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CLINICAL STUDY

Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy for malignant peritoneal mesothelioma

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ABSTRACT

OBJECTIVES: The aim of this study is to evaluate the results of treatment of diffuse malignant peritoneal mesothelioma (DMPM) by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) at a single center.

METHODS: We conducted a retrospective single-center observational cohort study of consecutive patients with DMPM treated by CRS-HIPEC at the Department of Surgery I of the University Hospital in Olomouc, Czech Republic.

RESULTS: Data on a total of 16 patients were processed. The study group of 16 patients had six (37.5 %) women. The mean age was approximately 62 years. Complete cytoreduction was achieved in all patients (100 %) (CC0: 75 %, CC1: 25 %). All patients underwent a closed form of HIPEC with cisplatin and doxorubicin for 90 min. The mean hospital stay was 13.5 days, including 4.38 days in the ICU (13.5±5.07 and 4.38±1.49, respectively). Major postoperative complications (CD grades 3–4) occurred in four patients (25 %). In-hospital mortality was 6.25 %. In the study group, the median overall survival was 20 months, and the median disease-free survival was 10.3 months.

CONCLUSIONS: Under the conditions at our specialized center, CRS-HIPEC is considered as an effective, affordable, and safe therapy with OS, DFS, morbidity, and mortality rates comparable to those reported in the literature *(Tab. 5, Fig. 2, Ref. 28).* Text in PDF *www.elis.sk*

KEY WORDS: cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, malignant mesothelioma, cisplatin, doxorubicin.

Introduction

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare type of aggressive tumor arising from the mesothelium of the serosal membranes lining the peritoneal cavity. It is indicative of a very poor prognosis. It shows morphological similarities with pleural mesothelioma and is associated with asbestos exposure in both cases (1). Compared to pleural mesothelioma, it is more common in younger individuals and women and more often shows an epithelioid histotype (2). Researchers have considered the contribution of SV40 viruses (3), as well as the importance of mutations in the tumor suppressor gene BRCA-associated protein 1 (BAP-1), which increase the risk of asbestos-induced malignancies and were first described in a Turkish family with an autosomal dominant pattern (4). In the USA and Western Europe, the incidence of peritoneal mesothelioma has remained consistent for nearly 40 years, reaching approximately 0.04–0.11 and 0.07–0.16 newly diagnosed cases per 100,000 inhabitants per year in women and men, respectively (5). Approximately 0.08 % of all newly diagnosed cancers in the Czech Republic are peritoneal mesotheliomas (6).

Histologically, peritoneal mesothelioma is divided into four subtypes: epithelioid (the most common form), accounting for 86 % of all types; mixed (biphasic/sarcomatoid), 9 %; biphasic, 3 %; and mesenchymal/sarcomatoid, 2 % (7). A histopathological subset of peritoneal mesothelioma has a less aggressive form, including multicystic peritoneal mesothelioma and well-differentiated papillary peritoneal mesothelioma. Both diseases generally affect women of reproductive age with no history of asbestos exposure and indolent clinical behaviors.

The clinical symptoms of DMPM are usually very poor. Therefore, this disease is often diagnosed very late. Manzini (8) described three basic clinical manifestations of the disease: (1) patients with increased abdominal volume due to massive ascites and large tumor nodules associated with weight loss and abdominal pain; (2) patients with acute problems requiring acute surgical treatment; and (3) patients with vague fever and weight loss

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with a picture of inflammatory bowel disease. In the early stages of the disease, uncharacteristic symptoms such as fatigue, loss of appetite and weight, vague temperatures, dyspnea, abdominal discomfort, nausea, vomiting, and diarrhea appear. The primary diagnostic method for this disease is a CT scan of the chest and abdomen with findings of multiple small nodular lesions on the peritoneum, "omental cake," and diffuse thickening of the mesentery. Diagnostic laparoscopy provides essential information leading to the diagnosis and extent of the disease, with a view of the entire abdominal cavity, determination of the extent of the peritoneal carcinoma index (PCI), and collection of samples for histopathological examination. Currently, no staging system has been validated for DMPM. Through the Peritoneal Surface Oncology Group Initiative (PSOGI), the level of DMPM involvement has been divided into four stages: T1, T2, T3 and T4 which represent PCI 1–10, PCI 11–20, PCI 21–30, and PCI 30–39, respectively (9).

