Current Status and Future Directions in Gastric Cancer with Peritoneal Dissemination

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KEYWORDS

- Peritoneal carcinomatosis • Gastric cancer • Treatment • Cytoreductive surgery
- HIPEC

KEY POINTS

- Combined cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) might be an additional therapeutic option for highly selected patients with peritoneal carcinomatosis arising from gastric cancer.
- Complete macroscopic cytoreduction (CC-0/1) is a precondition for a possible survival benefit.
- Consistent preoperative patient selection including laparoscopy is crucial to obtain complete macroscopic cytoreduction.
- Further prospective randomized trials are needed to assess the roles of cytoreductive surgery and HIPEC as an inherent part of an interdisciplinary treatment concept for patients with advanced gastric cancer and to standardize HIPEC protocols.

INTRODUCTION

Although the incidence of gastric cancer decreased during the past years, it is still the fourth most common newly diagnosed cancer worldwide and the second leading cause of cancer-related death.[1] Peritoneal metastasis is a common sign of advanced tumor stage, tumor progression, or disease recurrence in patients with gastric cancer. It might be already present in 5% to 20% of patients undergoing gastric resection in curative intent.[2] In a retrospective analysis of 1172 patients with gastric cancer after R0 resection, the peritoneal recurrence rate was 29%. In this study, the median time from recurrence at any location to death was 6 months.[3] Sasako and colleagues[4] demonstrated the peritoneum to be the most frequent first site of recurrence (38.1%)

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during a 5-year follow-up period after curative resection of gastric cancer. This tumor manifestation is mostly associated with poor prognosis. The multicentric prospective evolution of peritoneal carcinomatosis (EVOCAPE) 1 study reported a mean and a median overall survival for the natural course of the disease of 6.5 and 3.1 months, respectively. The mean age of the 125 included patients was 60.5 years (range 21–96 years). Most of the patients showed advanced T stage of the primary tumor (55 pT3, 62 pT4), 73 patients were diagnosed with synchronous peritoneal carcinomatosis (58.4%), and 19 patients had additional liver metastases (15.2%).[5] Despite the significant improvement in survival of patients with advanced gastric cancer during the past 20 years with the use of palliative systemic polychemotherapy, the results remain unsatisfactory.[6–9] Considering that patients with inoperable and/or locally advanced gastric cancer with or without distant and peritoneal metastases have been included, clinical trials with modern systemic chemotherapy show median survival rates ranging from 9 to 14 months.[10–12] Data for patients in the appropriate clinical condition with peritoneal metastasis only are not available. However, combined cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) as an inherent part of an interdisciplinary treatment concept might be a promising additional treatment option for a highly selected part of patients with limited peritoneal carcinomatosis arising from gastric cancer.

PATHOPHYSIOLOGY

In contrast to hematologic or lymphatic metastasis, peritoneal carcinomatosis is mostly caused by continuous tumor growth or tumor cell dissemination. Ikeguchi and colleagues[2] could demonstrate a strong correlation between the area of serosal invasion and the number of detectable free abdominal tumor cells. The first step in the development of peritoneal metastasis is the detachment of single tumor cells from the primary carcinoma. Based on fast tumor growth, lack of lymphatic drainage, and other mechanisms, these cells reach the abdominal cavity and are disseminated with the peritoneal fluid. Direct cell-to-cell contact via adhesion molecules such as intracellular adhesion molecule 1 and CD44 leads to binding to mesothelial cells with consecutive induction of apoptosis and breaking of their intercellular junctions. By reaching the extracellular matrix, the tumor cells bind integrins and cause degradation, leading to an invasion of submesothelial cell layers. Moreover, free tumor cells can directly bind to specific structures of the extracellular matrix or the greater omentum and cause tumor infiltration.[13]

CLINICAL PRESENTATION

In most cases, peritoneal carcinomatosis is oligosymptomatic or asymptomatic during a long period and therefore often initially diagnosed intraoperatively. The development of malignant ascites might be the first specific sign of progressive peritoneal tumor dissemination. Moreover, patients with peritoneal carcinomatosis may develop abdominal pain, stenosis of canalicular structures, and paralytic or mechanic ileus. These complications may be accompanied by general symptoms of malignant diseases such as deterioration of general condition, weight loss, and fever (**Box 1**).

