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ORIGINAL ARTICLE

# Ten-year experience with peritoneal mesothelioma

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## *Summary*

***Purpose:*** *Peritoneal mesothelioma is a rare disease that remains confined to the peritoneal surfaces for long. Cytoreductive surgery (CRS) combined with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is the most effective treatment and complete cytoreduction is the most significant prognostic indicator of long-term survival. This study attempted to present the results of CRS in combination with hyperthermic intraperitoneal chemotherapy in patients with peritoneal mesothelioma and identify the prognostic indicators of survival.*

***Methods:*** *The files of patients with peritoneal mesothelioma were retrospectively reviewed. Morbidity, hospital mortality, recurrences, and the sites of recurrence were recorded. Survival and recurrence were correlated to performance status, age, extent of peritoneal dissemination, tumor grade, tumor volume, and completeness of cytoreduction.*

***Results:*** *From 2005-2017, 29 patients underwent 33 cytoreductions for peritoneal mesothelioma. Hospital mortality and morbidity were 3% and 27.3% respectively. The median and 8-year survival were 66 and 62% months, respectively. The completeness of cytoreduction was the single prognostic indicator of survival, and the tumor grade the single prognostic indicator of recurrence.*

***Conclusion:*** *CRS combined with HIPEC is the therapeutic strategy that may provide long-term survival.*

***Key words:*** *CRS, HIPEC, peritoneal mesothelioma, recurrence, survival*

## Introduction

Peritoneal mesothelioma is a rare entity accounting for 10-30% of all mesothelioma cases recorded in developed countries [1,2]. Malignant peritoneal mesothelioma originates from the mesothelial cells and is a highly aggressive malignancy [3]. An increase of new cases has been noted around the world over the past years. The new recorded cases annually in the USA are approximately 400. In Greece 5-10 new cases are estimated to appear every year but the majority of them are pleural mesotheliomas [4,5]. Prior asbestos exposure in combination with simian virus 40 infection is considered the main known etiologic factor of mesothelioma development [5,6].

The median survival using systemic chemotherapy is approximately 12 months [7,8]. Cytoreductive surgery (CRS) with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) have shown to improve prognosis and increase overall survival [9,10]. The purpose of cytoreduction is the resection of the entire macroscopically visible tumor while the purpose of intraperitoneal chemotherapy is the eradication of the microscopic residual tumor. Five-year survival after CRS and

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HIPEC has been reported to be significantly higher than systemic chemotherapy varying from 29 to 93% [5,9,11-13].

The objective of this study is to present the results of CRS in combination with HIPEC in peritoneal mesothelioma patients and identify the prognostic indicators of survival.

## Methods

The data of patients with peritoneal mesothelioma treated from 2005-2017 were retrospectively reviewed. Patients over 16 years of age, with acceptable performance status (Karnofsky performance scale >50%), normal renal function (blood urea <50mg/dl and creatinine <1.5mg/dl), WBC >4000, platelets >100000, normal hepatic function, capable to undergo major surgery were considered eligible for CRS and HIPEC. Patients with recent history of severe heart or pulmonary disease, poor performance status (Karnofsky performance scale <50%), abnormal liver-renal-hematological profile were excluded from treatment. Additionally, patients with distant metastatic disease, pregnant women or patients with psychiatric or addictive disorders were excluded.

The extent of peritoneal dissemination was assessed preoperatively using abdominal CT scan and the peritoneal cancer index (PCI) was grossly estimated. The patients that were likely to have extensive dissemination at the peritoneal surfaces of the small bowel underwent diagnostic laparoscopy. Distant metastases, gross infiltration of the mesentery and infiltration of the anti-mesenteric edge of the small bowel were exclusion criteria.

The extent of previous surgery was assessed using prior surgical score (PSS) [14].

