Key factors for successful cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy to treat diffuse malignant peritoneal mesothelioma: results from specialized peritoneal cancer center in China

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Objective: To investigate independent factors for the efficacy and safety of cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of diffuse malignant peritoneal mesothelioma (DMPM).

Method: The clinical database of 110 DMPM patients treated with CRS + HIPEC at our hospital was retrospectively analyzed. Independent prognostic factors were screened using univariate and multivariate analyses and the safety of the perioperative period was evaluated based on adverse events.

Result: Among the 110 patients with DMPM, 34 (30.9%) had a peritoneal cancer index (PCI) < 20 and 76 (69.1%) had PCI ≥ 20; 59 (53.6%) patients achieved completeness of cytoreduction (CC) 0/1 and 51 (46.4%) cases achieved CC 2/3. At the median follow-up of 43.3 (95%CI: 37.3–49.4) months, 48 (43.6%) patients were still alive and 62 (56.4%) patients died. The median overall survival was 32.6 months. Serious adverse events (SAEs) occurred in 41 patients (37.3%) and the perioperative mortality rate was 2.7%. Univariate analysis identified nine prognostic factors: Karnofsky performance status score, perioperative tumor markers, PCI, red blood cell infusion, pathological type, vascular tumor emboli, lymphatic metastasis, Ki-67 index, and perioperative SAEs (all \( p < 0.05 \)). Multivariate analysis identified four independent prognostic factors: pathological type (\( p = 0.007 \)), vascular tumor emboli (\( p = 0.044 \)), Ki-67 index (\( p = 0.044 \)), and SAEs (\( p = 0.004 \)).

Conclusions: CRS + HIPEC for DMPM treatment resulted in prolonged survival with acceptable safety. Tumor pathology and SAEs are key factors for successful CRS + HIPEC.

Introduction

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare malignancy derived from peritoneal mesothelial cells, first reported in 1908 [1], accounting for 7%–30% of all mesotheliomas [2–4]. The biological characteristics of DMPM include diffuse and invasive growth along the peritoneal surface. Histologically, DMPM can be divided into three major types: epithelioid, sarcomatoid, and biphasic, with the epithelioid type having a better prognosis [5].

Traditional treatments of DMPM mainly include intravenous/intraperitoneal (IV/IP) chemotherapy or palliative surgery, but their efficacy is poor and the median overall survival (OS) is less than 1 year [4]. With the continuous exploration of DMPM therapy, cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has improved the median OS up to 19–92 months [6].

Our team published a Chinese expert consensus on the diagnosis and treatment of DMPM in China [7], aiming to improve our understanding of DMPM mechanisms and promote standardized CRS + HIPEC procedures in China. However, there have been no large sample size reports on CRS + HIPEC to treat DMPM in China.

As a member hospital on the executive committee of Peritoneal Surface Oncology Group International (PSOGI), our center is the first in China to treat peritoneal metastasis (PM) of various origins, including DMPM. To date, over 1,800 patients with PM have been treated with standardized CRS + HIPEC procedures advocated by the PSOGI. This study aimed to retrospectively analyze our database on DMPM and identify the key factors for successful CRS + HIPEC to treat DMPM.

Patients and methods

Clinical data

This retrospective study was approved by the institutional review board of our hospital (2015–[28]). All patients signed informed consent to receive CRS + HIPEC treatment and to use the clinicopathological data for further researches and academic publications.
From April 2015 to May 2021, 110 DMPM patients treated with CRS + HIPEC were selected from the clinical database. The data included the clinicopathological features, treatment parameters and follow-up information. The following inclusion and exclusion criteria were satisfied for patient enrollment.

The inclusion criteria were as follows: (1) DMPM confirmed by histopathology with complete clinicopathological data and follow-up information; (2) Karnofsky performance status score (KPS) ≥ 60; (3) peripheral blood leukocytes ≥ 3.5 × 10⁹/L and platelets ≥ 80 × 10⁹/L; (4) acceptable liver function: total bilirubin, aspartate aminotransferase, alanine aminotransferase, <2× upper limit of normal (ULN); (5) acceptable renal function: serum creatinine <1.2 × ULN; and (6) heart, lung function and other major organs that can tolerate major surgery.

The exclusion criteria were as follows: (1) lung, brain, bone, liver and other distant metastases found on preoperative examinations; (2) obvious mesenteric contracture observed on imaging diagnosis; and (3) general physical condition and vital organs that cannot withstand major operations.

