Evidence-Based Medicine in the Treatment of Peritoneal Carcinomatosis: Past, Present, and Future

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The current treatment of peritoneal surface malignancies (PSMs) is moving from a nihilistic approach, into a combined modality approach offering selected patients long-term survival. As primary PSM are rare, extrapolation of data from clinical trials of related disease is necessary to develop treatment guidelines. Secondary PSM are more common, and therefore, treatment guidelines should be developed based on prospective clinical trials. We reviewed the published and ongoing clinical trials studying the treatment of PSM.


KEY WORDS: peritoneal surface malignancies; carcinomatosis; hyperthermic chemotherapy; clinical trial; cytoreduction

INTRODUCTION

In order to understand the rationale for the treatment of peritoneal surface malignancy (PSM) one must first comprehend the underlying biology of the disease, its pathology, the scope of the problem and its magnitude. Peritoneal carcinomatosis (PC) is defined as the dissemination of cancer cells in the peritoneal cavity resulting in deposition of malignant cells onto parietal or visceral peritoneal surfaces. Peritoneal carcinomatosis may be associated with accumulation of cancer cell containing fluid within the peritoneal cavity, malignant ascites.

Primary neoplastic diseases of the peritoneum are rare and include peritoneal mesothelioma and primary peritoneal carcinoma. However, secondary PSM of colorectal, ovarian, gastric, pancreatic, and appendiceal carcinoma origin is more common [1]. PSM can present as malignant ascites, multiple small tumor nodules, tumor masses in various sizes, confluent layers of tumor tissue enveloping peritoneal surfaces and organs, or disseminated mucin deposits known as pseudomyxoma peritonei (PMP).

PATHOPHYSIOLOGY

The peritoneum is a thin layer of mesothelial cells supported by a network of lymphatics and blood vessels. The pathophysiology and the molecular mechanisms underlying the formation of peritoneal carcinomatosis are incompletely understood. Metastatic tumor deposits within the peritoneal cavity by a distinctly different mechanism than hematogenous spread of malignant diseases to distant solid organs or lymphatic spread of tumor cells resulting in regional or distant nodal metastasis. Several theories were proposed to explain the formation of peritoneal carcinomatosis [2].

A concept known as “tumor rupture” theorizes that a malignant epithelial tumor originating within the peritoneal cavity (e.g., colorectal, gastric, or ovarian carcinoma) directly infiltrates the serosal layer resulting in exfoliation of neoplastic cells into the peritoneal cavity, resulting in peritoneal carcinomatosis; this process is facilitated by surgical manipulation [3,4]. Although this theory applies to some tumors, such as ruptured gastrointestinal stromal tumors (GIST) or other large solid epithelial tumors, it does not satisfactorily explain why or how low-lying rectal cancers with no direct communication with the peritoneal cavity can still result in peritoneal carcinomatosis. Also the observation that the incidence of peritoneal carcinomatosis following perforated adenocarcinoma of the colon is not significantly different than the incidence of peritoneal carcinomatosis following non-perforating tumors calls the “tumor rupture” theory into question.

One would think that exfoliation of cancer cells from a tumor would create a random distribution of PSM. However, in most cases the pattern of tumor cell spread throughout the peritoneal cavity is predictable [5]. Tumor remobilization entrapment is likely to occur following surgery. The lymphatic leakage combined with blood clots with the presence of growth factors recruited for wound healing process are fertile soil for peritoneal dissemination of disease.

Published 2009 Wiley-Liss, Inc.

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Received 20 April 2009; Accepted 29 April 2009
DOI 10.1002/jso.21323
Published online in Wiley InterScience (www.interscience.wiley.com).
Mucin production is the hallmark of secondary PSM. Extracellular or intracellular mucin secretion by cancer cells is associated with higher incidence of peritoneal spread. These observations form the basis of the “secretion theory” which suggests that the peritoneal surface serves as a barrier cancer cells impeding systemic cancer spread. However, it stands to reason that secretion of growth factors, nutritional factors, or other substances alone or as part of the mucin contained within tumor cells, would render the peritoneal surface barrier into a fertile area for the proliferation of microscopic tumor cell implants into clinically apparent peritoneal tumor nodules.