In the past, when combined treatment methods were not yet available, the disease used to have a very rapid course, with an overall survival of approximately 12 months from the diagnosis (10). With the introduction of multimodal treatments such as cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), as well as systemic chemotherapy as the standard of care for DMPM (11), which was recommended by the 2006 Milan Consensus Conference on Peritoneal Surface Malignancies, the median survival has increased to 31–92 months for >30 years (12, 13). Patients who do not receive this treatment or are unable to do so due to their overall condition have a significantly worse prognosis for overall survival compared to the cohort of patients receiving this treatment (14).

Since 2004, the standard systemic treatment has been a combination of cisplatin and pemetrexed as the first-line therapy, and since 2008, carboplatin has been in use as an alternative to cisplatin. Gemcitabine can be used in combination with cisplatin in patients who cannot receive pemetrexed (15). In 2020, dual checkpoint blockade therapy with nivolumab and ipilimumab was approved as the first-line treatment in patients with pleural mesothelioma. This benefit was mainly observed in patients with high-grade non-epithelioid mesothelioma (16).

This retrospective single-center observational cohort study aimed to analyze the safety, oncological radicality, morbidity, and mortality of combined treatment methods like CRS and HIPEC with systemic therapy in patients with DMPM at our institution between 2016 and 2021.

Materials and methods

This study prospectively collected data involving all the patients who were treated with CRS and HIPEC after the diagnosis of DMPM from February 2016 to December 2021 at the Department of Surgery I. at the University Hospital in Olomouc. The study was approved by the Ethics Committee of the Faculty Hospital Olomouc (EKFNOL-198/2022).

Each patient had routine preoperative examinations, including CT scans of the chest, abdomen, and pelvis. The extent of involvement was determined preoperatively using the PCI. Cytoreductive surgery followed by HIPEC was recommended for all patients in good condition after excluding extraperitoneal metastases. The patients were referred and indicated for a multidisciplinary team care. The systemic therapy (cisplatin and pemetrexed) was administered either preoperatively or postoperatively. The PCI score was recalculated at the start of surgery after examining the peritoneal cavity. Cytoreductive surgery included exploratory laparotomy, appendectomy, cholecystectomy, bilateral adnexectomy with hysterectomy, diaphragmatic, parietal, and pelvic peritectomy, omentectomy, and varying degrees of bowel resection with removal of tumor implants. HIPEC in patients with DMPM included intraperitoneal administration of cisplatin (45 mg/L) and doxorubicin (15 mg/L) for 90 minutes at 42.5 °C. HIPEC was administered in a closed form using the SKALA device (Czech Republic). Complete cytoreduction was defined as nodules > 2.5 mm in size (CC1) or as absence of visible tumor nodules (CC0). Postoperative follow-up was performed every 3 months for the first year with tumor markers (CA-125) and abdominal CT every 6 months. From the second year on, follow-up was performed every 6 months.

Tab. 1. Clinical, surgical and outcome parameters.

Clinical parameters
Sex
BMI
Age
ASA classification
Previous surgery
Previous chemotherapy
Surgical parameters
Operation time
Histotype
Perioperative PCI
Peritonectomy procedures
Resections
CC0 score
Number of anastomoses
Postoperative course
Outcome parameters
Date of death or last follow-up
Date of first clinical, radiographic or surgical recurrence

Tab. 2. Clinical parameters.