THERAPEUTIC OPTIONS AND SURGICAL TECHNIQUE

It is beyond question that the treatment of patients with advanced or recurrent gastric cancer is the domain of palliative systemic chemotherapy. Wagner and colleagues[7] showed in a meta-analysis of several randomized clinical trials that compared

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Box 1
Clinical signs of peritoneal carcinomatosis

- Malignant ascites
- Intestinal obstruction
- Palpable abdominal masses
- General symptoms of malignant diseases

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chemotherapy with best supportive care a significant overall survival benefit in favor of systemic chemotherapy and combined chemotherapy, respectively. Two prospective randomized trials using epirubin, cisplatin, fluorouracil (ECF) demonstrated a median survival of 8.9 and 9.4 months, respectively.[10,14] Comparable results with a median survival of 9.2 months were achieved in a randomized controlled trial using docetaxel, cisplatin, fluorouracil (DCF).[11] Cunningham and colleagues[15] reported a median survival of 11.2 months in a group of patients treated with EOX (epirubin, oxaliplatin, capecitabine [xeloda]) in the prospective randomized multicentric Phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer (REAL-2) trial. The addition of the anti-HER2 monoclonal antibody trastuzumab to a chemotherapeutic regimen consisting of cisplatin and 5-fluorouracil or capecitabine led to an improved overall median survival of 13.8 months in patients with *HER2*-positive advanced gastric cancer.[12] Nevertheless, the oncologic outcome of the subgroup of patients with peritoneal carcinomatosis is not reported in these trials and might be expected to be worse. Thus, additional treatment options are required to improve the oncologic outcome of this subset of patients.

The goal of the combined treatment concept consisting of CRS and HIPEC is to remove all visible tumor masses from the abdominal cavity as a precondition for peritoneal perfusion with highly concentrated chemotherapy to locally treat residual microscopic tumor cells. Hyperthermia may have additional antitumoral effects and enhances the penetration ability of the intraperitoneally administered cytostatic agents.[16,17] The surgical technique has been described in detail by Sugarbaker[18] in 1995. Although the principle of HIPEC is based on continuous peritoneal perfusion using inflow and outflow drainages and a heat-exchanger/pump system, the treatment protocol is not standardized. Thus, multiple different cytostatic agents are used for HIPEC and administered in open, semiopen, or closed abdomen technique. Intraperitoneal temperature is 40° to 42°C, and perfusion time ranges from 30 to 120 minutes.[19] A meta-analysis summarizing the results of 13 randomized trials evaluating adjuvant intraperitoneal chemotherapy (IPC) in 1648 patients (873 patients with and 775 patients without IPC) indicates an overall survival advantage for patients with IPC after curative gastric resection.[20] Moreover, Kuramoto and colleagues[21] could demonstrate in a prospective randomized trial comparing extensive intraperitoneal lavage and IPC with IPC and surgery only a significant 5-year survival benefit in favor of prophylactic extensive intraoperative peritoneal lavage and IPC after curative resection of gastric cancer. These data support the efficacy of HIPEC in patients with advanced gastric cancer.

DIAGNOSTIC PROCEDURES

Preoperative gastroscopy including endosonography should be performed in all patients with advanced gastric cancer to determine the resectability of the primary tumor and local lymph node status. Moreover, computed tomography (CT) scanning

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Box 2
Preoperative diagnostics

Mandatory diagnostic procedures

- Gastroscopy including endosonography

- CT

- Sonography

Recommended diagnostic procedures

- Diagnostic laparoscopy

Additional diagnostic procedures

- Contrast-enhanced sonography

- Magnetic resonance imaging

- PET or PET/CT

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of the thorax and abdomen with intravenous and intraluminal contrast media is mandatory to exclude distant metastasis and to determine the extent of peritoneal tumor dissemination. Liver metastasis should be assessed with additional ultrasonography.

In patients qualifying for CRS and HIPEC, a staging laparoscopy before cytoreduction is recommended to assess the extent of peritoneal tumor dissemination and to exclude disseminated small-nodule carcinomatosis of the small bowel. Additional diagnostics such as contrast-enhanced sonography, magnetic resonance imaging, and/or positron-emission tomography (PET)/CT may be helpful in case of unclear findings and should be performed if applicable (**Box 2**).

Diagnosis and Patient Selection

Several studies demonstrate that complete macroscopic resection (CC-0/1) is crucial for the improvement of survival after CRS and HIPEC in patients with peritoneal carcinomatosis arising from gastric cancer.[22,23] Thus, the achievability of CC-0/1 resection should be assessed with preoperative diagnostics as described. Moreover, survival was influenced by the intraoperative Peritoneal Cancer Index (PCI) showing

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Box 3
Preoperative diagnostics

Selection criteria

- PCI <12

- Complete macroscopic cytoreduction probable

- No evidence of distant organ metastasis

- Eastern Cooperative Oncology Group performance status ≤ 1

- Limited clinical relevant comorbidities

Exclusion criteria (STOP signs)

- Disseminated small bowel infiltration

- Ureteral stenosis

- Bilary tract stenosis/cholestasis

Table 1
Median and overall survival after CRS and HIPEC

Author, Year	n	Median Survival, mo	Survival Rate, %
Fujimoto et al,[27] 1997	48	16	31 (5 y)
Loggie et al,[28] 2000	17	10	0 (1 y)
Hall et al,[29] 2004	34	11	21 (5 y) CC-0/1
Glehen et al,[30] 2004	49	10	29 (5 y) CC-0/1
Yonemura et al,[31] 2005	107	11.5	27 (5 y) CC-0/1
Cheong et al,[33] 2007 (EPIC)	154	11	32 (5 y) CC-0/1
Yang et al,[34] 2010	21	43.4 (CC-0) 9.4 (CC-1)	43 (2 y) CC-0/1
Glehen et al,[22,35] 2010	159	9 (CC-0/1: 15)	23 (5 y) CC-0/1
Yang et al,[23] 2011	34	11	15 (2 y)

