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## Can hyperthermic intraperitoneal chemotherapy effectively control gastric cancer-associated peritoneal carcinomatosis?

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### Abstract

Gastric cancer-associated peritoneal carcinomatosis leads to a poor prognosis and low quality of life. The current systemic chemotherapy processes cannot effectively improve survival. Hyperthermic intraperitoneal chemotherapy (HIPEC) has been used as an alternative treatment to control this disease through recurrence prevention, definitive therapeutic modality, and symptom palliation. Although HIPEC has been demonstrated to yield favorable results mainly in some Asian studies, widespread adoption of this treatment is still debatable before larger prospective randomized controlled clinical trials confirm its effectiveness.

**Key words:** Hyperthermic intraperitoneal chemotherapy; Gastric cancer; Peritoneal carcinomatosis

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**Core tip:** Peritoneal carcinomatosis associated with gastric cancer leads to poor clinical outcomes and low quality of life. Hyperthermic intraperitoneal chemotherapy can potentially be used for the control of this disease.

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## INTRODUCTION

Peritoneal carcinomatosis (PC) of gastric cancer origin refers to the spreading of gastric tumor cells in the peritoneum<sup>[1]</sup>. PC is characterized by extremely poor prognosis with a residual lifespan of approximately 3-7 mo<sup>[2-5]</sup>. Therefore, the median survival of patients with PC treated with systemic chemotherapy is 9.5-12 mo<sup>[6,7]</sup>. In addition, intractable ascites may severely affect the quality of life and lead to particularly painful sensations and life-threatening consequences in these patients<sup>[8,9]</sup>.

In the past, these patients have been considered incurable and only received palliative systemic chemotherapy without surgical resection<sup>[10,11]</sup>. However, systemic chemotherapy, even with targeted agents, has yielded poor responses<sup>[12]</sup> due to the presence of the "plasma-peritoneal barrier," which separates organs inside the peritoneum from intravenous chemotherapeutic drugs<sup>[13]</sup>. Notably, in the 1980s, a new concept of a "locoregional disease" in patients with PC led to the identification of a new treatment strategy, cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC)<sup>[1]</sup>. After complete CRS of macroscopic tumor resection, intraperitoneal chemotherapy (IC) is performed to maximize the dosage and contact time of chemotherapeutic drugs delivered to intraperitoneal microscopic-free tumor cells while minimizing systemic toxicity. Prolonged drug retention in the peritoneal cavity and clearance from the systemic circulation are considered crucial attributes for the intraperitoneal approach<sup>[14,15]</sup>. Heat has also been proven to be synergistic with the antitumoral effects of chemotherapeutic agents (*e.g.*, mitomycin C, cisplatin, and oxaliplatin)<sup>[16,17]</sup>. Moreover, the addition of extensive intraoperative peritoneal lavage followed by IC with cisplatin yielded significant improvements in 5-year survival in a Japanese gastric cancer study<sup>[18]</sup>. The principle underlying this effect is that the use of a large amount of diluent inside the peritoneum before HIPEC could diminish a majority of free tumor cells, and the combined action of physical injury caused by heat and the chemotherapeutic toxin demolishes the remaining tumor cells<sup>[19]</sup>.

HIPEC has been used in three aspects of gastric cancer management. First, it has been used as an adjuvant approach following curative CRS to extend lifespan and reduce the rate of intraperitoneal recurrence in many Asian randomized clinical trials<sup>[19]</sup>. Second, CRS followed by HIPEC is the sole therapeutic modality in PC management, leading to long-term survival in well-selected patients. Third, HIPEC has been demonstrated to effectively palliate massive ascites and alleviate the need and frequency of paracentesis.

## A METHOD OF RECURRENCE PREVENTION

HIPEC is the most appealing prophylactic treatment of gastric cancer for those with a high risk of recurrence in the peritoneum after curative CRS<sup>[19]</sup>. According to the "tumor cell entrapment hypothesis" proposed by Dr. Sugarbaker, perioperative IC including peroperative HIPEC with or without early postoperative intraperitoneal chemotherapy (EPIC) should be performed to eradicate possible tumor cells released into the peritoneal cavity during cancer resection, transection of lymphatic channels or in cases with close resection margins, and tumor-contaminated blood spillage<sup>[20]</sup>. Several meta-analyses of prophylactic IC for carcinomatosis prevention have been published. Sun *et al*<sup>[21]</sup> stated a substantial extent of lifespan after HIPEC despite the use of different chemotherapeutic drugs (mitomycin C or 5-fluorouracil) and irrespective of whether adjuvant intravenous chemotherapy was applied. Mi *et al*<sup>[22]</sup> reported that HIPEC could reduce the 5-year recurrence rate in the peritoneum even with six different combinations of chemotherapeutic drugs (5-fluorouracil, mitomycin C, cisplatin, cisplatin and 5-fluorouracil, cisplatin and mitomycin C, mitomycin C and 5-fluorouracil). However, neither of these studies demonstrated increased postoperative morbidity after HIPEC<sup>[21,22]</sup>. Huang *et al*<sup>[23]</sup> and Yan *et al*<sup>[24]</sup> demonstrated a higher incidence of postoperative neutropenia and abscess formation after HIPEC