*Treatments*

All patients underwent maximal abdominal exploration with midline incision extending from the xiphoid process to the symphysis pubis. After lysis of the adhesions the PCI was estimated intraoperatively. Large volume disease was considered if peritoneal implants with lesion size greater than 0.5 cm or confluence of lesions were found. Cytoreductive surgery was possible using standard peritonectomy procedures [15]. The completeness of cytoreduction was assessed after surgical resection of the tumor according to Sugarbaker's criteria [14]. All patients that underwent CC-0 or CC-1 surgery received HIPEC with cisplatin (50mg/m$^2$) in combination with doxorubicin (15mg/m$^2$). After 2015 all patients were treated with additional intravenous ifosphamide (1300mg/m$^2$) and mesna (260mg/m$^2$). Mesna in the same dose was repeated 2 more times in 4 and 8 hrs. Patients that underwent CC-1 surgery received additionally early postoperative intraperitoneal chemotherapy (EPIC) under normal temperature.

HIPEC with the Coliseum technique was always administered after tumor resection and before the reconstruction of the alimentary tract. HIPEC was possible with a continuous closed circuit of four drains (two inlet and two outlet), one heat exchanger, and two roller pumps connected to the inlet and outlet drains (SunChip, Gamida Tech, France). The cytotoxic drugs were diluted in 2-3 lit of Ringer's lactate solution and the intra-abdominal temperature was maintained at 42.5-43°C during perfusion.

EPIC was given through a Tenckhoff catheter during the first 5 postoperative days. The chemotherapy regimen was 5-Fluorouracil (400mg/m$^2$) diluted in 1.5 lit of 1.5 hypotonic dextrose in water solution ($D_{1.5}W$). Patients with CC-2 surgery did not receive perioperative intraperitoneal chemotherapy.

All patients remained in the ICU for a minimum of 24 hrs after surgery. Patients treated with EPIC remained in the ICU for 5 additional days postoperatively until the completion of treatment. Postoperative complications were recorded and assessed according to the following criteria: The uncomplicated patients were assessed as grade 0. Grade 1 complications were those that required minor intervention, oral antibiotics, bowel rest or monitoring. Grade 2 complications were those that required IV antibiotics or bowel rest or chest tube draining. Grade 3 complications were those that required hospital readmission or surgical or radiological intervention. Grade 4 complications were those that produced chronic disability or organ resection or bowel diversion and grade 5 complications were those that resulted in death [16]. Grade 1 and 2 were assessed as minor complications and grade 3-5 as major complications. Survival was estimated from the time of surgery until the last follow-up or the time of death.

*Histopathology*

All specimens were examined in detail. The tumor grade as well as the histologic subtype were defined. The number of the resected and the infiltrated lymph nodes were also recorded.

*Follow-up*

All patients were followed-up every 3-4 months after initial treatment with physical examination, CT-abdominal and thoracic scanning, hematological-biochemical examinations, and tumor markers (CEA, CA 19-9, CA-125). Recurrences and the sites of recurrence were recorded.

*Statistics*

Statistical analyses were performed using the SPSS (Statistical Package for Social Sciences), version 17. The proportions of patients with a given characteristic were compared by $x^2$ or by Pearson's test. Differences in the means of continuous measurements were tested by the Student's *t*-test. Kaplan-Meier method was used for the construction of survival curves. The comparison of curves was possible using the log-rank-test. Multivariate analysis of survival was assessed with the Cox proportional hazard model for the identification of the prognostic variables of survival. Cut off points were set at clinically important values or after examining different possible points. Logistic regression analysis was used to identify the prognostic variables of recurrence. A two-tailed p value <0.05 was considered statistically significant.

**Table 1.** Patients' general characteristics

| *Characteristics* | *Patients, n* | *%* |
|---|---|---|
| M/F | 25/8 | 75.8/24.2 |
| Tumor grade | | |
| High | 28 | 84.8 |
| Low | 5 | 15.2 |
| Tumor volume | | |
| Large | 32 | 97 |
| Small | 1 | 3 |
| Ascites | 19 | 57.6 |
| CC-score | | |
| CC-0 | 12 | 36.3 |
| CC-1 | 13 | 39.4 |
| CC-2 | 2 | 6.1 |
| CC-3 | 6 | 18.2 |
| PSS | | |
| 0 | 5 | 15.2 |
| 1 | 17 | 51.5 |
| 2 | 8 | 24.2 |
| 3 | 3 | 9.1 |
| PCI | | |
| 0-13 | 12 | 36.4 |
| 14-20 | 9 | 27.2 |
| 21-39 | 12 | 36.4 |

M/F: male/female, CC: completeness of cytoreduction, PSS: prior surgical score, PCI: peritoneal cancer index

