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Chinese expert consensus on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancies

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Abstract

Locoregional spread of abdominopelvic malignant tumors frequently results in peritoneal carcinomatosis (PC). The prognosis of PC patients treated by conventional systemic chemotherapy is poor, with a median survival of < 6 mo. However, over the past three decades, an integrated treatment strategy of cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) has been developed by the pioneering oncologists, with proved efficacy and safety in selected patients. Supported by several lines of clinical evidence from phases Ⅰ, Ⅱ and Ⅲ clinical trials, CRS + HIPEC has been regarded as the standard treatment for selected patients with PC in many established cancer centers worldwide. In China, an expert consensus on CRS + HIPEC has been reached by the leading surgical and medical oncologists, under the framework of the China Anti-Cancer Association. This expert consensus has summarized the progress in PC clinical studies and systematically evaluated the CRS + HIPEC procedures in China as well as across the world, so as to lay the foundation for formulating PC treatment guidelines specific to the national conditions of China.

Key words: Expert consensus; Peritoneal carcinomatosis; Cytoreductive surgery; Intraperitoneal hyperthermic chemotherapy; Gastric cancer; Colorectal cancer; Ovarian cancer; Peritoneal mesothelioma; Pseudomyxoma Peritonei; Peritoneal sarcoma

Core tip: Cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) has been considered as the standard treatment for selected patients with peritoneal carcinomatosis (PC) in many established cancer centers worldwide. This Chinese expert consensus summarizes the mechanism of CRS + HIPEC to treat PC and its clinical efficacy in gastric cancer, colorectal cancer, ovarian cancer, pseudomyxoma peritonei, malignant peritoneal mesothelioma, and peritoneal sarcoma. Furthermore, a clinical pathway of CRS + HIPEC to treat PC has also been formulated.

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INTRODUCTION

Locoregional spread of abdominopelvic malignancies such as gastric cancer, colorectal cancer, ovarian cancer, pseudomyxoma peritonei (PMP), malignant peritoneal mesothelioma and primary peritoneal carcinoma, frequently results in peritoneal surface malignancies, generally known as peritoneal carcinomatosis (PC). At present, PC is generally regarded as a form of systemic and widespread metastasis and the terminal stage of disease that deserves only palliative care, with a median overall survival (OS) of about 6 mo[1-3].

With research into tumor biological behavior and advances in cancer treatment technology, revolutionary changes have taken place in understanding PC, which is currently regarded as a kind of locoregional cancer progression, but no longer a widespread terminal-stage cancer metastasis. Accordingly, an integrated treatment strategy of cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) has been developed by pioneering oncologists, with proved efficacy and safety in selected PC patients with PMP[4,5], gastric cancer[6,7], colorectal cancer[8], and ovarian cancer[9]. Gradually, CRS + HIPEC has been established and promoted in many cancer centers in Europe, America and Asia-Pacific regions[7,10,11].

This CRS + HIPEC treatment combines the advantages of surgical resection, locoregional chemotherapy, hyperthermal therapy and large-volume abdominal perfusion washing, in which CRS removes the peritoneal and abdominopelvic gross tumor, and the synergistic effects of HIPEC eradicate residual tumor nodules, micrometastases and free cancer cells. It is so far the most effective strategy to treat PC[12,13]. This Chinese expert consensus is to summarize the progress in PC clinical studies and systematically evaluate the CRS + HIPEC procedure, so as to lay the foundation for formulating PC treatment guidelines specific to the national conditions of China.

CLINICAL EPIDEMIOLOGY OF PC

PC is not an uncommon clinical condition. Serosal layer invasion of advanced gastric cancer is prone to forming PC, with 15%-50% of gastric cancer patients developing various degrees of PC at first diagnosis, and 35%-50% of postoperative cancer recurrence mainly in the form of PC[14]. About 10% of colorectal cancer patients develop PC at first treatment, 4%-19% of patients develop PC during follow-up after radical resection, and PC is the only form of recurrence in 25%-35% of the patients[15]. All of the epithelial ovarian cancer beyond FIGO (International Federation of Gynecology and Obstetrics) stage ⅡB will develop PC as a natural course of disease progression. The clinical pathological process of primary peritoneal carcinoma and peritoneal mesothelioma are typical PC disease courses. PMP is a rare condition, and mostly originates from the appendix; the clinical pathological

Table 1 Molecular weight and ratio of ascites to plasma drug concentration of chemotherapy agents used for hyperthermic intraperitoneal chemotherapy[17]

Drug	Molecular weight	Ascites to plasma concentration ratio
Doxorubicin	579.99	230
Melphalan	305.20	93
Mitomycin C	334.30	23.5
Cisplatin	300.10	7.8
Gemcitabine	299.50	500.0
Mitoxantrone	517.41	115-255
Oxaliplatin	397.30	16
Etoposide	588.58	65
Paclitaxel	853.90	1000
Docetaxel	861.90	552
5-Flurouracil	130.08	250
Floxuridine	246.20	75
Carboplatin	371.25	10

process is also typical PC[16].