Factor	n=16	
Female (%)	37.5	(6/16)
BMI (kg/m^2)	23.14	± 2.28
age (years)	62.5	± 14.53
ASA		
I	25.0	(4/16)
II	56.25	(9/16)
III	18.75	(3/16)
IV	0.00	(0/16)
Previous surgery %		
None	31.25	(5/16)
Abdominal resection	6.25	(1/16)
Biopsy	62.5	(10/16)
Previous chemotherapy %		
Yes	50.0	(8/16)
No	50.0	(8/16)

Clinical, surgical, and outcome parameters are shown in Table 1. In the outcome, parameters were defined as an interval between the date of the pathological diagnosis and the date of death or last follow-up. Disease-free survival was defined as an interval between the date of first cytoreduction and the date of the first clinical, surgical, or radiographic recurrence (or the date of death or last follow-up for patients documented to have no recurrence). Data were retrieved from the patients' medical records by the submitting surgeons. Clinical data were collected during the follow-up, and no patient was lost to follow-up. All statistical analyses were performed using either SPSS 23.0 (International Business Machines Corporation, Armonk, NY) or Prism 6.0 (Graphpad Software, Inc., La Jolla, CA, USA) software.

Tab. 3. Surgical parameters.

Factor	Total n=16	
Operation time (min)	298.56	± 79.13
Histotype %		
Epithelioid	93.75	(15/16)
Biphasic	6.25	(1/16)
PCI	16.19	± 7.77
Peritonectomy %		
Upper right	75.0	(12/16)
Upper left	75.0	(12/16)
Parietal	100.0	(16/16)
Pelvic	87.5	(14/16)
Jejunum	12.5	(2/16)
Resection %		
Omentum majus	93.75	(15/16)
Hemicolectomy	12.5	(2/16)
Colon transversum	6.25	(1/16)
Left hemicolectomy	0.0	(0/16)
Sigmoid resection	31.25	(5/16)
Subtotal colectomy	18.75	(3/16)
Anterior low resection	62.5	(10/16)
Jejunum resection	25.0	(4/16)
Appendectomy	75.0	(12/16)
Gastrectomy	6.25	(1/16)
Cholecystectomy	87.5	(14/16)
Pancreas resection	6.25	(1/16)
Liver resection	6.25	(1/16)
Bladder resection	0.0	(0/16)
Hysterectomy	18.75	(3/16)
Adnexectomy	18.75	(3/16)
Splenectomy	6.25	(1/16)
CC score		
0	75.0	(12/16)
1	25.0	(4/16)
HIPEC closed system %	100.0	(16/16)
Number of anastomoses	1.00	± 0.88
Anus praeter (%)		
Temporary ileostomy	18.75	(3/16)
Permanent ileostomy	6.25	(1/16)
Colostomy	0.0	(0/16)
Blood loss (ml)	587.5	± 254.03
Postoperative course		
Hospital stay (days)	13.5	± 5.07
ICU stay (days)	4.38	± 1.49
In-hospital mortality %	6.25	(1/16)

Values are presented as mean±standard deviation, number (%) or median, n.a.=not available (continuous data are shown as mean and standard deviations), ASA= American Society of Anesthesiologists

Results

Clinical characteristics

The study group of 16 patients had six (37.5 %) women (Tab. 2). The mean age was approximately 62 years; the youngest patient was operated on at the age of 37 years and the oldest at the age of 74 years. All of the patients who underwent surgery had normal body mass index values ranging from 18.5 to 25. Most of the patients had no major comorbidities, and only three (18.75 %) were described as having cardiac comorbidities (ischemic heart disease). Previous surgical intervention in the peritoneal cavity was performed in 11 patients (68.75 %), mostly diagnostic laparoscopy with biopsy material collection; only one patient (6.25 %) underwent bowel resection and omentectomy. Half of all patients underwent systemic treatment (with cisplatin and doxorubicin) before CRS and HIPEC, while the rest underwent systemic treatment postoperatively (Tab. 3).

