive cytology/histopathology for malignancy, known primary cancer without co morbid conditions which may cause exudative pleural effusion.

Talc pleurodesis was performed through a small bore chest tube (Pleurocan, B. Brown, Melsungen, Germany) in the form of slurry (4.5 g talc in/100 ml saline solution).

VATS pleurectomy was performed as follows: all apical and basal parts of parietal pleura were excised except mediastinal and diaphragmatic sides under general anesthesia.

All subjects in groups received systemic chemotherapy planned according to primary cancer. The systemic chemotherapy protocols were cisplatin based in all subjects. Interventional, histopathological data and chemotherapy protocols were given in Table 1.

### Statistical analysis

The Kaplan–Meier method was used to estimate the survival curve. Log rank (Mantel-cox) was used for comparison of groups. SPSS version 17 (SPSS Science, Chicago, Illinois) was used for the statistical calculations. $p < 0.05$ was accepted as significant in group comparisons.