Recent studies by Yonemura et al. [6,7] provide new insights into the peritoneal lymphatic anatomy. Their histological characterization of the peritoneal lymphatic system includes lymphatic stomata, peritoneal lymphatic orifices connecting the peritoneal surface with the sub-peritoneal lymphatic system, and the “milky spots”, small aggregates of lymphatic vessels, lymphocytes and macrophages present in the peritoneum as well as the omentum. According to several independent observations [8–11], cancer cells can pass through both lymphatic stomata and milky spots, and can be trapped within these anatomic compartments, where sub-peritoneal lymphatic system proliferation of cancer cells may ensue.

The pathophysiology of peritoneal carcinomatosis is a complex, incompletely defined, multi-step process involving cancer cells either exfoliated from tumors with direct communication to the peritoneal surface or delivered by the lymphatic system into the peritoneal cavity and sub-mesothelial spaces. Growth factors, angiogenic factors either embedded in mucin or secreted directly into the peritoneal cavity allow the implantation of cancer cells onto the peritoneal surface. The implantation usually begins in abdominopelvic regions rich in lymphatic stomata such as the greater omentum, diaphragm, and pelvis [12].

**EPIDEMIOLOGY**

Primary peritoneal surface malignancies are rare tumors and include peritoneal mesothelioma and primary peritoneal carcinoma.

Peritoneal mesothelioma more commonly affects females than males. According to the SEER data the overall incidence of mesothelioma in the US is 1.1 cases per 100,000 population at risk and peritoneal mesothelioma represents ~10–20% of all mesothelioma cases [13,14]. There are three subtypes of peritoneal mesothelioma: epithelial, multi-cystic, and biphasic.

Primary peritoneal carcinoma is a papillary carcinoma involving the peritoneal cavity in the absence of an obvious primary site [15]. It is considered a variant of ovarian cancer and accounts for 7–14% of ovarian carcinomas [16]. There are three types of primary peritoneal carcinoma: serous papillary carcinoma, mixed epithelial carcinoma, and malignant mixed Mullerian tumor. Secondary PSMs are more common than primary peritoneal malignancies (Table I) [17].

**CURRENT MANAGEMENT**

The current treatment of PSM is evolving and is predicated principally on consensus statements, which are based largely on retrospective data, as few disease-specific prospective clinical trials have been conducted to date. As primary PSM is rare, extrapolation of data from clinical trials of related disease was necessary to develop fundamental treatment guidelines. For example, the data obtained from clinical trials conducted on pleural mesothelioma are used to guide treatment of peritoneal mesothelioma and the data obtained from ovarian cancer trials form the basis of current treatment of primary peritoneal carcinoma [14,17]. Given the rarity of disease such as mesothelioma and primary peritoneal carcinoma it is highly unlikely that disease-specific pathways will be defined by Level I evidence.

Surprisingly, despite the relatively larger number of patients with secondary as compared to primary PSM treated each year, there remains a dearth of prospective clinical trials for PSM originating from common intraperitoneal epithelial malignancies, particularly colorectal carcinoma. PSM of colonic origin is treated typically by supportive measures or by palliative systemic therapy regimens. This represents a nihilistic treatment approach, which is ill conceived, as data supporting the delivery of systemic therapy for secondary PSM, particularly in the case of colorectal carcinoma, is derived from clinical trials reporting the results of treatment of distinctly different tumor biology—visceral metastasis of hematogenous origin, not peritoneal carcinomatosis. Surgical treatment has been historically reserved for palliation or emergencies such as visceral obstruction or perforation. The poor outcome and the negligible response rates of colorectal peritoneal carcinomatosis to systemic therapy, has engendered new therapeutic approaches superseding age-old nihilistic and palliative approaches. These new multi-modality treatments include cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC), and systemic therapy [18].