MECHANISMS OF ACTION OF HIPEC TO TREAT PC

The mechanisms of HIPEC to treat PC cover several aspects. (1) Pharmacokinetic advantages. The peritoneum-plasma barrier prevents the peritoneum from absorbing large-molecular-weight drugs, leading to high concentrations of HIPEC drugs in the abdominal perfusion solution, and relatively lower drug concentrations in peripheral blood. As a result, HIPEC increases the direct cytotoxic effects of drugs on peritoneal surface tumors, and reduces the systemic adverse effects at the same time. The concentration ratio of common chemotherapy drugs in abdominal perfusion solution and peripheral blood is summarized in Table 1[17]; (2) the tolerance of normal tissue and cancer tissue to hyperthermia is different. Hyperthermia has multiple adverse effects on cancer cells. First, hyperthermia causes tumor microvessel embolism at the tissue level, resulting in ischemic necrosis of tumor tissue. Second, hyperthermia disturbs cancer cell homeostasis and energy metabolism, activates the lysosomes, destroys the cytoplasm and nucleus, directly killing cancer cells in S and M phase of the cell cycle. Third, hyperthermia also disrupts cancer cell membrane proteins at the molecular level, and interferes with the synthesis of DNA, RNA and protein; and (3) the synergistic effects of hyperthermia and chemotherapy could be dramatically increased at 42 ℃, significantly enhancing the cytotoxic effects of many chemotherapeutic agents such as oxaliplatin, cisplatin and mitomycin C[18-20].

The timing of HIPEC treatment is crucial. The effect of postoperative peritoneal chemotherapy is inferior to the intraoperative chemotherapy because of the abdominal adhesions and catheter complications. HIPEC should be performed immediately after the completion of CRS, because at this time there is no peritoneal adhesion, minimal residual tumor burden, and homogeneous distribution of chemotherapy perfusion solutions in the abdominal cavity.

INDICATIONS AND CONTRAINDICATIONS

For PC originating from abdominopelvic tumors, such as gastric cancer, colorectal cancer, appendiceal cancer, ovarian cancer, primary peritoneal cancer and peritoneal mesothelioma, if the primary tumor could be radically resected or optimal cytoreduction could be achieved and there is no widespread systemic metastases, HIPEC is recommended as the treatment of choice on the following conditions: (1) age 20-75 years; (2) Karnofsky performance status scale > 70; (3) positive free cancer cells in ascites or abdominal lavage solution; (4) peritoneal metastasis with peritoneal cancer index (PCI) < 20; and (5) patients with high risk of peritoneal dissemination, such as tumor perforation, complete bowl obstruction, or tumor invading the serosa layer or adjacent organs. The contraindications are: (1) age < 20 or > 75 years; (2) any lung, liver, brain or bone metastasis, or prominent retroperitoneal lymph node metastasis during preoperative assessment; (3) moderate-severe contraction of mesentery; and (4) obvious contraindications for routine operation.

PREOPERATIVE EXAMINATIONS

Imaging examinations

Complete preoperative imaging could help select appropriate patients for CRS + HIPEC treatment and to formulate CRS procedures. Two major forms of preoperative imaging examinations are particularly useful. (1) Static imaging examination: after proper abdominopelvic preparation, the patients undergo abdominopelvic multi-detector row computed tomography (CT) plus multiplanar reconstruction. The overall sensitivity and specificity of such high-resolution three-dimensional CT examination could reach 78.1% and 92.3%, respectively. The detection sensitivity could be 90% for lesions ⩾ 0.5 cm in diameter, but reduced to 42.6% for lesions < 0.5 cm in diameter. The degree of fitness between the CT-PCI and the intraoperative PCI is 0.384-0.640[21]. Typical CT signs of PC include peritoneal thickening with contrast enhancement, thickening of the greater omentum dotted with nodules, streaks and cloud-like forms caused by uneven contrast enhancement, uneven distribution of the small intestines with enlarged or narrow lumens, contrast-enhanced nodules on the intestine mesentery showing a pepper-like sign, and ascites. Preoperative CT-PCI score could be estimated according to the typical imaging signs and lesion size, so as to determine the extent of PC. Apart from routine CT examination, positron emission tomography-CT