Perioperative assessments

All selected patients received perioperative assessments according to the Chinese expert consensus on CRS + HIPEC for PM [8], and the main contents included the following three aspects: (1) serological examinations: routine blood tests, liver and kidney function, coagulation function, B-type natriuretic peptide, and myocardial enzyme; (2) tumor markers (TMs) test: carcinoembryonic antigen, carbohydrate antigen (CA)199, CA125, and alpha fetoprotein; (3) imaging examinations: abdominal and pelvic enhanced computed tomography + three-dimensional reconstruction, oral gastrografin radiography of the whole digestive tract, kidney dynamics, and bone scan.

CRS + HIPEC procedure

All CRS + HIPEC procedures were conducted by a designated team focusing on PM treatment. The main steps of CRS, including evaluation of the peritoneal cancer index (PCI) and completeness of cytoreduction (CC) scores, are based on Sugarbaker’s procedures [9].

HIPEC was implemented by the open Coliseum technique with each drug dissolved into 3 L of heated saline at temperature 43 ± 0.5 °C, and the duration of HIPEC was 60 min with a flow rate of 400 ml/min. The major HIPEC regimens consisted of docetaxel 120 mg + cisplatin 120 mg or cisplatin 120 mg + mitomycin C 30 mg. Gastrointestinal or urinary tract reconstruction, drainage tube placement, and abdominal closure were sequentially performed after HIPEC.

Postoperative chemotherapy

Adjuvant chemotherapy was administered within 6–8 weeks after CRS + HIPEC, including pemetrexed plus cisplatin systematic chemotherapy and intraperitoneal chemotherapy.

Adverse events

The adverse events (AEs) were defined as complications directly attributable to the treatment within 30 days of CRS + HIPEC, and the severity of AEs was divided into five grades, according to the PSOGI textbook on PM [10]: grade I, diagnosis established, no intervention required for resolution; grade II, diagnosis established, medical treatment sufficient for resolution; grade III, radiological intervention required for resolution; grade IV, urgent definitive interventions often required in the operating room or surgical intensive care unit; and grade V, postoperative death. Serious AEs (SAEs) were defined as grade III–V AEs.

Follow up

Follow up consisted of general status, tumor response evaluation, AEs, and survival information. The frequency of follow-up was once every 3 months within 2 years after CRS + HIPEC, once every 6 months after 2 years, and once every year after 3 years. The last follow-up was conducted on August 24, 2021.

Study parameters

The study parameters included (1) clinicopathological characteristics, including age, history of adjuvant therapy, KPS score, prior surgery score (PSS), and preoperative tumor markers; (2) CRS + HIPEC-related parameters, including duration of surgery, number of organs and peritoneal resection, number of anastomotic stoma, PCI, CC score, and intraoperative volume; (3) survival, survival status, and OS; and (4) SAEs.

OS was defined as the time interval from the date of clinical diagnosis to the date of death or last follow-up. The PSS is a quantitative evaluation of the degree of prior surgery according to the PSOGI textbook on PM [10], and is a useful tool for assessing the reoperation adhesion events, and the extent of tumor cell entrapment.

Statistics analysis

Data were collected and analyzed using Microsoft Office 2016 and Statistical Package for Social Science 22.0 (SPSS 22.0, IBM Corporation, Armonk, NY, USA). Continuous variables were presented as mean ± SD or median (range) and analyzed using the t-test or rank sum test. Classified variables were presented as numbers and percentages and analyzed using Pearson’s χ² test or Fisher’s exact test. OS was estimated using the Kaplan–Meier method and the log-rank test. The best boundary values of continuous variables, named with cutoff values, were determined using the Youden index of the COX curve or median. Statistical significance was set at p < 0.05.

Results

Major clinicopathological characteristics

The clinicopathological characteristics of the 110 patients are presented in Table 1. There were 54 (49.1%) males and 56...
Table 1. Clinicopathological characteristics.

| Variable                          | Value            |
|-----------------------------------|------------------|
| Gender, n (%)                     |                  |
| Male                              | 54 (49.1)        |
| Female                            | 56 (50.9)        |
| Age (years), median (range)       | 55 (24–73)       |
| History of surgery, n (%)         |                  |
| No                                | 44 (40.0)        |
| Yes                               | 66 (60.0)        |
| PSS score, n (%)                  |                 |
| 0/1                               | 82 (74.5)        |
| 2/3                               | 28 (25.5)        |
| History of IV/IP chemotherapy, n (%) |           |
| No                                | 51 (46.4)        |
| Yes                               | 59 (53.6)        |
| History of targeted therapy, n (%) |            |
| No                                | 82 (74.5)        |
| Yes                               | 28 (25.5)        |
| KPS, n (%)                        |                 |
| <80                               | 16 (14.5)        |
| ≥80                               | 94 (85.5)        |
| BMI (kg/m²), median (range)       | 22.1 (15.6–32.1) |
| Pathological type, n (%)          |                 |
| Epithelioid                       | 88 (80.0)        |
| Non-epithelioid                   | 22 (20.0)        |
| Vascular tumor emboli, n (%)      |                 |
| No                                | 85 (77.3)        |
| Yes                               | 25 (22.7)        |
| Lymphatic metastasis, n (%)       |                 |
| No                                | 97 (88.2)        |
| Yes                               | 13 (11.8)        |
| Ki-67 index, n (%)                |                 |
| <9%                               | 19 (17.3)        |
| ≥9%                               | 91 (82.7)        |
| Increased preoperative TMs*, n (%) |              |
| No                                | 32 (29.6)        |
| Yes                               | 76 (70.4)        |