The current treatment of non-metastatic gastric cancer is primarily surgical combined with either adjuvant chemotherapy or chemoradiation. Peritoneal spread of gastric cancer is a common feature of gastric tumor biology, and is currently treated by palliative systemic therapy. Despite several clinical trials demonstrating efficacy of various forms of intraperitoneal (IP) chemotherapy in gastric cancer, this form of therapy has yet to become an accepted part of standard oncological

**TABLE I. The Incidence of Peritoneal Surface Malignancies**

<table>
<thead>
<tr>
<th></th>
<th>Worldwide incidence (new cases/year)</th>
<th>% Peritoneal dissemination*</th>
<th>Expected incidence of peritoneal carcinomatosis (new cases/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary PSM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary peritoneal cancer</td>
<td>20,000</td>
<td>100</td>
<td>20,000</td>
</tr>
<tr>
<td>Peritoneal mesothelioma</td>
<td>2,000</td>
<td>100</td>
<td>2,000</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Secondary PSM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1,023,152</td>
<td>15</td>
<td>153,472</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>933,937</td>
<td>40</td>
<td>373,574</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>204,499</td>
<td>60</td>
<td>122,699</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>232,306</td>
<td>25</td>
<td>58,076</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>709,941</td>
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PSM, peritoneal surface malignancies.
*Peritoneal dissemination at diagnosis and at disease recurrence.
*Incidence estimation from literature reports.
*Including appendecial cancers and pseudomyxoma peritonei.
practice. The topic of clinical trials comparing intraperitoneal to systemic therapy in gastric cancer was recently reviewed by Yan et al. [19].

Adenocarcinoma of the exocrine pancreas is associated with high rates of peritoneal carcinomatosis and is associated with the highest cancer mortality rate. The 5-year survival rate (2-5%) of this highly lethal malignancy has remained unchanged for over 30 years. Pancreatic cancer remains very difficult to treat and most patients are not resectable at time of disease presentation. Even for the relatively few patients that are able to undergo complete resection of disease and administration of adjuvant systemic therapy, the outcome remains poor (disease free survival of ~12 months) [20,21]. As most cases are diagnosed in the advanced stages of disease, and overall prognosis remains poor because of aggressive biology of disease and limited treatment options, novel therapeutic approaches are imperative.

Similarly, given the lack of effective screening tools and the protean clinical presentation of disease, ovarian cancer remains a formidable treatment challenge, as it is usually diagnosed at an advanced stage where peritoneal dissemination is present. The current treatment of PSM of ovarian origin remains extremely variable. Debulking surgery is advocated by many investigators and clinicians [22]. However, the extent or timing of surgery remains controversial and the definition of “optimal debulking” remains elusive [23]. Favorable response rates of ovarian cancer to platinum-based therapy have formed the basis for neoadjuvant systemic therapy followed by debulking surgery, which is currently favored. However, despite the promising initial response rates, recurrence rates are remain high and platinum-resistant tumors have proven unresponsive to multiple agents and current treatment modalities. The role of intraperitoneal therapy in ovarian cancer was established by several Phase III clinical trials. In a recent report of a prospective randomized clinical trial, intraperitoneal chemotherapy was found to be superior to systemic therapy [24]. Despite mounting evidence to suggest that multi-modality therapy for PSM of ovarian origin in the form of CRS and HIPEC may improve outcome, this has yet to be studied definitively.

THE RATIONAL FOR CYTOREDUCTIVE SURGERY AND HYPERTERMIC INTRAPERITONEAL CHEMOTHERAPY

Surgical therapy was traditionally used for the treatment of primary, non-metastatic epithelial malignancies. Successful treatment is highly dependent on complete resection of the primary tumor with surrounding healthy tissue with uninvolved microscopic resection margins (R0 resection). Surgical treatment of distant solid organ metastasis (e.g., liver, lung, etc.) has been shown to benefit selected patients and is accepted as a standard of practice mainly in colorectal cancer but also in several other kinds of tumors (renal cell carcinoma, melanoma, thyroid carcinoma, etc.), under specific circumstances such as long disease-free interval, single metastatic focus, response to systemic therapy, ability to achieve complete resection (R0), etc. Margin-negative resection is an essential endpoint in surgical oncology, without which surgical cure is unattainable. This benchmark of R0 tumor clearance is infrequently achievable in the treatment of peritoneal carcinomatosis.

The application of new surgical techniques for resection of tumor-bearing peritoneal surfaces and organs represented an aggressive approach to PSM, which was first reported by Sugarbaker [25], introducing a new concept, that of CRS. This was soon followed by the development of a novel staging system specifically for PSM and a scoring system to define the completeness of cytoreduction (CCR, Table II) [26].