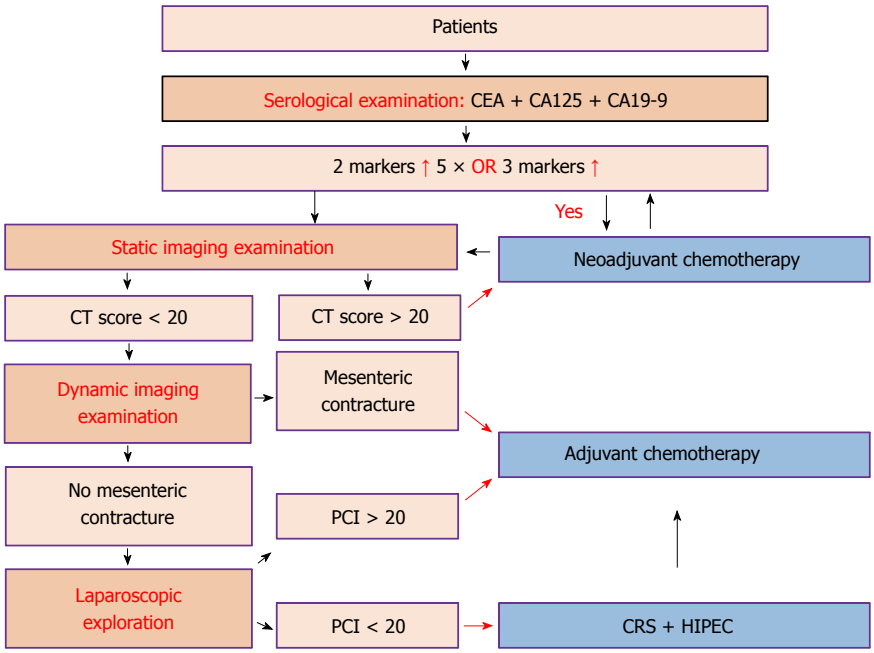

Figure 1 Clinical pathway for treatment of peritoneal carcinomatosis based on diagnostic systems. PCI: Peritoneal cancer index; CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen; CT: Computed tomography; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy.

examination is an alternative consideration; and (2) dynamic imaging: oral gastrografin radiography of the whole digestive tract could be used to observe the intestinal peristalsis, distribution status and the duration of the contrast medium to pass through the small intestine, so as to evaluate gastrointestinal motility, intestinal obstruction and mesenteric contracture. The following three imaging characteristics indicate that it is hard to achieve complete cytoreduction: (1) intestinal segmental obstruction; (2) intermingling existence of tumor, small intestine and mesentery; and (3) tumor nodules > 5 cm on the intestinal surface or mesentery. HIPEC should be carefully weighed if the above-mentioned features are obvious. Laparoscopic exploration is a proper choice when it is necessary to score the PCI, estimating whether the CCR0-1[22] resection is achievable before the final determination of whether the CRS + HIPEC procedure should be performed.

Hematological examination

Apart from routine hematological examinations, the detection of serum tumor markers is necessary and the combined detection of carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125 and CA19-9 is the first choice. CEA, CA125 and CA19-9 can also be used, respectively, to judge the extent of tumor invasion, ascites and peritoneal tumor burden, and proliferative activity of tumor cells in ascites or primary tumor[23-31].

Laparoscopic exploration and exfoliative cytology

In order to determine more accurately cancer stage, better evaluate the abdominal organ involvement, and determine the feasibility of complete cytoreduction, laparoscopic exploration is helpful if diagnosis cannot be established through imaging. Exfoliative cytology examination and pathological biopsy are both also important to establish the disease stage and treatment strategy. According to the examination results, the recommended clinical pathway is shown in Figure 1.

DETERMINATION OF PCI

Sugarbaker's PCI is the standardized intraoperative staging system to determine the PC burden[22]. The abdomen is divided into 13 areas, and the total score of each area is the PCI (Figure 2). PCI score is important to select appropriate patients for CRS + HIPEC.

CRS + HIPEC PROCEDURE

Cytoreductive surgery

CRS is performed under general anesthesia. The patient is placed in the lithotomy position, and pressurized inflatable insulating protective bags are wrapped around both lower extremities to prevent the formation of deep vein thrombosis. A preoperative conventional nasogastric tube and urinary catheter are installed.

The long midline xyphoid-pubic incision is made for proper abdominal exposure, so as to evaluate the PCI score thoroughly (Figure 2). Generally, CRS is performed in the following order: round ligament of liver, greater/lesser omentum, right/left upper quadrant, right/left diaphragmatic copula peritoneum, parietal peritoneum, right/left iliac fossa peritoneum, pelvic peritoneum, and small intestine mesentery.