Perioperative and postoperative surgical parameters

Without HIPEC, the mean operative time was 298.56 ± 79.13 minutes. Omentectomy was performed in all patients (only one patient had already undergone omentectomy as part of the previous surgery), and all patients also underwent parietal peritonectomy. Stripping of the diaphragm was reserved for patients with visible involvement of this part of the peritoneum (75 %). In some patients, cytoreduction required bowel resection, particularly in the right colon. One patient underwent multi-visceral resection, including gastrectomy, total duodenopancreatectomy, and subtotal colectomy with posterior pelvic exenteration, cholecystectomy, and splenectomy. Complete cytoreduction was achieved in all patients (100 %) (CC0: 75 %, CC1: 25 %). The number of anastomoses ranged from 0–3, and an ostomy was performed in four patients (25 %). All patients underwent a closed form of HIPEC with cisplatin and doxorubicin for 90 min. The mean blood loss was 587.5 ml (587.5 ± 254.03). The mean hospital stay was 13.5 days, including 4.38 days in the ICU (13.5 ± 5.07 and 4.38 ± 1.49, respectively). Major postoperative complications (CD grades 3–4) occurred in four patients (25 %) (Tab. 4), and one woman died due to acute renal failure and its complications after previous systemic treatment with cisplatin. Th in-hospital mortality was 6.25 %.

Tab. 4. Postoperative complications – Clavien-Dindo classification

CD1	37,50 (6/16)
CD3	25,00 (4/16)
CD5	6,25 (1/16)
CD2	31,25 (5/16)
CD4	0,00 (0/0)

Tab. 5. Outcome parameters - means and medians for survival time (months).

	Average	95% CI average	Median	95% CI median
OS	43.6	24.7–62.4	20.0	0–74.9
DFI	33.3	15.1–51.4	10.3	6.9–13.8

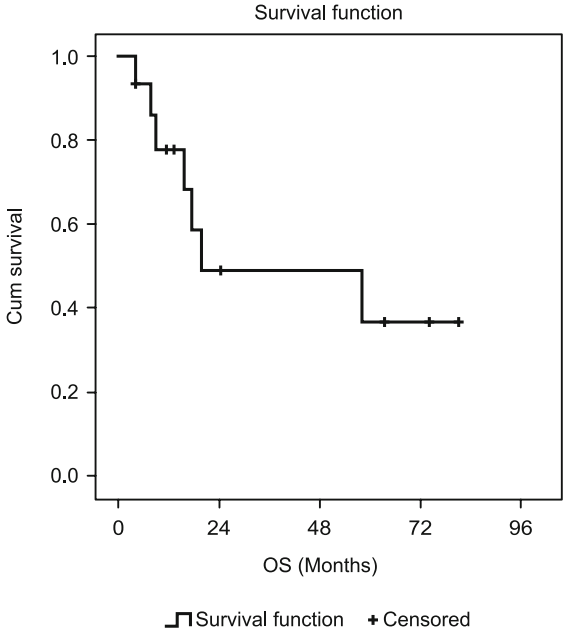

Fig. 1. Overall – survival in months – Kaplan-Meier.

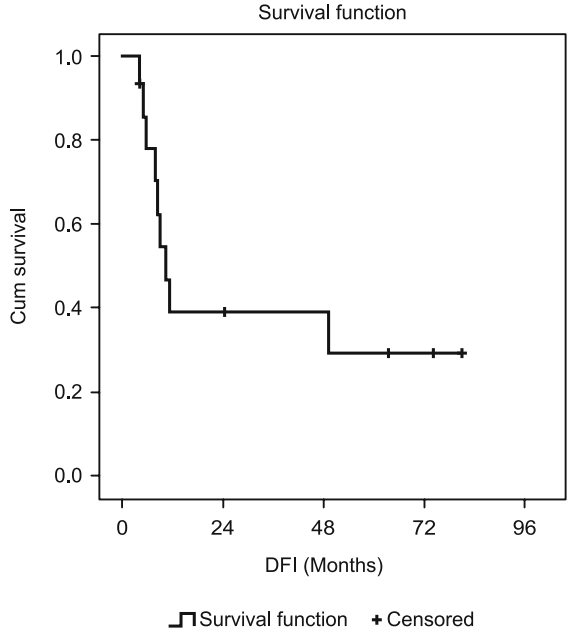

Fig. 2. Disease free survival in months.