The ability to attain surgical clearance of all grossly apparent peritoneal surface disease in patients without systemic metastasis served as the basic premise for aggressive CRS for PSM. However, surgery alone proved inadequate to achieve the anticipated survival benefit, as biologically important microscopic residual disease inevitably remained after radical attempts to obtain surgical clearance of all gross disease [27]. Viable tumor cells become sequestered in avascular intraperitoneal adhesions explaining partly the resistance to and ineffectiveness of systemic chemotherapy for peritoneal carcinomatosis [28]. As R0 resection is typically impracticable in PSM, and the relative tissue concentration of agents delivered systemically is decidedly low in peritoneal surface tumor deposits, more effective methods for eradicating residual peritoneal disease were pursued.

Animal studies showed that the direct intraperitoneal administration of cytotoxic agents results in significantly higher tissue concentrations as compared to systemic intravenous administration of the same agents. However, drug penetration of is limited to 2–3 mm of the superficial layer of the peritoneum. The presence of an anatomic barrier, the peritoneal-plasma partition, has enabled the exposure of the peritoneal surface to high local concentrations of chemotherapy. High regional doses of cytotoxic agents are possible through intraperitoneal delivery far in excess of doses that can be administered systemically [29–34]. High molecular weight agents such as Mitomycin C (334 Da), and Oxaliplatin (397 Da) have favorable pharmacokinetic profiles (AUC peritoneal fluid relative to plasma: Mitomycin C, 75:1; Oxaliplatin, 25:1) permitting well-tolerated dose-dense intraperitoneal therapy over prolonged periods with rapid tissue concentration (in residual tumor deposits and peritoneum), but limited systemic absorption or toxicity [35–37]. This particular therapeutic approach addresses both problems of microscopic residual disease and systemic chemotherapeutic resistance. With its reduced systemic toxicity and dose dense delivery, intraperitoneal chemotherapy provides distinct pharmacological advantage over systemic drug delivery [38,39].

The cytotoxic effect of hyperthermia is well known. However, effective killing of cancer cells is only possible at temperatures that will irreversibly damage surrounding normal tissues. Intraperitoneal hyperthermia, shown to be technically feasible [40], was integrated into the treatment paradigm of cytoreduction and intraperitoneal chemotherapy for peritoneal carcinomatosis in order to increase tissue penetration and cytotoxicity of the delivered anti-neoplastic agent into the peritoneal cavity following cytoreduction [41,42]. Hyperthermia cytotoxic effect is exerted primarily through inhibition of functions essential to DNA replication, transcription and repair [43,44]. However, the synergistic anti-tumor effect of combined hyperthermia and intraperitoneal chemotherapy provides the rationale for the current treatment approach to peritoneal carcinomatosis [41,45]. This synergistic cytotoxic effect of intraperitoneal hyperthermic (42–43°C) chemotherapy is an effective method for eradicating residual peritoneal surface disease up to 2.5 mm remaining in the abdomen after CCRO – 1 (Table II) CRS. Although HIPEC allows high local drug concentrations to exposed peritoneal surface tumors, one important limiting factor is the narrow depth of tissue penetration by the delivered heated cytostatic agent [46]. Depth of drug peritoneal penetration is limited to ≤3 mm from the parietal peritoneal surface [47,48]. Hence, the efficacy of HIPEC is inversely proportional to the volume of residual disease. Therefore the therapeutic benefit is maximized only when all grossly apparent disease is resected (complete cytoreduction, CCRO),
 Unlike the case of colorectal liver metastasis, where R0 resection is possible in approximately 90% of patients referred to surgical therapy, only about half of patients with peritoneal carcinomatosis undergo CCR0/1 resection. This is attributed mainly to delayed referral, lack of acceptance of CRS/HIPEC by the oncological community, lack of diagnostic tests to identify PSMs early in the natural history of disease.

Optimal therapeutic efficacy is achieved when intraperitoneal heated chemotherapy is administered immediately following maximal cytoreduction (CCR0–1), thereby minimizing trapping of viable peritoneal tumors cells in fibrin and post-operative adhesions, and maximizing kill of hypoxic tumor cells shed during resection [49]. Adhesions are lysed during cytoreduction to facilitate uniformity of distribution of chemotherapy containing perfusate, to maximize direct contact of drug with residual peritoneal tumor cells, and to harness the advantage of “thermo-chemotherapeutic” anti-tumor synergism [50–52].

