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Prevention and Treatment of Peritoneal Metastases from Gastric Cancer

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Introduction

Gastric cancer is a common and deadly disease. It is the fourth most commonly diagnosed cancer in the world with a 5-year survival rate of 25% [1, 2]. In follow-up, almost half of gastric cancer patients will develop peritoneal spread which results in a less than 5% 5-year survival rate [3–5]. Peritoneal metastases are a common finding in primary gastric cancer found in 5–20% of patients undergoing gastrectomy [6]. The peritoneum is also the most common location of first recurrence observed in about half of the patients [7]. Standard of care for treatment of primary or recurrence of gastric cancer involves surgery, intravenous chemotherapy, and radiotherapy. However, specific treatments for peritoneal metastases such as neoadjuvant systemic chemotherapy (NAC), neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), cytoreductive surgery (CRS), and perioperative chemotherapy which may include hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC) are currently being explored [8]. CRS and HIPEC and/or EPIC are already considered standard of care for appendiceal peritoneal metastases, peritoneal mesothelioma, and a limited extent of peritoneal metastases from colorectal carcinomatosis [9–11]. Gastric cancer with peritoneal metastases is aggressive, and current treatment efficacy remains controversial. The following is an attempt to summarize the role and efficacy of NACS, NIPS, CRS, and HIPEC and/or EPIC as a treatment for peritoneal metastases of gastric cancer (Fig. 24.1).

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Perioperative Intraperitoneal Chemotherapy as an Adjuvant Treatment

Local and intra-abdominal tumors are usually the most common and only sites of first recurrence in gastric cancer after curative resection [12–14]. This is true regardless of whether they underwent neoadjuvant chemotherapy or postoperative adjuvant treatment compared to surgical resection alone [15]. The peritoneal surfaces and liver remain the major sites of recurrence. Less localized recurrence is observed when extended lymphadenectomy as compared to limited surgery is used [16–18].

Although confined to the abdomen, peritoneal seeding has deadly consequences [19–22]. Sources of recurrence after curative resection are (1) spontaneous dissemination from the primary tumor and (2) traumatic dissemination of cancer cells during the surgical procedure. If the serosal surface is

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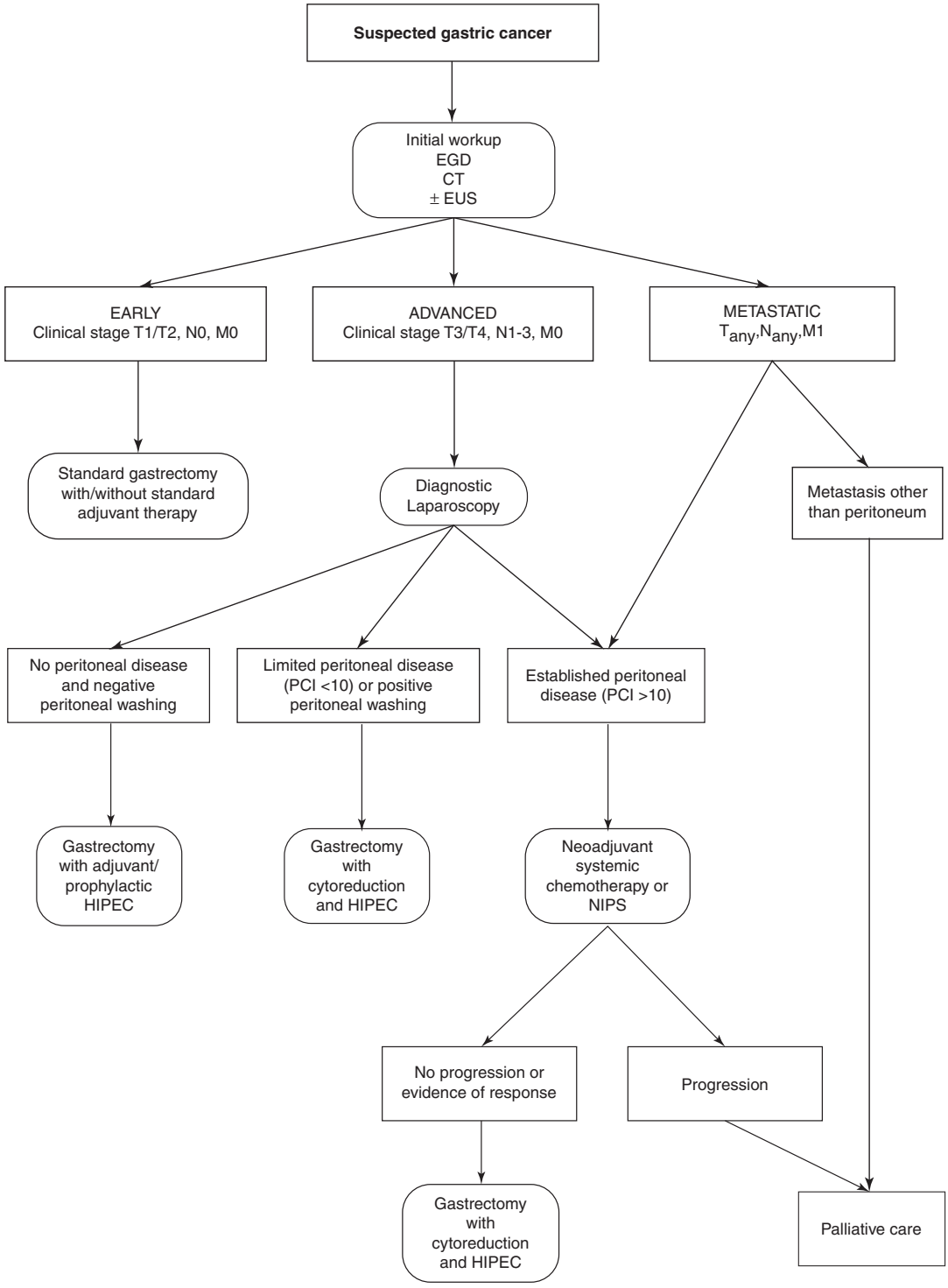