PSS: prior surgical scores; IV/IP: intravenous/intraperitoneal; KPS: Karnofsky performance status score; BMI: body mass index; TMs: tumor markers. *: any one of carcinoembryonic antigen, carbohydrate antigen (CA)199, CA125, and alpha fetoprotein was increased.

CRS + HIPEC information

The major CRS + HIPEC parameters are presented in Table 2. Among the 110 patients with DMPM, 34 (30.9%) had PCI < 20, 76 (69.1%) had PCI ≥ 20, 59 (53.6%) achieved CC 0/1, and 51 (46.4%) achieved CC2/3. The median organ resection was 1, and peritonectomy was 6. There were 62 (56.4%) cases without anastomosis, 29 (26.4%) cases with one anastomosis, and 19 (17.3%) cases with two anastomoses. The median operative time was 528 min. The median bleeding, red blood cell (RBC) infusion, and plasma infusion volumes were 500 ml, 2 U, and 600 ml, respectively.

Survival analysis

As of August 24, 2021, the median follow-up was 43.3 (95%CI: 37.3–49.4) months. There were 48 (43.6%) patients who were still alive and 62 (56.4%) patients who died, with a median OS of 32.6 (95%CI: 26.2–39.0) months (Figure 1).

Table 2. The parameters of CRS + HIPEC.

| Variable                          | Value            |
|-----------------------------------|------------------|
| PCI score, n (%)                  |                 |
| <20                               | 34 (30.9)        |
| ≥20                               | 76 (69.1)        |
| CC score, n (%)                   |                 |
| 0/1                               | 59 (53.6)        |
| 2/3                               | 51 (46.4)        |
| Operation time (min), median (range) |            |
| 1,905 (190–950)                  | 528 (190–950)    |
| Bleeding (ml), median (range)     |                 |
| 500 (0–3,000)                    | 500 (0–3,000)    |
| RBC infusion (U), n (%)           |                 |
| <5                                | 91 (82.7)        |
| ≥5                                | 19 (17.3)        |
| Plasma infusion (ml), median (range) |              |
| 600 (0–1,600)                    | 600 (0–1,600)    |
| Ascites (ml), median (range)      |                 |
| 1,000 (0–22,000)                 | 1,000 (0–22,000) |
| Urine volume (ml), median (range) |                 |
| 1,500 (200–4,500)                | 1,500 (200–4,500) |
| Liquid infusion (ml), median (range) |              |
| 5,930 (2,120–15,000)             | 5,930 (2,120–15,000) |

CRS + HIPEC: cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy; PCI: peritoneal cancer index; CC: completeness of cytoreduction; RBC: red blood cell; SAEs: serious adverse events.

Univariate analysis identified the following nine prognostic factors: KPS (p = 0.012), increased perioperative TMs (p = 0.003), pathological type (p = 0.004) (Figure 2A), vascular tumor emboli (p = 0.009) (Figure 2B), lymphatic metastasis (p = 0.039), Ki-67 index (p = 0.004) (Figure 2C), PCI score (p = 0.007), RBC infusion (p = 0.022), and SAEs (p = 0.006) (Figure 2D).

Factors in the univariate survival analysis (p < 0.05) were incorporated into the Cox regression model for multivariate analysis, delineating the following four independent prognostic factors: pathological type, vascular tumor emboli, Ki-67 index, and SAEs (Table 3).

Adverse events analysis

SAEs occurred in 41 (37.3%) of 110 patients, including 3 (2.7%) deaths on postoperative days 5, 14, and 18, respectively. Detailed information on grade III–IV SAEs is shown in Table 4. Furthermore, three factors were identified for perioperative SAEs: PSS (p = 0.045), PCI (p = 0.015), and CC (p = 0.006), based on the correlation analysis of SAEs and major clinicopathological and CRS + HIPEC characteristics. The three risk factors were included in the multivariate logistic regression analysis. CC 2/3 was the only independent risk factor for perioperative SAEs (p = 0.009, OR = 2.986, 95% CI: 1.312–6.712).