Fifteen out of 16 DMPM histotypes in our study group were of epithelioid type (93.75 %), and only one was biphasic (6.25 %).

Outcome parameters

In the study group, the median overall survival was 20 months (0–74.9 months), and the median disease-free survival was 10.3 months (6.9–13.8 months) (Tab. 5, Figs 1 and 2). In the study group, seven out of 16 patients (43.75 %) died, one patient had postoperative complications in the hospital, and the remainder had disease recurrence, three of which occurred within one year after CRS and HIPEC.

Discussion

DMPM is a rare and aggressive primary peritoneal malignancy, characterized by widespread multiple peritoneal metastatic tumor nodules. Therefore, conducting randomized trials to find the best treatment option for patients with DPMP is difficult.

The clinical manifestation is already very poor and manifests with nonspecific symptoms. CT scanning is a basic diagnostic method for DPMP (17). Recent data have also shown that a CT scan could help in the differential diagnosis of DMPM and other peritoneal surface malignancies (PSM) (18). Magnetic resonance imaging is an alternative cross-sectional imaging technique that has been suggested as being superior to CT in quantifying PCI in PSM (19). Fluorine-18 fluorodeoxyglucose (18F-FDG)-PET/contrast-enhanced CT (PET/CT) is a promising tool with sensitivity, specificity, and accuracy of 86 %, 89 %, and 87 %, respectively (20). However, cross-sectional imaging with CT for the preoperative evaluation of DMPM should be the preferred diagnostic modality because of its accessibility, affordable cost, short acquisition time, and ease of interpretation. The histopathological diagnosis of DPMP provides essential information, while diagnostic laparoscopy is the best way to obtain this information and assess the preoperative extent of the disease. Preoperative laparoscopy should be performed by a surgeon with expertise in treating peritoneal surface malignancies with midline placement of trocars to allow excision in a subsequent operation to prevent port-site recurrence and a thorough evaluation of the peritoneal cavity with an assessment of the PCI, serosa, and mesentery (17). Another option is a CT-navigated tru-cut biopsy, most often from the omental cavity. In our study group, the disease was diagnosed in 10 patients (62.5 %) by diagnostic laparoscopy, in one by open surgery, and in five by CT-navigated biopsy.

Since DMPM is a rare condition, no randomized phase III trials evaluating any systemic chemotherapy regimen based on this histology have been reported. Most reported studies are retrospective, with lower effectiveness and poorer quality evidence (21). Nevertheless, in 2004, the U.S. Food and Drug Administration (Rockville, Maryland) approved the combination of cisplatin and pemetrexed as a first-line medical therapy for patients with DMPM. In 2008, carboplatin was approved as an alternative to cisplatin (22). More recently, a significant interest has been paid to the use of immune checkpoint inhibitors, either alone or in combination with chemotherapy, in patients with mesothelioma. Most of the studies have been focused on patients with pleural mesothelioma, and the exact relevance of the results of this study for patients with DMPM is unknown (22). Based on the results of the PROMISE-meso trial (23) and Checkmate-743 study, which compared dual checkpoint blockade versus chemotherapy as a

first-line treatment in patients with pleural mesothelioma (24), the U.S. Food and Drug Administration approved the dual checkpoint blockade (nivolumab plus ipilimumab) in October 2020, especially in patients with high-grade non-epithelioid pleural mesothelioma. The data on the use of immunotherapy in patients with DMPM is very limited. Studies on the safety and efficacy of combined bevacizumab and anti-PD-L1 monoclonal antibody atezolizumab in cases of advanced and unresectable DMPM are yielding intriguing data (25).