Fig. 24.1 An algorithm for treatment of gastric cancer with and without peritoneal metastases

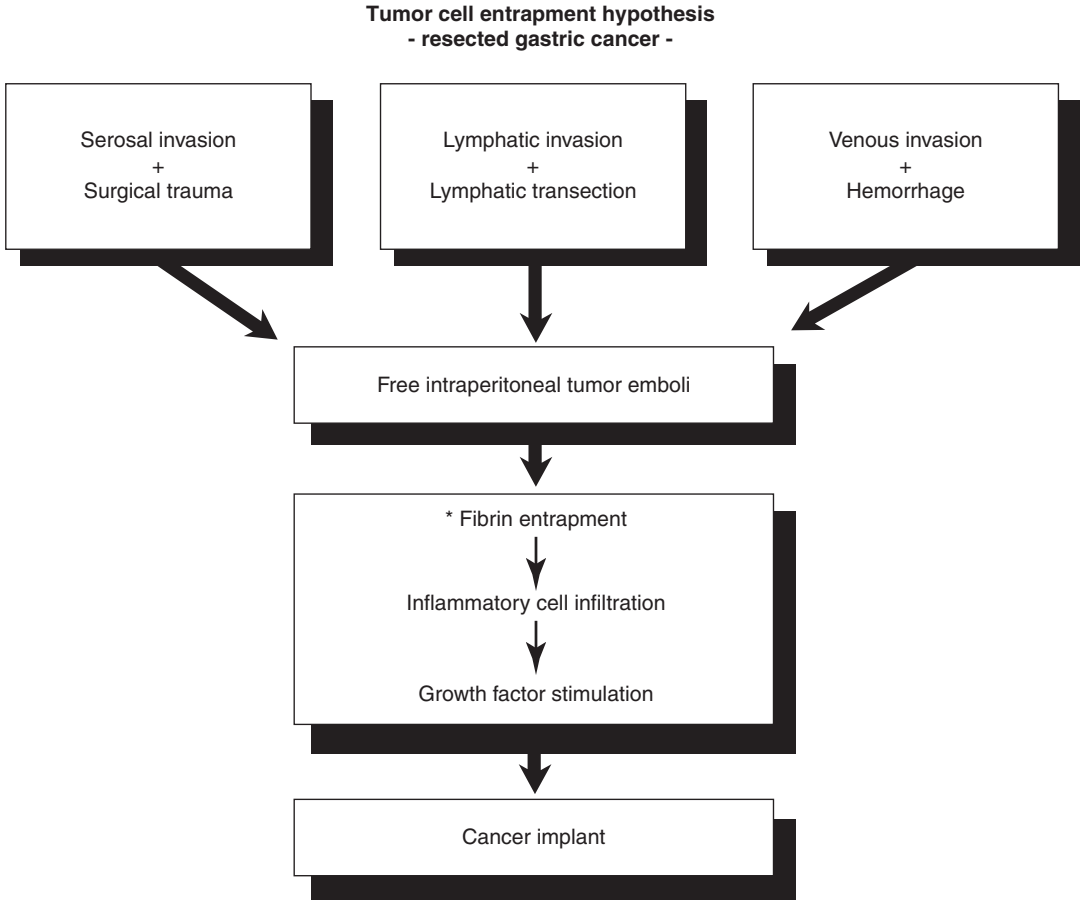


Fig. 24.2 The tumor cell entrapment hypothesis suggests three mechanisms for microscopic residual cancer cells in patients having an R-0 gastrectomy. (From Sethna et al. with permission [24])

involved with tumor, then spontaneous dissemination is more common, and patients are frequently found to have viable intraperitoneal cancer cells (positive cytology) [19, 21–23]. Tumor cells can also seed the intra-abdominal cavity during surgery according to the tumor cell entrapment hypothesis (Fig. 24.2) [24]. During surgery there is disruption of lymphatics, close margins of resection, and tumor-contaminated blood spillage. Iatrogenically disseminated tumor cells adhere spontaneously within minutes, and vascularization is facilitated by fibrin entrapment and the wound healing process. Cytokines, such as growth factors important for wound healing, may also promote tumor progression. The tumor cell entrapment hypothesis explains part of the pathogenesis of local and intra-abdominal recurrence and theoretically shows how adjuvant perioperative intraperitoneal chemotherapy can be beneficial.

Rationale of Perioperative Timing of Intraperitoneal Chemotherapy

Intraperitoneal chemotherapy should be administered perioperatively in order to access the tumor

cells prior to entrapment within fibrin and conversion into cancer progression within adhesive scar tissue. If chemotherapy is given after the formation of adhesive scars, then it will have uneven distribution and lack of uniform cytotoxicity for viable cancer cells. Kinetics of residual tumor cells change within 24 h of resection, and therefore a delay in local-regional treatments will decrease the cytotoxic effectiveness [24].

Perioperative Chemotherapy with D2 Gastrectomy

Perioperative intraoperative chemotherapy can limit progression of peritoneal dissemination after curative surgery; however, it cannot treat residual disease at systemic sites or metastases within lymph nodes. Therefore, a complete D2 lymphadenectomy is essential. Simple diffusion of chemotherapy only penetrates to 1 or 2 mm [25]. Local-regional chemotherapy is not effective in lymph nodes. Also, macroscopic peritoneal nodules larger than 1 or 2 mm have ineffective drug delivery, and visible nodules should be removed prior to treatment.