Discussion

In this study, CRS + HIPEC to treat DMPM improved the median OS to 32.6 months, with a 30-day perioperative SAE
rate being 37.3% and mortality rate being 2.7%. The nine prognostic factors revealed by univariate analysis could be divided into three categories: (1) parameters related to patient status and tumor burden such as KPS and PCI; (2) CRS + HIPEC-related parameters such as RBC infusion and SAEs; and (3) tumor biology-related parameters such as perioperative TMs, pathological type, Ki-67 index, vascular tumor emboli, and lymphatic metastasis. Multivariate analysis with Cox regression identified four independent prognostic factors: pathological type, vascular tumor emboli, Ki-67 index, and SAEs.

There have been several recent studies on CRS + HIPEC for the treatment of DMPM (Table 5) [11–23]. These studies varied widely in terms of the sample size, pathological type, disease severity, and clinical outcomes. In these studies, median OS ranged from 27 to 98 months. Two factors may account for the differences among these studies: (1) there are few medical institutions that can independently perform standardized CRS + HIPEC due to technical complexity and (2) DMPM is rare, with no specific symptoms leading to a high misdiagnosis rate. As a result, most patients are at an advanced stage with a heavy tumor burden when seeking treatment, rendering complete CRS impossible.

Of practical importance are the four independent prognostic factors identified by multivariate analysis: pathological type, vascular tumor emboli, Ki-67 index, and SAEs, which were similar to those in previous studies [24–27]. The first three factors are related to innate tumor biology; therefore, they cannot be changed by surgical intervention. However, the last one factor is closely related to the surgical techniques and perioperative management. These results suggest that the key to successful CRS + HIPEC treatment for DMPM is a correct understanding of tumor biology and optimal perioperative management.

In clinical practice, this study suggests that a tumor-biology-based strategy should be adopted for patient selection in CRS + HIPEC. Correct pathological diagnosis using key molecular biology information is the first step in patient selection. Additionally, effective and efficient perioperative management system are required to reduce perioperative SAEs.

In this study, CC 2/3 was found to be independently associated with SAEs, resulting in poor survival. As a tumor reduction degree score system, on the one hand, CC is related to the invasion degree of the tumor itself, and on the other hand, it is closely related to surgical techniques. Therefore, the first prerequisite is improvement of the surgical techniques. Oncologist surgeons should receive intensified specialist training in CRS + HIPEC operations to acquire essential expertise. Polanco et al. [28] indicated that in their institution, approximately 180 and 90 CRS + HIPEC procedures are required to improve operative and oncologic outcomes for PM patients, respectively. Patients should undergo surgery at specialized peritoneal cancer centers to reduce perioperative SAEs and achieve complete CRS.

The second approach is optimized perioperative management. The guidelines for perioperative care in CRS with or without HIPEC [29, 30] published in 2020 defined 37 strong perioperative recommendations for perioperative management, SAE reduction, and technical training. However,
perioperative care is currently characterized by a wide variation in protocols across centers. Therefore, standardization of perioperative management is urgently needed and further research is needed to reduce SAEs.

According to the PSOGI textbook on CRS + HIPEC for PM [10], SAEs are classified into nine organ systems. In our study, the most common postoperative SAEs was in the respiratory system, with pleural effusion (PE) accounting for 95.5%. Singh et al. [31] found that 73% of patients with mesothelioma required diaphragmatic interventions, increasing the incidence of postoperative PE. Campos et al. [32] also indicated that almost all patients required diaphragmatic peritonectomy as a part of their CRS. A total of 72/73 patients who underwent diaphragmatic peritonectomy developed PE, but only six patients required pleural drainage. Therefore, it was suggested that the routine use of pleural tubes was not advocated. However, in another study [33], Carboni et al. analyzed the feasibility of diaphragmatic interventions in CRS + HIPEC for PM. All patients who underwent diaphragmatic surgery were routinely placed on chest drains. The routine placement of chest drains may reduce the incidence of adverse respiratory events. Of all our patients, 22 (20.0%)
developed grade III–IV PE after CRS + HIPEC. These findings suggest that preventive chest drainage in patients undergoing diaphragmatic interventions may be beneficial.