**Table 2.** Univariate analysis of survival

| *Variables* | *p value* |
|---|---|
| Gender | 0.908 |
| Tumor grade | 0.101 |
| Tumor volume | 0.578 |
| Ascites | 0.404 |
| CC-score | 0.004 |
| PSS | 0.152 |
| Nodal involvement | 0.061 |
| PCI | 0.923 |

For abbreviations see footnote of Table 1

**Table 3.** Univariate analysis of recurrence

| *Variables* | *p value* |
|---|---|
| Gender | 0.242 |
| Tumor grade | 0.049 |
| Tumor volume | 0.455 |
| Ascites | 0.304 |
| CC-score | 0.987 |
| PSS | 0.165 |
| Nodal involvement | 0.639 |
| PCI | 0.554 |

For abbreviations see footnote of Table 1

## Results

From 2006-2017 29 patients underwent 33 cytoreductive operations for peritoneal mesothelioma. There were 21 males (72.4%) and 8 females (27.6%). The mean age of the patients was 59.8+15.6 years (range 16-81). The general patient characteristics are listed in Table 1. The mean hospital stay was 15 days. The morbidity rate was 27.3% (9 patients). Two patients (6.1%) had grade II complications, and 7 (21.2%) grade IV complications. One patient (3%) died during the immediate postoperative period because of sepsis from Acinetobacter infection.

The median survival was not reached. The mean survival was 67 + 7 months. Five- and 8-year survival rates were 74 and 66%, respectively (Figure 1). Univariate analysis showed that the CC-score was related to survival (Table 2). Multivariate analysis showed that the CC-score was the single prognostic indicator of survival (HR= 3.652, 95% CI= 0.786-16.974, p= 0.03).

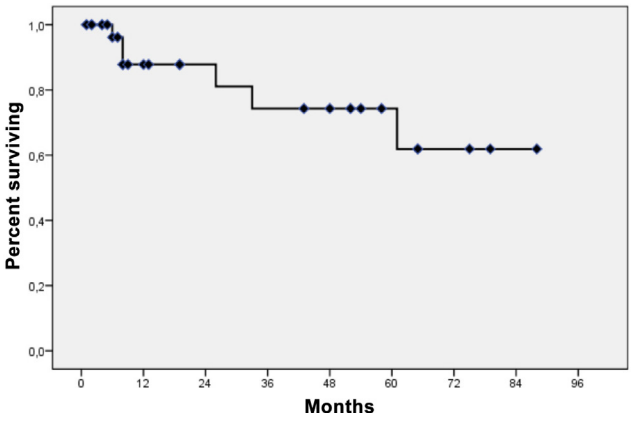


**Figure 1.** Overall survival of 33 cytoreductions.

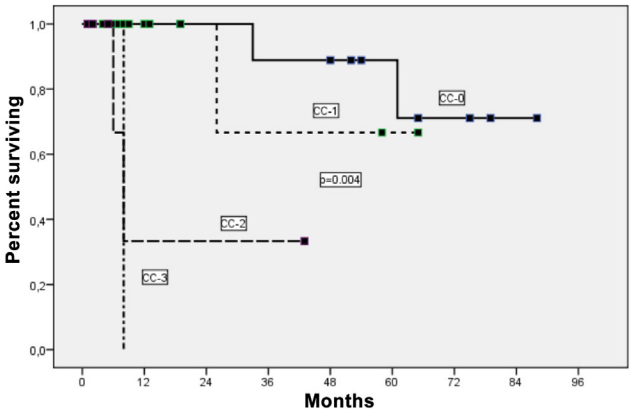


**Figure 2.** Survival of peritoneal mesothelioma in regard to completeness of cytoreduction (p=0.004).

*Histopathology*

The specimens were scrutinized by expert pathologists. The histopathologic type was high-grade peritoneal mesothelioma (epithelial type) in 28 cases (84.8%), and in 5 (15.2%) was low-grade (multi-cystic). Lymph node infiltration was observed in 5 cases (15.2%).

*Follow-up*

Recurrence was recorded in 15 (45.5%) cases. In 11 cases the recurrence was local-regional and in 4 distant. By univariate analysis it was found that the tumor grade was related to recurrence (Table 3). The tumor grade was found to be the single prognostic indicator of recurrence (p=0.009) by multivariate analysis.