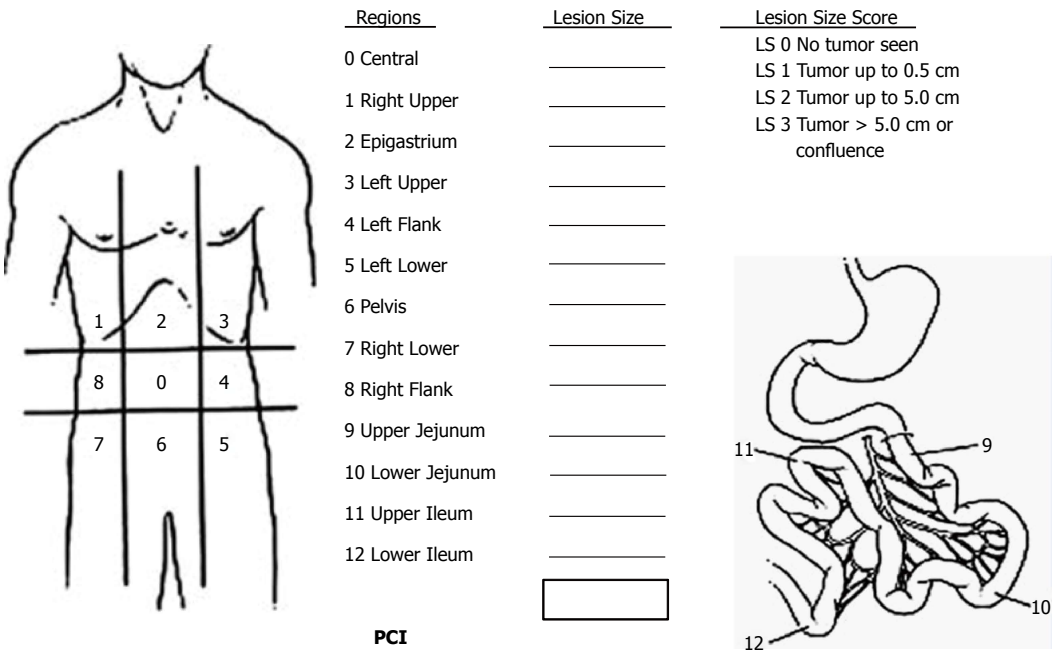

Figure 2 Peritoneal carcinomatosis index staging system[31]. PCI: Peritoneal cancer index.

The optimal CRS also includes stripping the whole parietal peritoneum, resecting the visceral peritoneum and tumor-involved intestinal tract. Cholecystectomy, splenectomy, rectectomy, hysterectomy and bilateral salpingo-oophorectomy are all necessary if tumor implants are observed in the gallbladder fossa, spleen fossa and Douglas cavity. A ball-tipped electrotome or electric evaporator could be used to carbonize the tumor tissue if the tumor is adhered to important organs and cannot be removed. At the completion of CRS, CC score is evaluated and recorded according to the Sugarbaker's criteria on the completeness of cytoreduction[22].

After CRS, open or closed HIPEC is performed. The chemotherapy drugs commonly used for HIPEC are cisplatin (20 mg/L), oxaliplatin (25 mg/L), mitomycin C (5 mg/L) and docetaxel (20 mg/L); each dissolved in 3 L warmed nature saline at 43 ± 0.5 ℃ and then delivered into the abdominal cavity from an automatic hyperthermia chemotherapy perfusion device through the inflow tube placed under the diaphragm at a speed of 400 mL/min. The temperature of the perfusion solution in the peritoneal space is monitored with a thermometer in real time. The total HIPEC time is 60-90 min; after which the perfusion solution is removed through the suction tube, and the abdominal cavity is washed with 2-3 L warm normal saline. Reconstruction of the gastrointestinal system is made before or after HIPEC, and an intestinal stoma is made if necessary. The abdominal wound is closed using a double-layer relaxing suture. After operation, the patient is delivered to the intensive care unit for recovery. When the condition becomes stabilized, usually 24-48 h later, the patient is transferred to the surgical oncology ward and receives early postoperative intraperitoneal chemotherapy.

Completeness of cytoreduction

The extent of CRS determined by Sugarbaker's criteria on the completeness of cytoreduction (CC)[22] is closely correlated with OS. A score of CC-0 indicates no residual peritoneal disease after CRS; CC-1, < 2.5 mm of residual disease; CC-2, residual tumor between 2.5 mm and 2.5 cm; and CC-3, > 2.5 cm of residual tumor or the presence of a sheet of unresectable tumor nodules.

ADVERSE EVENTS

The incidence of adverse events of CRS + HIPEC is 27%-56%[32], mainly including abdominal abscess, anastomotic leakage, biliary leakage, intestinal leakage, intestinal obstruction, incision dehiscence, pulmonary infection, hematological toxicity, deep vein thrombosis, pleural effusion, congestive heart failure, cerebral infarction, and moderate to severe hypoalbuminemia. These adverse events are correlated with PCI score, operation duration, the number of anastomoses and organ or peritoneum resected[33].