Literature Regarding Perioperative Intraperitoneal Chemotherapy for Advanced T-Stage Primary Gastric Cancer

There have been randomized and non-randomized trials regarding perioperative intraperitoneal chemotherapy as compared to surgery alone for resectable primary gastric cancer with and without peritoneal spread. Sugarbaker, Yu, and Yonemura published a meta-analysis in 2003 of articles published in English [7]. Xu et al. published a similar study in 2004 [26]. Yan et al. published a summary of randomized control trials concerning adjuvant intraperitoneal chemotherapy for resectable gastric cancer in 2007 [27]. Feingold et al. published the most recent summary of non-randomized and randomized studies in English of CRS and HIPEC and/or EPIC in gastric cancer [28].

Yan et al. selected 10 of 13 randomized controlled trials that were judged to be of fair quality to be used in the meta-analysis [27]. There was a survival benefit associated with HIPEC (hazard ration [HR] = 0.060; 95% CI = 0.43–0.83; p = 0.002) or HIPEC with EPIC (HR = 0.45; 95% CI = 0.29–0.68; p = 0.0002). There was a marginal effect with normothermic intraoperative intraperitoneal chemotherapy (NIPEC) but no significant improvement in survival with EPIC alone or delayed postoperative intraperitoneal chemotherapy (Fig. 24.3) [27].

Although there may be a survival benefit, intraperitoneal chemotherapy can increase morbidities. Even the most experienced peritoneal surface oncology centers that remove all macroscopic disease and then administer intraperitoneal chemotherapy have a higher morbidity and cost [29–31]. Yan et al. discussed an association of improved overall survival with HIPEC with or without EPIC after resection of advanced gastric primary cancer; however, with EPIC there was an associated greater risk for intra-abdominal abscess (RR = 2.37; 95% CI = 1.32–4.26; p = 0.003) and neutropenia (RR = 4.33; 95% CI = 1.49–12.61; p = 0.007) [27]. Yu et al. also saw an increased risk of intra-abdominal abscess with the use of intraperitoneal chemotherapy, especially in the early postoperative setting, compared to the control patients [32]. Theoretically, intraperitoneal chemotherapy should have less systemic toxicity as compared to systemic chemotherapy. However, the meta-analysis demonstrated a significantly higher risk of neutropenia in the intraperitoneal chemotherapy arm [27].

Most of the trials studied by Yan were completed in Asia, and it is unknown if they can be compared with gastric cancer in Western countries. It is possible that perioperative chemotherapy may be better in Western patients with more advanced disease and less lymph nodes dissected. Data does suggest a role of HIPEC with or without EPIC to improve overall survival for advanced primary gastric cancer with advanced T-stage and no peritoneal metastases. A prospective multi-institutional randomized controlled trial (GASTRICHIP) with well-defined eligibility criteria, interventions, and end points is currently in progress in France [33].

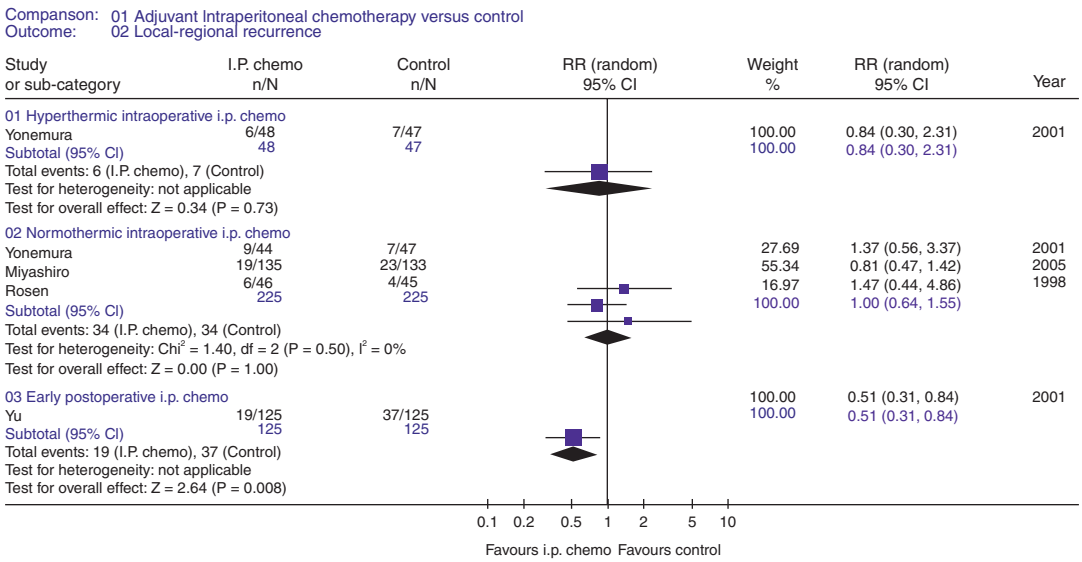


Fig. 24.3 Forest plot of the relative risk (RR) of the local-regional recurrence with adjuvant intraperitoneal (IP) chemotherapy versus controls for advanced gastric cancer. The studies were analyzed according to the regimens of intraperitoneal chemotherapy used. The estimate of the RR of each individual trial corresponds to the middle of the squares, and horizontal line gives the 95% confidence interval (CI). On each line, the numbers of events, expressed as a fraction of the total number randomized, are shown for both treatment groups. For each subgroup the sum of the statistics, along with the summary RR, is represented by the middle of the solid diamonds. (From Yan et al. with permission [27])

Gastric Cancer with Peritoneal Metastases

In the past, gastric cancer with peritoneal dissemination was thought to be uniformly lethal. Prospective studies had a median survival of less than 6 months [34]. Although response rates to systemic chemotherapy regimens have improved, there has not been a corresponding improvement in survival rates [35]. There may be some increased effectiveness with palliative gastric cancer resections in patients with peritoneal metastases; however there are no long-term improvements in survival.

