

Morbidity and mortality of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in advanced gastric cancer

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Abstract: Gastric cancer (GC) is one of the leading cancer causes of death worldwide with high incidence of mortality. With limited available data from the previous literature, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) seems to provide substantial survival benefits to the advanced GC patients, especially in those with peritoneal carcinomatosis (PC). However, it is also considered as a high morbid approach. This review summarizes the current evidence regarding the perioperative safety of CRS-HIPEC in advanced GC patients. According to the currently available evidence, CRS-HIPEC causes surgery-related morbidity including abscess, fistula, and anastomotic leak, and chemotherapy-related morbidities such as leucopenia, anemia, thrombopenia, and heart, liver or renal toxicity. The incidence of the morbidity and mortality approximate 20% and 4.8% respectively, which are comparable to a major gastrointestinal surgery. Repeated evidence demonstrates that incidence of morbidity or mortality is significantly influenced by the institutional experience. Centers undertaking this treatment strategy must aim to minimize morbidity and mortality by learning from the experienced units and carefully selecting candidate patients. Patients with advanced age or greater disease burden seem to be at greater risks and thus application of CRS-HIPEC on them must be based on an extensive evaluation and multi-disciplinary team (MDT) discussion.

Keywords: Morbidity; mortality; cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy (HIPEC); gastric cancer (GC)

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Introduction

Gastric cancer (GC) is one of the leading cancer causes of death worldwide with high incidence and cancer-related mortality (1). The highest rates of GC in the world occur in Eastern Asia. In China, GC is one of the most common malignancies, and its diagnosis usually occurs at a late stage when treatment becomes difficult. Although, there have been rapid progresses in research and clinical care in GC during the past few years, patients with GC and peritoneal carcinomatosis (PC) have limited intervention options due

to poor response to systemic chemotherapy, and the survival rate is extremely low. Once GC spread to the peritoneum, the 5-year survival is expected to be less than 5% (2).

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to dramatically improve survival in patients with PC from colorectal cancer, and similar findings have also been reported in patients with advanced GC with PC (2,3). In a recent report, in patients with adjuvant HIPEC performed with R0 gastric surgery, the 3- and 5-year overall survival rate was 94.0% and 86.8% in patients with

HIPEC and 59.1% and 53.4% in patients without HIPEC ($P < 0.0001$) respectively (4).

With an increasing number of centers applying the cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) approach; its safety becomes an important issue. Chemotherapy agents are known to cause systematic toxicity to normal tissues and deteriorate wound-healing process. High procedure-related morbidity and mortality related to the CRS-HIPEC approach has been under debate for years. To this end, the aim of this review is to summarize the current evidence regarding the perioperative safety of CRS-HIPEC in advanced GC patients.

Types

The morbidity after CRS-HIPEC can be divided into two major parts: surgery-related ones and chemotherapy-related ones. Chemotherapy is known to influence the wound healing process, and increases the risks of infectious complications. Intraoperative application of it may cause the surgery-related morbidity include abscess, fistula, and anastomotic leak, which are found to be the most common ones by the systematic review from Gill *et al.* (3). Other surgical related morbidities includes postoperative ileus, wound infection, bleeding, thrombosis and lung embolism (5). It seems that all these morbidities are also commonly seen after gastrectomy, while whether application of HIPEC further increase their incidence remains an unsolved question without direct evidence. However, Mizumoto *et al.* found that HIPEC did not increase postoperative morbidity, instead it reduced the postoperative complication rate (6). The authors argued that this was because disease burden has been identified as a prognostic indicator not only to the survival but also to the postoperative complications, HIPEC may help to decrease morbidity via reducing the tumor burden in the patients with PC. Such findings are undoubtedly promising, but solid proven still requires further demonstration in other databases or centers.

When compared with the systematic chemotherapy, one evident advantage of HIPEC is that it delivers high concentrations of chemo agents directly into the abdominal cavity, which may theoretically reduce systemic toxicity (7). However, the cytotoxic agents used for HIPEC, though in lower concentration compared with the systematic chemotherapy, are still partly released into the circulation, which inevitably lead to the systematic side effects include leucopenia, anemia, thrombopenia, and heart, liver or renal

toxicity. In addition, catheter-related complications are also related to the HIPEC, but is relatively less frequently reported compared with the other morbidities (7).

Incidence

CRS-HIPEC is considered as a high morbid procedure. The early attempt from Fujimura *et al.* reported a morbidity of 50% and a reoperation rate of 33.3% (8). Better outcomes have been reported by later studies, ranging from 9.6% to 55.6%, with a median rate approximating 20%; the reported mortality rate varies between 0% and 14.3%, with a median rate of 4.8% (3).

Whether such morbidity and mortality rate is higher than the CRS alone is still inconclusive. Data from colorectal cancer patients are quite similar to the gastric ones. Chua *et al.* reported the morbidity rates ranged from 12% to 52% and the mortality rates ranged from 0.9% to 5.8% in colorectal patients with CRS-HIPEC (9), which is actually comparable to the data from GC patients with PC. The authors also stated that the overall morbidity and mortality rates of CRS-HIPEC are comparable to that of a major gastrointestinal procedure, a Whipple's procedure for example (9). Owing the fact that GC with PC is a fatal status with conventional interventions, such morbidity and mortality rate seems acceptable.