**CLINICAL TRIALS: COLORECTAL CANCER**

Despite advances in early detection of colorectal carcinoma through periodic screening, peritoneal disease spread continues to be a common mode of disease progression, as up to 10% of patients with colorectal adenocarcinoma have synchronous peritoneal spread at the time of primary resection, and up to 25% of patients with recurrent colorectal cancer have disease confined to the peritoneal surface [53,54]. Peritoneal carcinomatosis represents a major treatment challenge in oncology. Once considered a variant of systemic spread of disease, peritoneal carcinomatosis of colorectal origin was treated with systemic chemotherapy alone. Systemic multi-drug chemotherapy has not altered the natural history of peritoneal carcinomatosis, as patients suffer disease progression and functional deterioration due to visceral obstruction, malignant ascites and cancer cachexia over a limited median survival of 6–9 months [54–56].

Novel first-line 5-fluorouracil (5-FU)/leucovorin (LV)-based chemotherapeutic regimens to treat hematogenous metastases (liver and lung) of colorectal carcinoma, including Oxa1iplatin (FOLFOX) and Irinotecan (IFL, FOLFIRI) with or without targeted antibody therapy utilizing Bevacizumab (IFL/Bevacizumab) or Cetuximab, have increased response rates (Fig. 1) and median survival (12–20 months) significantly over what has been the benchmark systemic therapy regimen over the past four decades—5-FU or 5-FU/LV [57–67]. However, long-term survival for patients with hematogenous systemic disease spread remains poor, and the outcomes for patients with advanced disease confined to peritoneal surfaces treated with these modern agents, indeterminate.

Peritoneal carcinomatosis of colorectal cancer origin has long been considered to have a dismal prognosis. A multi-center prospective study determined median survival in this group of patients to be 5 months [55]. A retrospective analysis of patients with colorectal cancer and peritoneal carcinomatosis reported median overall survival of 7 months [54]. The therapeutic paradigm for peritoneal carcinomatosis has shifted from systemic therapy alone to a multi-modality approach consisting of CRS followed by HIPEC, an approach that has shown promising oncological outcomes.

A recently published multi-center registry study of over 500 patients with peritoneal carcinomatosis of colorectal origin treated with this multi-modality approach reported median overall survival of 19.2 months, and 3- and 5-year overall survival rates of 39% and 19%, respectively [68]. For patients with no macroscopic residual disease after cytoreduction (CCR0) in that study, 3- and 5-year overall survival was 47% and 31%, with median survival of 32.4 months. Importantly, these outcomes are similar to those reported following complete resection of colorectal liver metastases. Treatment with adjuvant systemic chemotherapy after cytoreduction and perioperative hyperthermic chemotherapy was an independent predictor of improved survival on multivariate analysis. This study, though retrospective in nature, suggested that improved outcomes were possible with a combined modality treatment approach incorporating CRS, regional intraperitoneal chemotherapy with or without adjuvant systemic therapy in patients that could otherwise expect limited survival ranging from 5 to 8 months [53–55]. Overall survival in a large international registry study was consistent with that reported in prior smaller Phase II studies of combined cytoreduction and perioperative HIPEC for peritoneal carcinomatosis of colonic origin [68–71]. A single-institution, randomized controlled (Phase III) trial demonstrated the superiority of this combined modality approach for patients with colorectal peritoneal carcinomatosis over adjuvant systemic therapy with or without surgical palliation [72].

One hundred five patients with colorectal peritoneal carcinomatosis were randomly assigned to receive “standard” 5-FU/LV, systemic chemotherapy or HIPEC with Mitomycin C (HIPEC: Mitomycin C, 35 mg/m² at 41 °C for 90 min) following aggressive cytoreduction. After a median follow-up time of 22 months, median survival was increased significantly in the CRS/HIPEC arm of the study: 22.4 versus 12.9 months; hazard ratio = 0.55: 95% CI, 0.32–0.95. The analysis was conducted on an intent-to-treat basis and study design required randomization prior to operation such that only 37% underwent complete cytoreduction (CCR0). Considering that the maximum benefit achieved with HIPEC comes from a complete cytoresection, the results of the experimental arm should be considered underestimated. This was the first randomized trial which showed survival benefit in patients with colorectal carcinomatosis treated with cytoreduction and HIPEC when compared to palliative chemotherapy [72]. However, the study utilized a dated systemic therapy regimen consisting of 5-FU (400 mg/m² IV bolus) and Leucovorin (80 mg/m² IV) administered weekly for 26 weeks or until progression, intolerable toxicity or death, with or without palliative surgery.