The perioperative mortality of CRS + HIPEC is 0%-11% in the US, with the most common causes being intestinal leakage, bone marrow suppression, respiratory failure, infection by methicillin-resistant *Staphylococcus aureus* and pulmonary embolism. Poor risk factors include massive malignant ascites, poor performance status, and intestinal obstruction[32]. In a randomized controlled clinical study for gastric carcinoma PC from China[7], nine serious adverse events occurred in 68 cases; four in the CRS group (11.7%) and five in the CRS + HIPEC group (14.7%,

Table 2 Results of phase Ⅱ clinical studies on colorectal peritoneal carcinomatosis treated with hyperthermic intraperitoneal chemotherapy[35]

Ref.	Year	Patients	Mean follow-up (mo)	Overall survival in years				
				1	2	3	4	5
Schneebaum *et al*	1996	15	15	-	-	-	-	-
Elias *et al*	1997	23	12	88%	55%	40%	-	-
Fujimura *et al*	1999	14	-	51%	-	21%	-	-
Loggie *et al*	2000	38	27	60%	39%	24%	-	-
Cavaliere *et al*	2000	14	30	-	64%	-	-	-
Witkamp *et al*	2000	29	38	82%	45%	23%	-	-
Beaujard *et al*	2000	21	12	50%	-	-	-	-
Piso *et al*	2001	17	39	-	-	-	75%	-
Elias *et al*	2001	64	36	60%	47%	36%		27%
Culliford *et al*	2001	47	17	-	-	-	-	28%
Zoetmulder *et al*	2002	35	-	-	-	-	-	20%
Shen *et al*	2003	40	52	60%	-	24%	-	-
Pilati *et al*	2003	34	14	-	31%	-	-	-
Pestieau *et al*	2003	99	-	100%	-	-	-	30%
Glehen *et al*	2004	53	-	55%	-	-	-	11%
Total	-	543	10-52	-	> 40%	-	-	20%

P = 0.839), and the median survival was 5.0 and 3.0 mo, respectively. Serious adverse events are independent negative prognostic factors for survival.

There are two interesting phenomena observed after CRS + HIPEC: (1) few patients require a second operation for intra-abdominal adhesion; and (2) Iitra-abdominal adhesion is less than expected for patients who undergo second-look surgery.

Although the incidence of adverse events is high for CRS + HIPEC, the prognosis of these patients would be even worse without this procedure[34].

CLINICAL EFFICACY OF CRS + HIPEC IN PC

Colorectal cancer PC

Data from single center phase Ⅱ studies of CRS + HIPEC for colorectal cancer PC (Table 2)[35] showed a 3-year survival rate of 21%-40%, which is significantly better than for systemic chemotherapy. A systematic review by Glehen *et al*[36] on 506 patients with colorectal cancer PC treated by CRS + HIPEC revealed a median overall survival rate of 19.2 mo, and 3- and 5-year survival rates of 39% and 19%, respectively.

The Netherlands Cancer Institute conducted the first phase Ⅲ prospective randomized controlled clinical study, which randomly divided colorectal PC patients into palliative surgery plus systemic chemotherapy (5-fluorouracil/leucovorin) group (*n* = 51) and CRS + HIPEC + systemic chemotherapy group (*n* = 54). The median OS was 12.6 and 22.4 mo (*P* = 0.032) for the two groups, respectively. Although the complete cytoreduction rate for the study group was < 40%, the survival rate was higher than any other treatment strategies so far, and the result is convincing[8]. When the median follow-up time extended to 8 years (72-115 mo), the median OS was still 12.6 mo for the former group, but the latter was 22.2 mo (*P* = 0.028)[37], proving once again that CRS + HIPEC can prolong the survival time of colorectal carcinoma PC patients.

A series of clinical studies on colorectal cancer PC treatment has been conducted at Zhongnan Hospital of Wuhan University and Hubei Provincial Cancer Clinical Study Center[38]. Retrospective case-control results showed that the median OS of the treatment group was 13.7 mo (95%CI: 5.0-16.5 mo), significantly higher than that of 8.5 mo (95%CI: 4.7-12.4 mo) in the control group (*P* = 0.02)[39]. A phase Ⅱ clinical study showed that the 1-, 2-, 3- and 5-year survival rates can reach 70.5%, 34.2%, 22% and 22%, respectively.

At present, CRS + HIPEC have been widely accepted in many European countries and Australia as standard care for selected patients with colorectal PC. The 5-year survival rates for such patients treated by CRS + HIPEC was > 50% in the Netherlands, about 25% in the United Kingdom, 30% in France, 35% in Australia and > 30% in the United States. Therefore, the Peritoneal Surface Oncology Group International (PSOGI) considers it imperative to perform prophylactic HIPEC for patients with colorectal cancer to reduce the risk of peritoneal metastases, so as to evaluate how effective such an approach is in reducing the risk of peritoneal metastases as well as liver metastases. Currently, prospective controlled clinical studies on prophylactic HIPEC for patients with colorectal cancer with a high risk of peritoneal metastases have been carried out by several cancer treatment centers to assess the safety and feasibility of this approach for prevention of peritoneal recurrence of colorectal cancer.