In our group, all patients were referred to a multidisciplinary team care (MDT) to determine the best therapeutic option. MDT is considered the best practice in cancer treatment and is an integral component of coordinated cancer care (17). Patients were categorized into three groups based on a comprehensive pretreatment workup.

- Patients with extraperitoneal disease and/or poor general status not allowing major abdominal surgery and/or with clearly non-resectable peritoneal metastases at initial assessment may benefit from palliative systemic treatment.
- Patients with no extraperitoneal disease, fit for major abdominal surgery, and with disease amenable to complete resection based on complete CRS combined with HIPEC.
- Patients with no extraperitoneal disease and ineligible for major abdominal surgery should be evaluated for preoperative treatment in order to become suitable for curative intervention.

Over the past 30 years, several retrospective single-center or multicenter publications and a recent meta-analysis (26) reported long-term progression-free and overall survival in selected patients with DMPM undergoing CRS and HIPEC, with a median range of 34 to 92 months. CRS and HIPEC carry rates of severe complications that range from 30 % to 41 % and rates of postoperative mortality ranging from 2.0 % to 2.6 % (17). The PSOGI commissioned a steering committee to elaborate clinical guidelines since the diagnosis and management of DMPM need standardization. These guidelines were presented by Kusamura et al for peritoneal mesothelioma: PSOGI/EURACAN clinical practice guidelines for diagnosis, treatment, and follow-up. In recommendation 18, rather than palliative systemic chemotherapy, CRS-HIPEC is recommended in patients with DMPM, provided that the patient´s clinical condition is sufficient for a major operation, the disease is resectable, and the treatment is performed in a specialized PSM center. Four factors are analyzed to constitute an absolute contraindication for CRS-HIPEC in patients with DMPM, namely sarcomatoid histology, massive small-bowel serosa involvement, concomitant pleural disease, and/or retroperitoneal and/or cardiophrenic lymph node involvement (recommendation 19). As stated by Kusamura et al (17), should the PCI value be ≤ 17, then the median OS is 63.2 months; should the value be >17, the median OS is only 10.3. Therefore, the median OS in our study group was 20 months, when the average PCI was 16.19, as compared with other studies with higher numbers of patients after CRS-HIPEC. In all our patients, CRS was followed by HIPEC with the combination of cisplatin and doxorubicin as per recommendation 24 of the PSOGI guidelines, stating that cisplatin and doxorubicin are the best drug regimens recommended for HIPEC in DMPM patients (17). The median DFS in our group was 10.3 months, as compared to 13.9 and 25.1 months in studies with patients with a lower average PCI (27). Postoperative complications after CRS-HIPEC for DMPM have been reported in 8–90 % of the cases, with mortality reaching 5 % (28). We report the major postoperative complications according to Clavien-Dindo classification grades III and IV in 25 % of cases. Most of these were intraperitoneal fluid collection and pneumonia cases. Acute renal failure was the cause of death in one case (6.25 %) after neoadjuvant SC.

Conclusion

This is the first retrospective cohort study of patients with DMPM treated with combined surgical and oncological therapy, CRS-HIPEC, in the Czech Republic and Slovak Republic. Under the conditions at our specialized center, CRS-HIPEC is considered as an effective, affordable, and safe therapy with OS, DFS, morbidity, and mortality rates comparable to those reported in the literature. The selection of patients for CRS-HIPEC to achieve long-term survival and high quality of life is crucial. A limitation of our results lies in the small number of patients in our study group, which is attributable to the extremely rare incidence of DMPM and frequent preference for systemic chemotherapy by clinical oncologists. Early diagnosis, for instance through abdominal ultrasonography screening, would further enhance the treatment outcomes.

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