Risk factors

Very limited data are available regarding the risk factors of morbidity and mortality in GC patients undertaken CRS-HIPEC. To the best of our knowledge, the only reported "independent" prognostic indicator for postoperative complications for CRS-HIPEC of gastric origin is, nevertheless, institution ($P < 0.0001$) (10). Although the same study also reported that old patients (more than 60 years old) suffered a much higher rate of postoperative complications than the younger ones (44.7% vs. 23.4%, $P = 0.10$), or early postoperative intraperitoneal chemotherapy was also associated with morbidity of 60% while the others morbidity was 28.8%, these factors, together with other common risk factors such as sex, performance status, neoadjuvant therapy, and period of procedure were not identified as independent prognostic factors in the multivariate analysis (10).

Such results are certainly unexpected, but it still can be explained with the limited number of included patients in most studies. Larger scale studies are still needed to

establish specific risk factors of morbidity and mortality in CRS-HIPEC in GC patients. On the other hand, we believe it remains reasonable to carefully evaluate and select the patients with the common risk factors of CRS-HIPEC morbidity including advanced age, smoking, high disease burden (such as PC index) and poor completeness of cytoreduction (CC) (6,11,12) before more specific data regarding GC are available.

How to improve?

The purpose of this review is to summarize the current evidence regarding the perioperative safety of CRS-HIPEC in advanced GC patients. This is of critical importance because its morbidity and mortality needs to be weighed against the survival benefits, and centers undertaking this treatment strategy must aim to minimize the morbidity and mortality to actually bring the benefits to the advanced GC patients.

Techniques and experiences

Although HIPEC seems to be a simple procedure, data from the previous studies clearly and strongly emphasize the importance of the institution experience (10,13,14) and individual (14) experience of surgeons performing it, which both substantially influence both mortality and morbidity.

As stated above, Glehen *et al.* found that institution was the only independent prognostic indicator of postoperative complications in their database ($P < 0.0001$) (10). Based on such data, choosing the right institution seems paramount during the treatment. Direct interpretation of such results may be discouraging since it seems new centers should not further attempt this strategy due to the high morbidity and mortality. However, data from the colorectal cancer studies have brought some good news in this regard. Many studies have demonstrated impressive reductions in morbidity and mortality are approachable over time in specialized centers (15).

The improvement, or so-called “learning curve”, consists of a combination of surgical and institutional awareness of this issue. For example, from a surgical or technical point of view, Feingold *et al.* suggested technical tips such as complete drainage and lavage before GI reconstruction, fresh cutting edges for anastomotic construction and avoidance of excessive peritoneal stripping to reduce morbidity and mortality after CRS-HIPEC (16). At the same time, a institutional awareness and willingness to learn from experienced centers to understand the infrastructure requirements are also needed to improve the CRS-HIPEC service (17). Multi-disciplinary

team (MDT) may be of great assistance in this regard.

Patient selection

Of course, it is important to note that, the “experience” and “learning curve” consists of not only “how” to apply HIPEC, but also “when and to whom” to perform this intervention. The improved surgical decision-making and patient selection remain critical to provide better outcomes to the patients.

Selection of patients can be at least divided into two steps. The first step is to determine whether CRS-HIPEC is of any survival benefits to a candidate patient. In this regard, Peritoneal Cancer Index (PCI) and CC should be carefully evaluated. Glehen *et al.* reported that no patient was alive at 6 months when they had a PCI more than 19 and none at 3 years when they had a PCI more than 12 (10). Given high morbidity and mortality rates after the approach, performing CRS-HIPEC in patients with high PCI should be carefully re-considered.

CC is another factor determining the effect of CRS-HIPEC. Early retrospective data reported median survival of 60 months in patients with CC0 in PC of colorectal origin (18). Review of the GC data also revealed similar outcomes. Scaringi *et al.* reported median survival for patients who underwent CC0 resection is 15 months, while the ones with CC2 only had median survival of 3.9 months ($P = 0.007$) (19). Patients with CC0 or CC1 have a doubled median survival compared to the ones with CC2 or higher (7.9 *vs.* 15 months) (10), which highly suggests that the CRS-HIPEC approach should be applied only when surgeons are confident of a CC0.

Another step is to evaluate whether a patient is at higher risks of the morbidity or even mortality that might overwhelm the benefit of CRS-HIPEC. Though failed to be identified as an independent risk factor, old patients still suffer a much higher rate of postoperative complications than the younger ones (44.7% *vs.* 23.4%, $P = 0.10$) (10). Other prognostic indicators including disease burden and CC also influence the eventual benefit of CRS-HIPEC to the patient. We suggest that MDT should discuss carefully on those high-risk cases to determine whether CRS-HIPEC or other intervention (including the palliative ones) should be further applied.

Conclusions

With limited data from the previous literature, CRS-

HIPEC still seems to provide substantial survival benefits to the advanced GC patients. However it is also a high morbid approach, causing surgery-related morbidity including abscess, fistula and anastomotic leak, and chemotherapy-related morbidities such as leucopenia, anemia, thrombopenia and heart, liver or renal toxicity. The incidence of the morbidity and mortality is reported to be approximating 20% and 4.8% respectively, and is significantly influenced by the institutional and individual experience. Centers undertaking this treatment strategy must aim to minimize morbidity and mortality by learning from the experienced units and carefully selecting candidate patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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