The absolute survival benefit of ~10 months in that study was offset by considerable treatment-related morbidity (Grade 4 morbidity = 45%) and mortality (8%) in the study arm. A significant proportion of treatment-associated complications (median operative blood loss 4,000 ml; small bowel fistula, 15%; operative site infection, 6%; renal failure, 6%; pancreatitis, 2%) have been hypothesized to be due to the high dose of intraperitoneal hyperthermic Mitomycin C, which was administered in the context of the trial. Reductions in intraperitoneal Mitomycin C doses have been recommended on that basis. Others have demonstrated significantly lesser treatment-related morbidity (23–35%) and mortality (0–4%) than reported in the Netherlands Cancer
Institute (NKI) randomized trial with HIPEC utilizing reduced Mitomycin doses [73].

The NKI trial demonstrated benefit of CRS with HIPEC for patients with colorectal carcinomatosis, and it challenged the predominant therapeutic nihilism that has been the norm for patients with this disease [72]. The actual contribution of the regional therapy (HIPEC) to the observed survival benefit, despite the considerable cost in terms of treatment-related morbidity evident in that trial, remains in question. However, acceptable therapeutic toxicity has been reported in other studies with relatively lower doses of intraperitoneal Mitomycin C without apparent compromise in treatment efficacy.

Modern multi-agent systemic therapy combining cytotoxic and targeted biological agents has been able to achieve median survival exceeding 20 months for Stage IV colorectal cancer. However, the most common mode of distant disease spread in these studies has been hematogenous dissemination. Patients with peritoneal carcinomatosis with metastatic disease confined to the peritoneal surface treated with complete (CCCR0) cytoreduction and HIPEC showed median survival exceeding 40 months (range 28–60 months) [50]. The actual benefit of modern systemic chemotherapy incorporating combinations of 5-FU, Leucovorin, Oxaliplatin, Irinotecan, Bevacizumab, Panitumumab, and Cetuximab for patients with advanced colorectal carcinoma confined to the peritoneal surface is unknown.

A standardized, evidence-based approach is currently lacking for patients with PSM of colorectal origin. A collaborative trial with surgical quality assurance and modern multi-drug chemotherapy incorporating critical assessment of disease burden, determinants of complete cytoreduction, treatment-related toxicity, quality of life (QOL), and survival is imperative. The NKI trial, although not perfect, has provided the basis and impetus for further study. Future randomized trials will use a new reference study arm of appropriately selected patients with potentially curable regionally advanced colorectal carcinoma confined to the parietal peritoneal surface.

Based on the consensus statement of the Peritoneal Surface Oncology Group (PSOG) published in 2007 [74], a prospective randomized clinical trial was designed by the United States Military Cancer Institute (USMCI) and the American College of Surgeons Oncology Group (ACOSOG). This inter-group trial will start accruing patients in 2009. Patients with newly diagnosed peritoneal dissemination of colon adenocarcinoma at time of initial presentation or time of disease recurrence, those without hematogenous metastasis (lung, liver, bone, brain, distant nodal, e.g., periaortic lymph node), systemic therapy or CRS-naive (aside from adjuvant systemic therapy and resection of the primary colonic tumor) for Stage IV disease, and those with good performance status and intraperitoneal disease (carcinomatosis) deemed suitable for complete cytoreduction (PCI\(<20\)) will be eligible for study. Patients will be randomly assigned to either best available systemic therapy or CRS + HIPEC followed by best systemic therapy. Patients that fail systemic therapy will be crossed over to the multi-modality arm at time of disease progression (Fig. 2). The primary endpoint of this multi-center clinical trial is overall survival. Secondary aims are to determine whether the CRS followed by HIPEC and best available systemic therapy is superior to best available systemic therapy alone in terms of improving progression free survival (PFS; disease progression or death from randomization), QOL, circulating tumor cell (CTC) burden, and aggregate treatment-related toxicity.