Currently, 10 patients (30.3%) are alive without evidence of disease, 6 patients (18.2%) died because of disease, 8 (24.2%) died because of other causes, and 9 (27.3%) are alive with recurrence.

## Discussion

Mesothelioma is a rare malignant disease arising from the mesothelium. The pleural cavity is the most frequent site of origin. Peritoneal mesothelioma accounts for 10-30% of all mesotheliomas. Very rare sites of origin are the pericardium, the tunica vaginalis and the ovarian epithelium [17]. Although asbestos appears to be the most important risk factor, more recent studies show that 20-40% of the patients (particularly the females) do not refer previous exposure [6,17,18].

Malignant peritoneal mesothelioma is an infrequent and highly aggressive neoplasm. The median survival with systemic chemotherapy rarely exceeds one year [7,8].

Dedrick et al. described the advantages of intraperitoneal chemotherapy administration compared to intravenous in the treatment of peritoneal metastases [19]. Intraperitoneal drug administration results in high response rates within the abdominal cavity because the peritoneal space to plasma barrier provides dose intensive therapy [20]. The absorption of large molecular weight substances is delayed when they are administered intraperitoneally. This enhances the exposure of the peritoneal surfaces to these compounds while the systemic toxicity decreases [21]. Spratt et al. described first the effect of hyperthermia in combination with intraperitoneal chemotherapy establishing its beneficial effect on a patient with pseudomyxoma peritonei [22].

Malignant peritoneal mesothelioma shows a preference to males aged between 50 and 70 years that is probable due to prior environmental asbestos exposure [23]. Females show improved survival compared to males while older female patients show worst outcome compared to younger ones [24]. This finding was not reproduced in our study probably due to the small number of women involved.

Peritoneal mesothelioma is classified in two main categories: Low-grade peritoneal mesothelioma, which includes well differentiated papillary and mylticystic mesothelioma, and diffuse malignant peritoneal mesothelioma (high-grade) that has three histologic subtypes: epithelial, sarcomatoid and biphasic [25]. In the present study 28 specimens (84.8%) were histopathologically diagnosed as epithelial mesotheliomas. The tumor grade was found to be related with recurrence and was the single prognostic indicator of recurrence. Nodal involvement is not usual, it appears in <6% and is associated with poor prognosis [11]. Retroperitoneal lymph node sampling should be routinelly performed as recommended at PSOGI meeting in 2016 [26].

Systemic chemotherapy in the treatment of peritoneal mesothelioma is ineffective and is currently used for palliation only [9,10]. The combination of cisplatin and pemetrexed systemically shows a median survival of only 13 months [27].

CRS with HIPEC is the only treatment strategy with a glimpse of hope. The completeness of cytoreduction has been proved to be the most significant indicator of long-term survival [10,28, 29].

The cytotoxicity of intraperitoneal chemotherapy is increased with heat [19,20,21]. The effect of several cytotoxic drugs has been investigated but the most effective has not yet been identified [30]. Platinum alone or in combination with pemetrexed, doxorubicin, ifosfamide or mitomycin-C has been effectively used [31]. Carboplatin or cisplatin combined with mitomycin-C or doxorubicin are the most commonly used drugs and show the most promising results both in overall and disease free survival [30-32].

Cytoreduction with perioperative chemotherapy is a complex procedure that is associated with relativelly high morbidity and low mortality rate. In general, the morbidity varies from 25 to 40% and the mortality from 1 to 10% for patients with peritoneal malignancy of any primary [13,28,33-35]. Sugarbaker et al. have reported morbidity of 23.5% and mortality of 7% in 68 patients treated

for peritoneal mesothelioma [12]. Similar results have also been reported from other relevant studies [2,5,9,10,12,13].

Five-year survival rate varies between 29 and 59% with a median follow-up of 37-72 months [5,9,11-13]. In a multicentric study with 405 patients 3- and 5-year survival rates were 60 and 47% respectively with median survival of 53 months [13].

## Conclusion

Complete or nearly complete cytoreduction combined with HIPEC is a safe and beneficial treatment that improves prognosis and overall survival.

## Conflict of interests

The authors declare no conflict of interests.

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