Gastric cancer PC

There are several non-randomized clinical studies of CRS + HIPEC for treatment of gastric PC (Table 3)[40-50]. Yonemura *et al*[50] conducted the largest series of studies, which demonstrated that the 1- and 5-year survival rate for the 83 patients with gastric PC treated with CRS + HIPEC (mitomycin C, etoposide and

Table 3 International studies on gastric peritoneal carcinomatosis treatment by cytoreductive surgery + hyperthermic intraperitoneal chemotherapy

Ref.	Patients	Staging criteria	CCR0 *n* (%)	HIPEC	Morbidity *n* (%)	Mortality *n* (%)	Median follow-up (mo)	Median survival (mo)	Overall survival in years		
									1	2	5
Yonemura *et al*[42]	107	Japanese General Rules for Gastric Cancer Study	47 (43.9)	Open technique, MMC 30 mg, DDP 300 mg, Etoposide 150 mg, 8 L of normal saline, 42-43 ℃, 60 min	23 (15.9)	3 (2.8)	46	11.5 CCR 0: 19.2 CCR 1-3: 7.8	35.5%	13.1%	6.7%
Yonemura *et al*[50]	83	Japanese General Rules for Gastric Cancer Study	28 (33.7)	Open technique, MMC 30 mg, DDP 300 mg, Etoposide 150 mg, 8 L of normal saline, 42-43 ℃, 60 min	-	-	46	CCR 0: 13.9 CCR 1-3: 6.8	43.0%	-	11.0%
Yonemura *et al*[43]	48	Japanese General Rules for Gastric Cancer Study	-	Open technique, MMC 30 mg, DDP 300 mg, 8 L of normal saline, 42-43 ℃, 60 min	9 (19.0)	2 (4.0)	-	-	-	-	61.0%
Scaringi *et al*[44]	26	Gilly's Classification	8 (30.8)	Close technique, MMC 120 mg, DDP 200 mg, 6 L of normal saline, 42-43 ℃, 90-120 min	10 (38.5)	1 (3.8)	-	6.6 CCR 0: 15 CCR 1-3: 3.9	-	-	-
Fujimoto *et al*[45]	15	-	-	Close technique, MMC 30-50 mg, 44.7-48.7 ℃, 120 min	2 (13.3)	0	-	7.2 ± 4.6	-	-	-
Fujimoto *et al*[6]	71	TNM Classification	71 (100.0)	Close technique, MMC 10 mg/mL, 44.5-45 ℃, 120 min	2 (2.8)	0	7	-	88.0%	76.0%	2.0%
Hall *et al*[46]	34	-	7 (21.0)	Close technique, MMC 10 mg/mL, 40 ℃, 120 min	12 (35.0)	0	-	8	27.0%	23.0%	6.0%
Fujimura *et al*[47]	31	Japanese General Rules for Gastric Cancer Study	2 (16.0)	Open technique, MMC 20 mg/m^2, DDP 200 mg/m^2, 6 L of normal saline, 42-52 ℃, 90-120 min	6 (19.4)	0	-	9	33.3%	8.3%	0.0%
Hamazoe *et al*[48]	42	-	40 (95.0)	Close technique, MMC 10 μg/mL, inflow temperature 40-45 ℃, outflow temperature 40-42 ℃, 60 min	2 (4.8),	0	> 6	77	90.0%	80.0%	64.3%
Kim *et al*[49]	52	TNM Classification	-	Close technique, MMC 10 μg/mL, inflow temperature 44 ℃, 20 min	19 (36.5)	0	38	36	-	-	32.7%
Yang *et al*[7]	68	Sugarbaker's Classification	20 (58.5)	Open technique, MMC 30 mg, DDP 120 mg, 42 ℃, 120 min	5 (14.7)	0	32	PCI ≤ 20 13.5 PCI > 20 10.2			
Chen *et al*[40]	500	-	-	Open technique, Chlorhexidine diacetate hydrate 0.6 g, 4 L of distilled water, 43 ℃, 4 min	-	-	-	-	88.7%	66.2%	63.6%
Zhu *et al*[41]	52	-	-	Open technique, DDP 50 mg/L, MMC 5 mg/L, 43 ℃, 60 min	-	-	72	-	76.9%	69.2%	55.2%

cisplatin) was 43% and 11%, respectively. The Lyon Research Center reported that 1- and 5-year survival rate was 48% and 16%, respectively, and the median survival was 10.3 mo[35].