CRS and HIPEC as an Effective Strategy

There is potential for long-term survival for patients with gastric cancer and peritoneal metastases as a result of cytoreductive surgery and HIPEC. There are single-institution data and phase II studies that support use of this strategy (Table 24.1) [20, 29–31, 36–40]. Glehen et al. studied 159 patients with a median follow-up of 20.4 months. There was a median overall survival of 9.2 months, but the 5-year survival rate was 13% [30]. Although CRS and HIPEC is less effective for gastric cancer than results from other peritoneal surface malignancies, CRS and HIPEC results in an improvement for gastric cancer versus surgery alone. Gastric cancer patient with peritoneal metastases treated with CRS and HIPEC were the only patients that reported a 5-year survival [37, 38, 41].

These studies may underestimate the potential of CRS with HIPEC, as there was no strict patient selection criteria utilized. The extent of peritoneal metastases as measured by Sugarbaker's peritoneal cancer index (PCI) significantly influences survival and is correlated with the completeness of cytoreduction [42]. Cytoreductive surgery must reduce the residual disease to a minimum for intraperitoneal chemotherapy to be effective (due to minimal chemotherapy penetration). Glehen et al. demonstrated a 5-year survival of 23% with median survival

Table 24.1 Reports of patients with gastric peritoneal metastases treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Reference	Year	N	Anticancer agent used during HIPEC	Median survival (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)
Fujimoto et al. [20]	1997	48	MMC	16	54	41	31
Hirose et al. [36]	1999	17	MMC-cisplatin-etoposide	11	44	–	–
Rossi et al. [37]	2003	13	MMC-cisplatin	15	–	–	–
Glehen et al. [38] CC-0 or CC-1	2004	49 25	MMC	10.3 21.3	48 74.8	–	16 29.4
Hall et al. [31] CC-0	2004	34	MMC	– 11.2	– 45	–	–
Yonemura et al. [29] CC-0	2005	107 47	MMC-cisplatin-etoposide	11.5 15.5	– –	– –	6.5 27
Scaringi et al. [39] CC-0	2008	32 8	MMC-cisplatin	6.6 15	–	–	–
Glehen et al. [30] CC-0	2010	159 85	Various	9.2 15	43 61	18 30	13 23

Adapted from Glehen et al. with permission [40]
CC-0 complete macroscopic cytoreduction; *CC-1* residual tumor nodules <5 mm; *MMC* mitomycin C; *N* number of patients

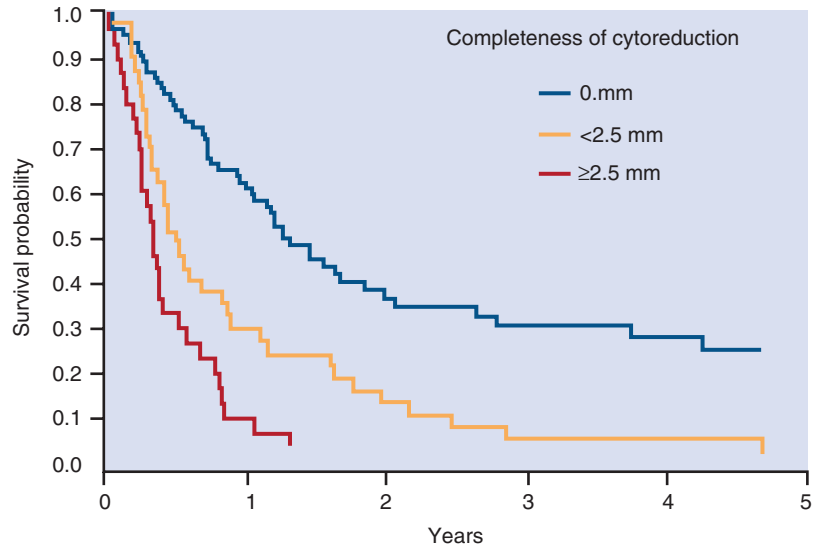


Fig. 24.4 Overall survival of 159 patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy according to completeness of cytoreductive surgery. (From Glehen et al. with permission [30])

of 15 months in patients after a complete macroscopic resection (Fig. 24.4) [30]. Yonemura et al. demonstrated a similar 27% 5-year survival rate and 15.5 months median survival [29]. Hall et al. reported a 11.2-month overall survival after CRS and HIPEC with mitomycin C; however there was no patient alive after 2 years who had residual disease at CRS [31]. CRS with a minimum residual disease burden is essential for effective HIPEC. HIPEC used with macroscopic disease does not improve survival. HIPEC can have morbidity and therefore should not be used for patients with bulky residual disease, although palliative use for ascites may always be considered [43, 44].