This study will define the role of CRS + HIPEC in the modern-day management of peritoneal carcinomatosis of colon origin.

**CLINICAL TRIALS: GASTRIC CANCER**

Adenocarcinoma of the stomach is the fourth most common cancer and the second leading cause of cancer death worldwide, with almost a million new cases per year (Table 1). The incidence of the disease decreased in the United States and other parts of the world, mainly of distal, intestinal type gastric cancer. On the other hand, the incidence of proximal diffuse type adenocarcinoma of the gastric cardia has been increasing, particularly in the western countries [75]. Although survival has improved over the past three decades, 5-year survival remains relatively low at 25%, exceeded in severity only by cancer of the lung (16%), esophagus (16%), liver (11%), and pancreas (5%).

Peritoneal dissemination of adenocarcinoma of the stomach is common, either at presentation, in the form of malignant ascitis, macroscopic tumor deposits or microscopic dissemination detected by cytology of peritoneal washings, or as a manifestation of recurrent disease, which is either locoregional or peritoneal [76,77]. Hence, peritoneal dissemination is a major pattern of therapeutic failure, occurring in 38–60% of patients with recurrent gastric adenocarcinoma [78,79]. Serosal invasion, scirrhous-type stromal reaction and female gender are three independent predictors of peritoneal dissemination. In a study conducted in resected gastric cancer patients, the detection of free tumor cells in peritoneal washings was also shown to be an independent adverse prognostic factor [80].

Peritoneal cancer cells detected by intraoperative peritoneal washings are associated with higher rates of recurrence of gastric cancer [81]. Tumor cells spread by the mechanisms described above, principally by entrapment within fibrin exudates, which protect cancer cells from host defenses [82]. An evolution in surgical treatments in the form of CRS and HIPEC is directed against this mechanism of tumor cell spread to peritoneal surfaces. Data have emerged recently recognizing the oncological benefits of adjuvant perioperative intraperitoneal chemotherapy for PSM of gastric origin.

Surgical treatment is the mainstay of gastric cancer treatment. An absolute requirement for potentially curative resection is complete resection of all disease-bearing sites. Outcome after complete resection is mainly related to serosal penetration and the extent of regional lymph node involvement. Extended lymphadenectomy (D2 resection) is accepted as standard of practice in East Asia; however, it remains controversial in western countries. So-called D2 lymphadenectomy is considered an appropriate option where surgeons can demonstrate acceptable operative morbidity and mortality.

Adjuvant systemic chemotherapy following potentially curative gastric resection is a viable option for the reduction of disease recurrence and disease-related mortality. In a meta-analysis of 14 randomized trials evaluating the role of adjuvant chemotherapy, only a small survival advantage was found compared to surgery alone [83].

A neoadjuvant regimen of epirubicin, cisplatin, and infused fluorouracil (ECF) was shown in a prospective randomized trial (MAGIC trial) to increase 5-year overall survival by an absolute 13% (36% vs. 23%) as compared to resection alone [84]. This approach of neoadjuvant therapy was adopted by many medical centers, mainly in Europe.
Combined modality therapy with chemotherapy and external beam radiation was shown in a large prospective randomized clinical trial (Intergroup 0116) to improve 5-year overall survival by an absolute 11% [85]. Despite the major criticism of this trial showing poor quality of surgical resection (54% D0 resections), and the fact that prior clinical trials showed no benefit for either radiation therapy alone or combined with chemotherapy, this form of pre–post-operative combined modality therapy was widely adopted, and represents a current standard of practice mainly in North America and Europe.

Many cytotoxic agents have been studied for the treatment of metastatic adenocarcinoma of the stomach. Multiple clinical trials evaluating the efficacy and toxicity of various single- and multi-agent regimens showed fair response rates. However, median survival in treated Stage IV remains modest, 6–16 months [86]. As the most common site to harbor dissemination of gastric adenocarcinoma is the peritoneal cavity combined with locoregional disease-recurrence, most patients with advanced gastric cancer stand to benefit from intraperitoneal therapy.