Chen *et al*[40] at China Medical University conducted clinical studies on intraperitoneal chemotherapy to treat gastric cancer, in which 500 patients with gastric cancer who underwent radical resection were divided into three groups: Group A (n = 198) treated by peritoneal lavage with 4 L of distilled water at 43 ℃ for 10 min after radical resection; Group B (n = 89) treated by peritoneal lavage with 0.6 g chlorhexidine acetate dissolved in 4 L distilled water at 43 ℃ for 4 min after radical resection; and Group C (n = 213) treated by peritoneal lavage with 4 L normal saline for 4 min at room temperature after radical resection. The results showed that the effect was the same between Groups A and B, with no significant difference. The

5-year survival rates for the first two lavage groups and control group were 63.8% and 51.2%, respectively.

Zhu *et al*[41] at Shanghai Ruijin Hospital also studied the clinical efficacy of HIPEC to treat advanced gastric cancer. The 1-, 2- and 4-year survival rates for patients who underwent surgery plus HIPEC were 85.7%, 81.0% and 63.9%, respectively, which was better than that of those who underwent simple surgery (77.3%, 61.0% and 50.8%).

Yang *et al*[7,14,34] at Zhongnan Hospital of Wuhan University have conducted a series of clinical studies on CRS + HIPEC to treat gastric cancer PC. A phase Ⅰ clinical study demonstrated the safety of the therapy. In a phase Ⅱ study, 28 patients who underwent CRS + HIPEC treatment showed a 6-, 12-, 18- and 24-mo survival rate of 75%, 50%, 43% and 43%, respectively. For patients with PCI ≤ 20 *vs* > 20, the median OS was 27.7 mo (95%CI: 15.2-40.3 mo) *vs* 6.4 mo (95%CI: 3.8-8.9 mo) (P < 0.001), respectively. For patients with CCR0, CCR1 and CCR2-3, the median OS was 43.4 mo (95%CI: 26.9-59.9 mo), 9.4 mo (95%CI: 7.4-11.4 mo), and 8.3 mo (95%CI: 3.0-13.6 mo) (P = 0.001), respectively. A prospective randomized phase Ⅲ clinical study showed that the median survival time in the control group (n = 34) and treatment group (n = 34) was 6.5 mo (95%CI: 4.8-8.2 mo) and 11.0 mo (95%CI: 5.0-11.9 mo) (P = 0.046), respectively. The median OS for synchronous gastric cancer PC was 12 mo (95%CI: 8.1-15.9 mo) and there was no significant difference in the rate of serious adverse events between the two groups.

Ovarian cancer PC

There is no standard treatment for advanced ovarian cancer. The conventional treatment of stage Ⅲ/Ⅳ ovarian cancer is based on optimal CRS followed commonly by intravenous platinum/taxane-based chemotherapy, but the majority of patients will relapse within 5 years. A phase Ⅱ clinical study conducted by the Italian National Cancer Institute on 27 patients with recurrent ovarian cancer who were treated with HIPEC (cisplatin + mitomycin C) showed a 2-year survival rate of 55%, and a median survival time to tumor local progression time of 21.8 mo[51]. It is worth noting that a phase Ⅲ clinical study containing 415 patients with advanced ovarian cancer showed that the median survival for intravenous plus intraperitoneal combined chemotherapy group was 65.6 mo, compared with 49.7 mo in the systemic intravenous chemotherapy group[52]. This study was evaluated as showing significant progress in clinical gynecological oncology by American Society of Clinical Oncology, and the United States National Cancer Institute also issued a statement to recommend intravenous and intraperitoneal chemotherapy for these patients. Two case-control studies reported recently the advantage of CRS + HIPEC in ovarian cancer. Cascales-Campos *et al*[53] reported a case-control study of 87 patients with stage ⅢC/Ⅳ ovarian cancer. Of the 87 patients, 52 were treated with HIPEC (paclitaxel 60 mg/m^2, 60 min, 42 ℃) and 35 were in the control group. The result showed that the 1-year disease-free survival was 81.0% *vs* 66.0% and 3-year disease-free survival was 63.0% *vs* 18.0% (P < 0.05). Multivariate analysis revealed that HIPEC was an independent prognostic factor for OS. In another case-control study by Safra *et al*[54] from Israel, patients with recurrent ovarian cancer were included in the proportion of 1:3; 27 patients had recurrent epithelial ovarian cancer treated with CRS + HIPEC and 84 matched control patients only had systemic chemotherapy. The median progression-free survival was 15 mo in the HIPEC group and 6 mo in the systemic chemotherapy group (P < 0.01). The 5-year survival rate was significantly higher in the HIPEC group than in the controls (79% *vs* 45%, P < 0.05).