Unfortunately, even if completely cytoreduced, HIPEC is less useful for patients with high burden of peritoneal metastatic disease. Glehen et al. showed that one of the strongest prognostic factors was extent of carcinomatosis [30]. When the PCI was greater than 12, despite a complete cytoreduction, there were no survivors

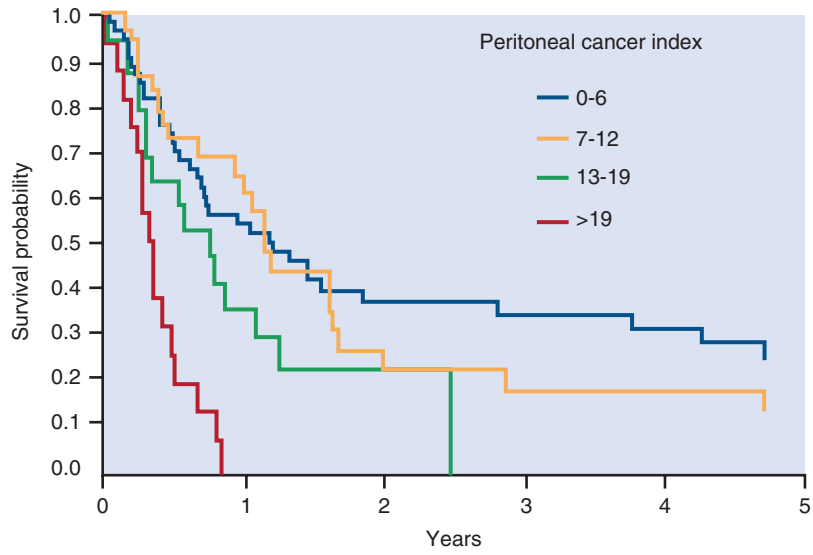


Fig. 24.5 Overall survival of 159 patients treated by complete cytoreductive surgery according to extent of peritoneal metastases assessed by the peritoneal cancer index. (From Glehen et al. with permission [30])

greater than 3 years (Fig. 24.5) [30]. Fujimoto et al. reported 40–50% 5-year survival for limited peritoneal metastases but only an 18% 1-year survival for patients with extensive peritoneal metastases [20]. Cytoreduction with HIPEC in gastric cancer patients with a PCI score greater than 12 may be contraindicated.

Yang et al. have provided the first and only phase III study regarding CRS and HIPEC in gastric cancer presenting with peritoneal metastases. They used cisplatin (120 mg) and mitomycin C (30 mg) in 6000 ml of normal saline at 43C for 60–90 min. Median follow-up was 32 months, and 97.1% (33 of 34) of patients after CRS died, but 85.3% (29 of 34) of CRS and HIPEC patients died. Median survival was 6.5 months (95% CI 4.8–8.2 months) after CRS and 11 months (95% CI; 10.0–11.9 months) in CRS and HIPEC group ($p = 0.046$) [43]. There was similar morbidity between the groups. The independent predictors in a multivariate analysis for improved survival were synchronous peritoneal metastases, CC 0–1 cytoreduction, more than six cycles of systemic chemotherapy, and no adverse events. Glehen et al. suggested that HIPEC should be reserved for patients with limited peritoneal carcinomatosis [30]. Also, the prognostic factors analyzed by Yang et al. suggest that it should be restricted to a limited patient population (Table 24.2) [43].

Table 24.2 Selection of gastric cancer patients with peritoneal metastases for gastrectomy, peritonectomy, and perioperative chemotherapy

Clinical features		
Young age (<65 years)		Lymph nodes, negative or limited extent
Low operative risk (no other diseases)		No liver metastases
Patient symptoms present		Peritoneal cancer index <12
Pain Bleeding Perforation	Obstruction Ascites	Expect complete clearing of the primary cancer

Adapted from Glehen et al. with permission [40]

Role of Laparoscopy for Patient Selection

Laparoscopy has three important roles in the management of gastric cancer. First, laparoscopy may select and exclude patients with intra-abdominal metastases who would not benefit from an aggressive and complex procedure that is unlikely to improve their survival. If a primary gastric cancer patient is found to peritoneal metastases or would otherwise not be able to be completely cytoreduced, HIPEC would not be warranted, and the morbidity of laparotomy could be avoided [45, 46]. Laparoscopy is useful to show that patients have clinically absent

peritoneal metastases. Recent randomized trials suggest that neoadjuvant chemotherapy should be used for gastric cancer patients free of peritoneal disease [47].

Second, laparoscopy performed in primary gastric cancer patients can select those patients with a low volume (P1 or PCI < 10) of peritoneal metastases for CRS with gastrectomy and HIPEC. In these patients with minimal disease who can undergo complete cytoreduction, a 5-year survival of 25% is expected.

A third use of laparoscopy is serial exams in patients with a greater extent of peritoneal metastases. If the peritoneal metastases respond on repeated laparoscopic examination, CRS with gastrectomy and HIPEC is considered a treatment option. The use of laparoscopy with NIPS (neoadjuvant intraperitoneal and systemic chemotherapy) will be described in the following sections.

Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

If patients have peritoneal dissemination, the effects of systemic chemotherapy are disappointing. Preusser et al. demonstrated that an aggressive systemic chemotherapy regimen can have a 50% response rate in advanced gastric cancer; however this response is less robust in patients with peritoneal metastases [48]. Ajani et al. gave neoadjuvant chemotherapy, and the failure of the regimen was most common with peritoneal metastases [49]. Systemic chemotherapy alone for primary gastric cancer with peritoneal metastases is not satisfactory.

Neoadjuvant chemotherapy for gastric cancer can be modified to address peritoneal seeding by combining systemic and intraperitoneal chemotherapy. Chemotherapy may gain access to small peritoneal cancer nodules via the systemic circulation and by diffusion from a chemotherapy solution within the peritoneal cavity. Yonemura and coworkers proposed a prospective phase II study to identify the efficacy and assess toxicities in patients with gastric cancer with peritoneal metastases [50]. The following summarizes this study.

Patients Treated

In this phase II study, Yonemura and coworkers treated patients with peritoneal metastases identified by laparoscopy, laparotomy biopsy, or cytology from ascites. To qualify for NIPS, patients must have (1) proven peritoneal seeding by histology or cytology; (2) no hematogenous or remote lymph node metastases; (3) be less than or equal to 65 years; (4) have an Eastern Clinical Oncology Group score of 2 or less; (5) adequate bone marrow, liver, cardiac, and renal function; and (6) no other severe medical comorbidities or synchronous malignancies.