Abbreviation: EPIC, early postoperative intraperitoneal chemotherapy.

a significant survival benefit for patients with a PCI of less than 12.[22] The PCI (Washington Cancer Center Washington, DC, USA) allows the assessment of the extent of peritoneal surface malignancy.[24,25] The numerical score ranging from 0 to 39 combines lesion size and tumor localization in 13 abdominopelvic regions (regions 0–12). Esquivel and Chua[26] showed that preoperative CT mostly underestimates the extent of peritoneal tumor dissemination. In particular, the involvement of small bowel that is common in patients with advanced gastric cancer is not sufficiently detected with CT. Thus, additional staging laparoscopy is recommended to assess the PCI before CRS and HIPEC and to allow for consistent preoperative patient selection. The main selection criteria are summarized in **Box 3**. Moreover, individual patient motivation, operative risk, and the expected postoperative quality of life should be taken into account. All patients's cases should be discussed in an interdisciplinary tumor board before the institution of CRS and HIPEC.

CLINICAL OUTCOMES IN THE LITERATURE

Several case series could demonstrate overall median survival rates between 9 and 16 months.[22,27–31] In a prospective randomized phase III clinical trial with 68 patients with peritoneal carcinomatosis arising from gastric cancer that compared CRS and HIPEC to CRS only, Yang and colleagues[23] could demonstrate median survival rates of 11 and 6.5 months, respectively. After complete macroscopic cytoreduction (CC-0/1),

Table 2
Morbidity and mortality after CRS and HIPEC

Author, Year	n	Overall Morbidity Rate, %	Mortality Rate, %
Glehen et al,[30] 2004	49	27	4
Yonemura et al,[31] 2005	107	21.5	7
Cheong et al,[33] 2007	154	22.7	2.6
Shen et al,[36] 2009	43	43	4
Yang et al,[34] 2010	21	14.3	10.7
Glehen et al,[22] 2010	159	n.r.	6.5

Table 3
Safety of gastric resections

Author, Year	No. of Gastric Resections	Overall Leakage Rate, %	Leakage Rate After GE, %
Sugarbaker,[38] 2002	45	Not reported	0
Glehen et al,[30] 2004	39	5.1	0
Kusamura et al,[39] 2006	29	11	0
Levine et al,[40] 2007	60	Not reported	Not reported
Piso et al,[37] 2009	37	8.5	0

Abbreviation: GE, gastric resection.

median survival increased to 13.5 months in the CRS plus HIPEC group. Synchronous peritoneal carcinomatosis and additional systemic chemotherapy were positive prognostic factors. Gill and colleagues summarized the data of 1 prospective controlled study, 3 retrospective case series, and 6 prospective case series, for a total number of patients of 445. In this recent systematic review, the median survival after CC-0/1 resection was 15 months (range 9.5–43.4 months).[32] Overall median survival and 1- to 5-year survival rates are summarized in **Table 1**. Despite minimal improvement of the median survival with the use of CRS and HIPEC, the percentage of long-term survivors is up to 30% higher.

COMPLICATIONS AND CONCERNS

Postoperative complications after CRS and HIPEC consist of surgery-related morbidity and chemotherapy-associated toxicity. Although the classification of perioperative morbidity and toxicity is not standardized, the overall morbidity rates range from 14% to 43% (**Table 2**). In the systematic review published by Gill and colleagues, overall morbidity and mortality rates were 21.5% and 4.8%, respectively.

Piso and colleagues[37] showed that there is no increased leakage rate if gastric resection is performed during CRS and HIPEC. The leakage rates after gastric resection in patients with peritoneal carcinomatosis of different origins are summarized in **Table 3**.

In conclusion, published data show that CRS and HIPEC can be performed with low mortality and acceptable morbidity rates in patients with peritoneal carcinomatosis arising from gastric cancer. Nevertheless, the significant operative risk has to be considered during the patient selection process for the combined treatment concept.

SUMMARY

Although a substantial survival benefit after CRS and HIPEC could be demonstrated for patients with peritoneal carcinomatosis arising from other tumor entities such as colorectal cancer, the efficacy of the combined treatment concept in patients with gastric cancer remains controversial. Published data show that survival can be improved in a highly selected subgroup of patients with peritoneal carcinomatosis of arising from gastric cancer. However, complete macroscopic cytoreduction seems to be crucial for positive results. Further randomized clinical trials comparing CRS and HIPEC to modern systemic chemotherapy are needed to determine the role of CRS and HIPEC as part of an interdisciplinary treatment strategy. Moreover, the results of ongoing clinical trials using new intraperitoneal drugs, drug combinations, or

intraperitoneal antibodies such as catumaxumab may help to optimize the intraperitoneal treatment and lead to further improvement of oncologic outcome.

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