More importantly, Spiliotis *et al*[9] from Greece conducted a double-blind prospective phase Ⅲ clinical trial on CRS + HIPEC in patients with recurrent ovarian cancer. All 120 patients had stage ⅢC/Ⅳ ovarian cancer and experienced disease recurrence after initial surgical treatment and first-line systemic chemotherapy. They were randomized into two groups. Group A comprised 60 patients treated with CRS + HIPEC and then systemic chemotherapy. Group B comprised 60 patients treated with CRS only and systemic chemotherapy. The mean survival was 26.7 mo in Group A *vs* 13.4 mo in Group B (P < 0.01), and the 3-year survival was 75.0 % for Group A *vs* 18.0% for Group B (P < 0.01). In the HIPEC group, the median survival did not differ between patients with platinum-resistant disease and platinum-sensitive disease (26.6 mo *vs* 26.8 mo).

PMP

PMP is the best indication for HIPEC. Four studies evaluating the efficacy of CRS + HIPEC to treat PMP found that the 5-year survival rates were 66%-97%, the adverse events rates were 27%-44%, and the mortality rates were 2.7%-13%[55-57]. Recently, a French multicenter clinical study including 301 PMP patients treated by CRS + HIPEC revealed that the 5-year survival rate was 73% and the disease-free survival rate was 56%, and CRS + HIPEC has become the standard treatment for PMP[5].

Malignant peritoneal mesothelioma

Twenty studies (Table 4) have evaluated the efficacy of CRS + HIPEC to treat malignant peritoneal mesothelioma. The median OS for patients treated with CRS + HIPEC was 29.5-100 mo[58], which was significantly higher than in historical controls (12-17 mo) as previously reported. HIPEC, no deep tissue invasion, age < 60 years and optimal CRS are independent prognostic factors for survival improvement[59]. These data suggest that patients with malignant peritoneal mesothelioma are good candidates for CRS + HIPEC.

Peritoneal sarcoma

Even with radical surgical resection as initial treatment,

Table 4 Results of hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma[58]

Ref.	Patients	Country	Median follow-up (mo)	Median OS (mo)	Median DFS (mo)	Morbidity	Mortality
Baratti *et al*	12	Italy	27	-	24	-	0%
Baratti *et al*	12	Italy	64	-	11	8.3%	0%
Blackham *et al*	34	United States	72	40.8	9.1	-	-
Brigand *et al*	15	France	46.7	35.6	-	-	0%
Chua *et al*	20	Australia	18.1	29.5	7.2	65.0%	5%
Sebbag *et al*	33	United States	21.3	31	-	33.0%	3%
Tudor *et al*	20	Australia	18	30	8	65.0%	5%
Deraco *et al*	61	Italy	20	-	28	23.0%	0%
Deraco *et al*	116	Italy	-	31.4	14.4	41.3%	2.6%
Loggie *et al*	12	United States	45.2	34.2	-	33.0%	8%
Ma *et al*	12	Turkey	10	-	-	90.0%	20%
Macuks *et al*	12	Turkey	-	-	-	-	-
Markman *et al*	19	United States	25	19	-	-	-
Feldman *et al*	49	United States	-	92	17	25.0%	-
Chua *et al*	26	Australia, Italy, France, United States, United Kingdom, Germany	54	-	-	26.9%	0%
Schaub *et al*	104	United States	49.4	52	20.8	-	-
Yan *et al*	401	Australia, Italy, France, United States, United Kingdom, Germany	33	53	-	46.0%	2%
Yano *et al*	17	United Kingdom	13	-	-	41.0%	12%
Yonemura *et al*	21	Japan	-	-	-	46.2%	-
Elias *et al*	26	France	54	> 100	40	54.0%	4%

OS: Overall survival; DFS: Disease-free survival.

the recurrence rate of peritoneal sarcoma can reach 58%-85%[60]. Currently, there is no evidence to indicate that adjuvant therapy improves the survival of these patients. A phase I study including 60 patients with peritoneal sarcoma from Italy evaluated the efficacy of HIPEC in peritoneal sarcoma. The results showed the median time to tumor partial progression was 22 mo, and OS was 34 mo[61]. Histopathology stage and optimal CRS are the key factors for survival improvement.

CONCLUSION

The comprehensive treatment strategy of CRS + HIPEC is an integration of technical advantages of CRS to reduce the tumor burden and HIPEC to eradicate the residual tumor foci, micrometastases and peritoneal free cancer cells, so as to completely eliminate both the primary tumor and metastases[15,62]. Several lines of evidence from well designed clinical studies have indicated that CRS + HIPEC is an effective strategy to treat PC. At the Ninth International Congress on Peritoneal Surface Malignancies held in Amsterdam, the Netherlands, 2014, the PSOGI officially proposed the International Recommendations for Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). CRS + HIPEC is recommended as the standard treatment for appendiceal mucinous cancer, colorectal PC, and malignant peritoneal mesothelioma, and it is a recommended therapy for ovarian cancer and gastric cancer with PC. The PSOGI also emphasized the necessity to carry out strictly designed prospective multicenter randomized clinical studies to improve the treatment strategy and efficacy, and to promote this comprehensive treatment approach in clinical oncology.

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