Qualifying patients had a peritoneal port system (Bard Port, C.R. Bard Inc., USA) inserted into the abdominal cavity under local anesthesia with the tip placed within the cul-de-sac of Douglas.

Chemotherapy Regimen

Prior to administration of chemotherapy, 500 ml of saline was instilled into the peritoneal cavity, and fluid was removed for cytology. Docetaxel 40 mg and carboplatin 150 mg were used for intraperitoneal chemotherapy in addition to 1000 ml of saline over 30 min. Methotrexate 100 mg/m^2 and 5-fluorouracil 600 mg/m^2 in 100 ml of saline over 15 min were administered intravenously the same day. This regimen was administered weekly for two cycles. After the second cycle, peritoneal wash cytology was again performed. If cytology was positive, neoadjuvant chemotherapy was continued for two more cycles. Peritoneal cytology testing is repeating after the fourth cycle, and the process is continued as long as cytology is positive.

If cytology became negative, upper endoscopy, repeat laparoscopy, and CT scan were performed. If tumors showed no demonstrable change, then two more cycles were administered. The number of NIPS chemotherapy cycles was controlled by the effect on the primary cancer and peritoneal cytology. Complete cytoreduction was required for prolonged survival in prior studies that examined peritoneal metastases. Therefore, the goal of

the NIPS regimen was complete or near complete response of metastases on small bowel surfaces [36, 51–53].

The Japanese General Rules for Gastric Cancer Study was used to determine the peritoneal stage as (P1) peritoneal metastases in the upper abdomen above the transverse colon, (P2) several countable metastases in the peritoneal cavity, and (P3) numerous metastases in the peritoneal cavity [54]. Distribution and size of peritoneal metastases were recorded at laparoscopy and at surgery. Tumor location, size, and number were evaluated before and after NIPS to determine effects of neoadjuvant chemotherapy.

Surgery for Gastric Cancer with Peritoneal Metastases After Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

Gastrectomy and peritonectomy were performed if peritoneal wash cytology became negative or there was a partial response to neoadjuvant chemotherapy. Patients with progressive disease or who continue to have positive cytology despite 4–6 cycles of NIPS were not candidates for surgery.

If peritoneal metastases on small bowel surfaces were eliminated by NIPS, there was a possibility that gastrectomy and parietal peritonectomy could achieve a complete cytoreduction. Sugarbaker and Yonemura reported the use of peritonectomy for peritoneal metastases to cytoreduce the peritoneal surface and facilitate total resection of the primary gastric cancer [55, 56]. Peritonectomies required for gastric cancer have been described [7]. The epigastric peritonectomy includes any prior midline abdominal scar with the preperitoneal epigastric fat pad, xiphoid process, and round and falciform ligaments (Fig. 24.6). The anterolateral peritonectomy removes the greater omentum with the anterior layer of peritoneum from the transverse mesocolon, peritoneum of the right paracolic gutter along the appendix, and the peritoneum in the right subhepatic space. Sometimes the peritoneum of the left paracolic gutter must also be removed (Fig. 24.7). The subphrenic peritonectomy takes the peritoneal surfaces from the medial half of the right and left hemidiaphragm as well as the left triangular ligament (Fig. 24.8). The omental bursa peritonectomy starts with cholecystectomy and then removes the peritoneal covering of the porta hepatis, hepatoduodenal ligament, and floor of the omental bursa including the peritoneum

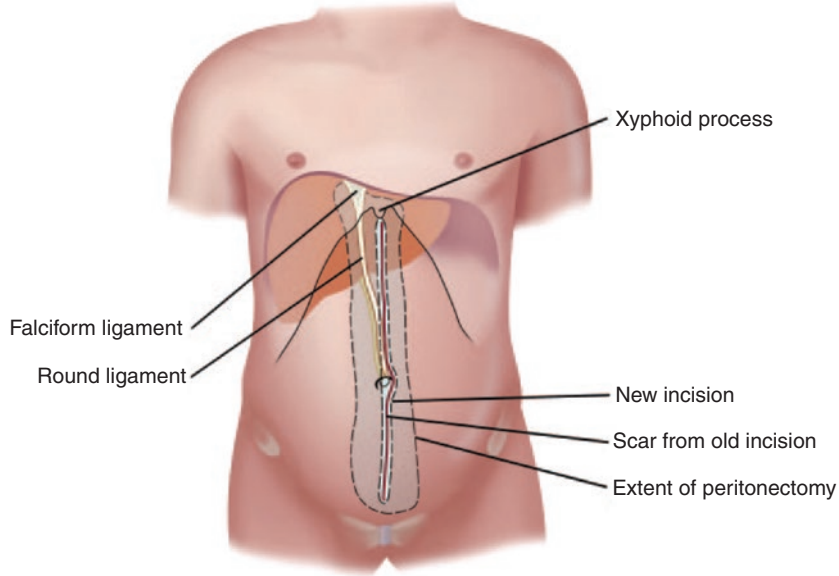


Fig. 24.6 Epigastric peritonectomy

overlying the pancreas (Fig. 24.9). If tumor was within the cul-de-sac, a pelvic peritonectomy was also performed, and electroevaporative surgery strips the peritoneum from the pouch of Douglas (Fig. 24.10). Sometimes, the pelvic peritonectomy will necessitate removal of the rectosigmoid colon. Visceral resections and parietal peritonectomies were performed to completely remove gross disease.

Any complications related to chemotherapy and peritonectomy were prospectively collected and verified retrospectively.