However, for patients with poor tumor biology (non-epithelioid type, vascular tumor emboli, and Ki-67 > 9%), CRS + HIPEC cannot provide better survival. Kusamura et al. found that patients with Ki-67 > 9% are unlikely to benefit from CRS + HIPEC [27]. Some studies have explored the efficacy of neoadjuvant chemotherapy for DMPM, with mixed results. In a study by Naffouje et al. [34] to investigate the impact of chemotherapy and its timing on survival in DMPM patients, 1,740 patients were divided into five groups: (0) no treatment, (1) chemotherapy only, (2) surgery only, (3) neoadjuvant chemotherapy + surgery, and (4) surgery + adjuvant chemotherapy. The median survival times were 3.6, 11.1, 57.4, 52.3, and 55.0 months in groups 0–4, respectively. No statistical differences in OS were found among groups 2–4, and the timing of the addition of chemotherapy did not have any statistical impact on OS. In another study [35], 126 patients treated with CRS + HIPEC were divided into four groups according to the preoperative treatment: (1) only neoadjuvant chemotherapy, (2) only adjuvant chemotherapy, (3) perioperative chemotherapy, and (4) no chemotherapy before or after CRS + HIPEC. The results showed that neoadjuvant chemotherapy had a negative effect on patient survival. However, according to Yin’s report, the drug sensitivity detection technology of the patient-derived tumor-like cell cluster model may provide an accurate chemotherapy for refractory DMPM patients, prolonging their survival [36]. A limitation of this study is its single-center retrospective design with a moderate sample size. The results of this study need to be further verified through multicenter, randomized controlled studies.

In conclusion, this study suggests that CRS + HIPEC treatment in specialized peritoneal cancer centers could improve survival with acceptable safety. The key to improving the efficacy is enhanced perioperative management to reduce SAEs.

Table 5. The literatures of DMPM treated with CRS + HIPEC.

| Authors               | Year | No.  | Epithelioid (%) | Non-Epithelioid (% | Pathological type (%) | PCI Median/mean | Median OS (months | Mortality (%) | III–IV SAEs (%) |
|-----------------------|------|------|-----------------|--------------------|------------------------|----------------|-----------------|---------------|----------------|
| Shi, et al. [11]      | 2021 | 20   | 20 (100.0)      | 0 (0.0)            |                        | NA             | 8               | 27            | 5.0           | 15.0           |
| Brandl A, et al. [12] | 2020 | 19   | 17 (89.5)       | 2 (10.5)           |                        | 17             | NA              | NA            | 0.0           | 0.0            |
| Kyziridis D, et al. [13] | 2019 | 33   | 33 (100.0)      | 0 (0.0)            |                        | 19             | 12              | 67            | 3.0           | 21.2           |
| Cashin PH, et al. [14] | 2019 | 32   | 27 (84.4)       | 5 (15.6)           |                        | 19             | NA              | NA            | 0.0           | 21.8           |
| Verma V, et al. [15]  | 2018 | 216  | 206 (95.4)      | 10 (4.6)           |                        | NA             | NA              | 61            | NA            | NA             |
| Gilani SNS, et al. [16] | 2018 | 76   | 69 (90.8)       | 7 (9.2)            |                        | 15             | NA              | 98            | NA            | NA             |
| Li YC, et al. [17]    | 2017 | 100  | 93 (93.0)       | 7 (7.0)            |                        | 17             | NA              | 63            | 2.0           | 38.9           |
| Stamou K, et al. [18] | 2015 | 20   | NA              | NA                 |                        | 17             | NA              | 47            | 10.0          | 25.0           |
| Ithemelandu C, et al. [19] | 2015 | 161  | 147 (91.3)      | 14 (8.7)           |                        | 18             | NA              | 77            | NA            | 17.4           |
| Magge D, et al. [20]  | 2014 | 65   | 55 (84.6)       | 8 (12.3)           |                        | 12             | NA              | 46            | 6.2           | 35.4           |
| Hommell-Fontaine J, et al. [21] | 2013 | 28   | 22 (78.6)       | 6 (21.4)           |                        | 23             | NA              | 37            | NA            | NA             |
| Baratti D, et al. [22] | 2013 | 108  | 93 (86.1)       | 15 (13.9)          |                        | 17             | NA              | 63            | 1.9           | 38.9           |
| Yan TD, et al. [23]   | 2009 | 401  | 318 (79.3)      | 83 (20.7)          |                        | 27             | 76              | 33            | 2.7           | 34.5           |
| This study            | 2021 | 110  | 88 (80.0)       | 22 (20.0)          |                        | 27             | 76              | 33            | 2.7           | 34.5           |

DMPM: diffuse malignant peritoneal mesothelioma; CRS + HIPEC: cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy; PCI peritoneal cancer index; OS: overall survival; SAEs: serious adverse events; NA: not available. *: biphasic/sarcomatoid.

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