with four different combinations of chemotherapeutic drugs (5-fluorouracil, mitomycin C, cisplatin and mitomycin C, mitomycin C and 5-fluorouracil) but with no effect on mortality rate. Moreover, sole prophylactic HIPEC or HIPEC combined with EPIC yielded survival benefits. Yonemura *et al*<sup>[25]</sup> reported a 5-year survival rate reaching 42% in a study group comprising 15 Cy+/P0 patients with combined cisplatin and mitomycin C regimen. Grossly, this prophylaxis strategy in patients with nodal metastasis or serosal invasion has been proven effective and safe. Nevertheless, a large percentage of these randomized clinical trials were conducted in Asian countries, and clinical trials in Western countries were scant<sup>[19]</sup>.

## A DEFINITIVE THERAPEUTIC MODALITY

In 1996, Yonemura *et al*<sup>[15]</sup> reported a 5-year-survival rate of 11% in a study of treatment with HIPEC using regimen of cisplatin and mitomycin C and etoposide, after CRS in 83 patients with PC. The first study of the West reported in 1999 was a phase II study of 42 patients receiving HIPEC with mitomycin C regimen. Sayag-Beaujard *et al*<sup>[26]</sup> reported an overall median survival of 10.3 mo and a 5-year survival rate of 8%. However, a low tumor load (peritoneal cancer index, PCI) and complete cytoreduction [completeness of cytoreduction (CC) score = 0] would lead to ideal survival. One 49-patient study by Glehen *et al*<sup>[27]</sup> published in 2004 showed that the median survival reached 21.3 mo and 5-year survival rate increased to 29.4% after CC-0/1 resection and HIPEC with mitomycin C regimen. This improvement in clinical outcomes demonstrated the significance of proper patient selection and technical progress in complete cytoreduction as experience increased.

However, the patients may face risks of complications and mortality. Gill *et al*<sup>[28]</sup> summarized the results of ten studies and demonstrated a complication risk of 21.5% and average mortality rate of 4.8%. Common complications included ileus, anastomotic leakage, intra-abdominal abscess, digestive fistula, and hematologic toxicity<sup>[28-31]</sup>. Therefore, appropriate selection of candidates for this treatment is essential. During preoperative evaluation, a low PCI score and low CC score are essential prognostic factors. Moreover, preoperative PCI scores indirectly forecast the possibility of complete cytoreduction during operation. Yonemura *et al*<sup>[32]</sup> demonstrated complete cytoreduction of 86%, 39%, and 7% in their patients when the PCI score was  $\leq 6$ ,  $>7$ , and  $> 13$ , individually. Suitable indications of CRS and HIPEC for gastric cancer-related PC should include younger age ( $< 60$  years), low PCI scores (lower than 10 points), no para-aortic lymph node involvement, no distant metastasis, and a high possibility of complete cytoreduction<sup>[27,30,32-34]</sup>.

## A METHOD OF SYMPTOM PALLIATION

For symptomatic patients with malignant ascites and complete cytoreduction deemed impossible<sup>[19]</sup>, many oncologists have suggested performing HIPEC to relieve the symptoms caused by ascites related to PC<sup>[35]</sup>. Yonemura *et al*<sup>[36]</sup> and Fujimoto *et al*<sup>[37]</sup> advocated effective resolution of ascites in patients after HIPEC treatment. In addition, some studies have reported the successful use of laparoscopic HIPEC to palliate the ascites-related symptoms, to reduce the frequency of repeated paracentesis, and to avoid any significant morbidity or mortality<sup>[38]</sup>. Moreover, laparoscopic HIPEC could shorten the operation time and length of admission<sup>[39,40]</sup>.

## PERSPECTIVE

In the past two decades, the use of CRS and HIPEC in gastric cancer-related PC management has been debatable. Although preliminary data from Asian studies were scrutinized with considerable skepticism, indications of HIPEC in PC treatment remain elusive. Additional large prospective randomized controlled clinical trials are warranted to achieve consensus regarding the use of HIPEC as a gold standard.

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