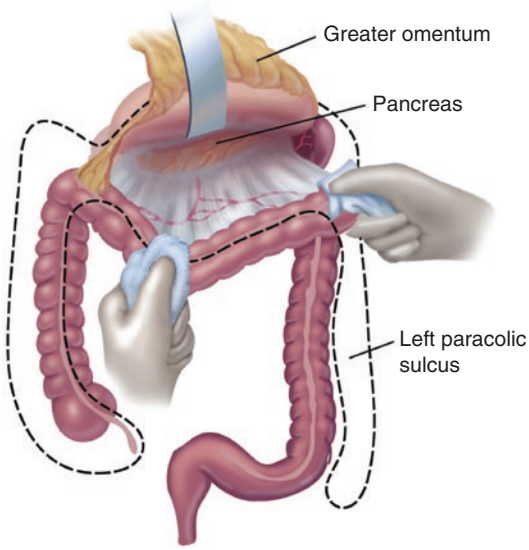


Fig. 24.7 Anterolateral peritonectomy

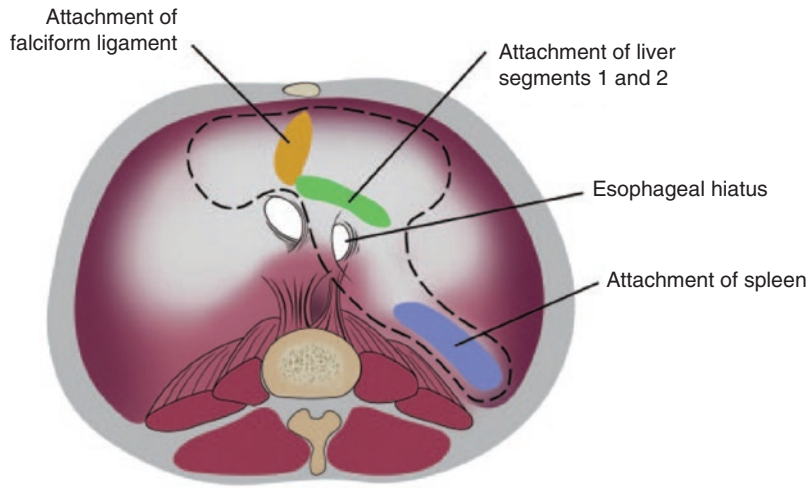
Results After Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

Table 24.3 shows the clinical characteristics of the 194 patients. Average age was 51.5 years. One hundred four patients had primary gastric cancer, and 90 patients had recurrent peritoneal metastases. Peritoneal fluid cytology was positive in 137 patients and negative in 57 patients prior to NIPS. There was complete resolution of peritoneal metastases after NIPS chemotherapy in 24.3% of patients. After induction treatment, 152 patients underwent surgery.

Operative interventions, such as total gastrectomy ($n = 94$), subtotal gastrectomy ($n = 17$), and small bowel resection ($n = 44$), are displayed in Table 24.3. Left and right subdiaphragmatic peritonectomy and pelvic peritonectomy were completed in 44, 31, and 61 patients, respectively. Complete cytoreduction was achieved in 103 (67.7%) of patients.

Figure 24.11 demonstrates overall survival of the 194 patients. Median survival was 15.8 months for the 152 patients who had received surgical intervention versus 7.5 months for patients who did not have an operation. Median survival of the 194 patients was 14.4 months. One-year survival was 54% for all patients. There was a significant survival difference ($p = 0.03$) between patients who underwent operative intervention versus those who did not. There was a higher median survival of

Fig. 24.8 Subphrenic peritonectomy



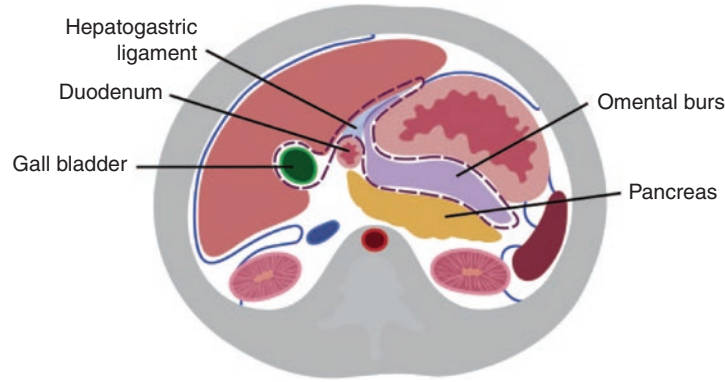


Fig. 24.9 Omental bursa peritonectomy

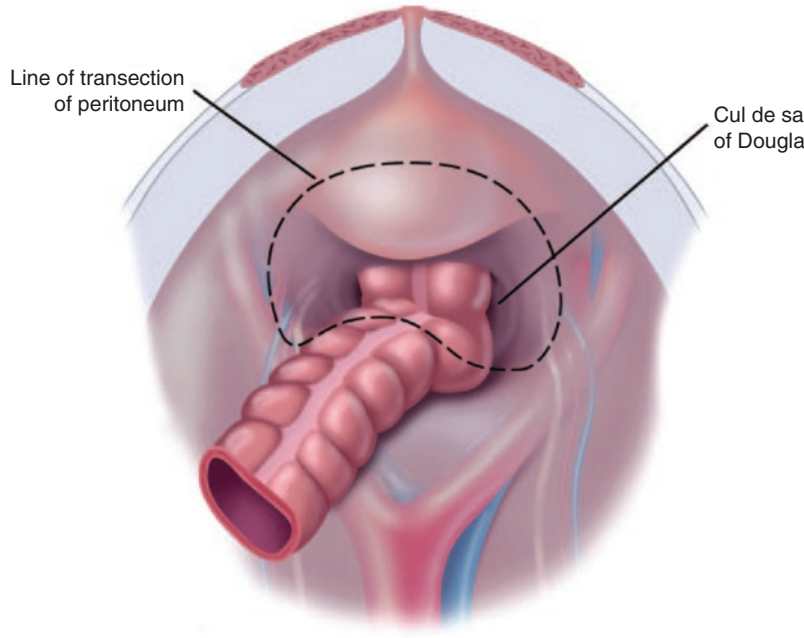


Fig. 24.10 Pelvic peritonectomy

18 months for patients who received a complete cytoreduction. There was no difference between primary and recurrent disease after cytoreduction with a median survival of 17.6 months versus 14.1 months, respectively ($p = 0.39$).

Adverse Events from Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS) and Cytoreductive Surgery

The most common chemotherapy-related grade 3 or 4 adverse events were bone marrow suppression and diarrhea. Bone marrow suppression occurred after three courses in three patients, after five courses in three patients, and after six courses in four patients. Less common adverse events were port site infection ($n = 2$) and renal failure ($n = 1$). After cytoreduction with peritonectomy, 18 patients (14%) developed complications. Two patients had pneumonia and one patient developed renal failure. Six patients had an anastomotic leak, and two patients had an abdominal abscess. The overall operative mortality rate was 1.5% (2 of 133 patients). These patients died of multiple organ failure from sepsis from abdominal abscess [40].

Table 24.3 Clinicopathological characteristics of 194 gastric cancer patients with peritoneal carcinomatosis

Variables	No. of patients
Age, years (range)	51.5 ± 12.6
Male/female ratio	89/105
Histological diagnosis	
Well/intermediately differentiated adenocarcinoma	7
Poorly/undifferentiated adenocarcinoma	187
Organ resections	
Right diaphragmatic copula	31
Left diaphragmatic copula	44
Total gastrectomy	94
Subtotal gastrectomy	17
Pelvic peritoneum	61
Colectomy	68
Small bowel resection	44
Cytology before BIPS	
Negative	57
Positive	137
Cytology after BIPS	
Negative	152
Positive	42
Pathological response to BIPS	
Grade 0	63
Grade 1	38
Grade 2	24
Grade 3	27

From Canbay et al. with permission [60]

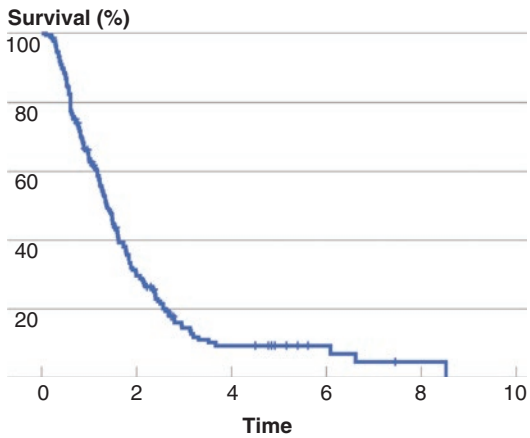


Fig. 24.11 Overall survival in 194 gastric cancer patients with peritoneal carcinomatosis. (From Canbay et al. with permission [60])

Clinical Data Supporting Complete Cytoreduction as the Goal in Management of Gastric Cancer Patients with Peritoneal Seeding

Complete cytoreduction is crucial in the surgical treatment for carcinomatosis from appendiceal and colon cancer. Five-year survival for complete cytoreduction was 54% versus 15% for incomplete cytoreduction as reported by Culliford et al. [57]. Glehen et al. also reported a median survival difference of 32 months and 8.4 months for patients with macroscopic complete resection versus incomplete cytoreduction, respectively [58]. This has shown that complete cytoreduction had better survival rates in gastric cancer [59, 60]. There is a difference in biological aggressiveness between colon and gastric cancers; however, macroscopic complete cytoreduction is necessary for long-term survival with peritoneal metastatic disease in these diseases. If there is P3 dissemination, complete cytoreduction should not be attempted. NIPS was shown to diminish disease on intestinal surface and facilitate complete cytoreduction.

Palliative Benefits to All Patients with Cancerous Ascites

There was improvement in symptoms for the 78 patients who had ascites [40]. These benefits occurred in patients with primary gastric cancer and also in patients with recurrent disease. Cunliffe et al. hypothesized that peritoneal metastases are nourished via ascites as well as blood supply. Therefore, peritoneal implants should be treated via a combined intraperitoneal and intravenous approach [61]. Intravenous chemotherapy has minimal effects on peritoneal metastases, and intraperitoneal chemotherapy alone has a less than 30% effect on ascites [31, 32, 48, 49]. The bidirectional chemotherapy (intraperitoneal and intravenous) has a response rate of 57% with 100% resolution of ascites [40].

Chemotherapy Agents Selected for Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

Different chemotherapy regimens have been used for NIPS such as docetaxel, cisplatin, and paclitaxel. Fujiwara et al. irrigated the abdominal cavity with doses of docetaxel between 40 and 60 mg/m^2 dissolved in 1 L of saline [62]. Canbay et al. administered intraperitoneal docetaxel (30 mg/m^2) and cisplatin (30 mg/m^2) [60]. Kitayama's group administered paclitaxel at 20 mg/m^2 in 1 L of normal saline over 1 h [63].

In summary, NIPS should be considered in gastric cancer patients with peritoneal metastases. It has maximal benefits for small volumes of peritoneal surface metastases and is reliable treatment for symptomatic ascites. Bidirectional chemotherapy may be the preferred strategy for preoperative chemotherapy of gastric cancer with peritoneal metastases.

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