Most studies comparing intraperitoneal chemotherapy to systemic therapy or surgery alone were conducted in the adjuvant setting. Yan et al. [19] recently reviewed all clinical trials studying intraperitoneal chemotherapy in its various different forms in resectable gastric cancer. Searching all public domains, 106 published reports were identified, of which were 14 prospective randomized clinical trials. One trial was excluded from the analysis because it compared hyperthermic to normothermic intraperitoneal chemotherapy. In the 13 randomized clinical trials analyzed, 1,648 patients were randomly assigned to receive either intraperitoneal chemotherapy (n = 873) or no intraperitoneal therapy (n = 775). Results of this analysis are summarized in Table III. Only one clinical trial evaluated the role of HIPEC in gastric adenocarcinoma compared surgery + HIPEC to surgery alone. The next step in the design of a clinical trial is randomization of patients undergoing CRS + HIPEC to receive chemotherapy (either pre- or post-operatively) or not.

Based on the data accumulated thus far from Phase II and small Phase III trials, a multi-center prospective randomized clinical trial is in its planning stages by the European Union Network of Excellence on Gastric Cancer (EUNE). This trial will study the added value of HIPEC to the current paradigm in the treatment of gastric cancer established by the MAGIC trial. Patients with serosal invasion (T3–4); lymph node metastasis (N1) or patients with positive peritoneal cytology will be included. All patients will receive three cycles of platinum-based therapy as defined by the MAGIC trial (Fig. 3), followed by D2 resection. Patients will be then randomized to undergo surgery with HIPEC or surgery alone.

**CLINICAL TRIALS: OVARIAN CANCER**

Ovarian cancer is a major health problem worldwide, with an estimated 205,000 new cases year [17]. Therapy is dependent on the stage disease a time of diagnosis. This disease remains a formidable treatment challenge, as most patients with ovarian carcinoma are diagnosed at advanced stage of disease [87]. Therefore, frontline therapy for many newly diagnosed ovarian cancers includes CRS followed by combined platinum- and taxane-based systemic therapy [88–92]. In patients whose extent of disease precludes primary resection, primary chemotherapy is given, followed by interval debulking after three cycles of therapy. However, 60–70% of patients will suffer disease recurrence and disease-related mortality [88,89]. The two most frequent patterns of recurrence are locoregional (lymph node) and peritoneal surface dissemination. CRS may be applied as frontline therapy, interval debulking or at the time of disease recurrence. The principal goal of CRS is optimal debulking, removing all primary disease and, if possible, all metastatic disease, as the size of the disease remaining after debulking correlates with survival [93,94].

The high percentage of recurrent disease despite optimal treatment can be explained by residual tumor nodules remaining after cytoreduction, which is characteristically resistant to systemic chemotherapy.

Intrapерitoneal chemotherapy is an attractive mode of treatment for ovarian carcinoma, which typically remains confined to the peritoneal cavity for most of its natural history. In a Phase III clinical trial (GOG 172) reported by Armstrong et al., [24] post-operative intraperitoneal chemotherapy combined with systemic therapy was shown to be superior to systemic chemotherapy alone. Catheter-related problems remain the greatest obstacle for early (EPIC) or delayed (DPIC) intraperitoneal chemotherapy as shown by another report of the same clinical trial [95]. Fifty-eight percent of the patients did not complete six cycles of intraperitoneal therapy. In 34% of these patients intraperitoneal treatment was discontinued due to catheter-related complications. Altogether, post-operative intraperitoneal chemotherapy was shown in three randomized controlled trials to result in an overall and progression-free survival benefit when cisplatin is administered intraperitoneally in patients with Stage III, optimally debulked ovarian carcinoma [24,90–91]. In the study, reported by Albers et al., [90] optimally debulked patients (n = 546) with Stage III ovarian carcinoma were randomized to receive either intravenous cyclophosphamide and cisplatin versus intravenous cyclophosphamide and intraperitoneal cisplatin (100 mg/m²). Estimated significant improvement in median overall survival was achieved in the intraperitoneal treatment group (49 months vs. 41 months). In the study reported by Markman et al. [91], patients (n = 462) that underwent optimal debulking, were randomized to receive either IV paclitaxel followed by IV cisplatin, or IV carboplatin, then IV paclitaxel followed by intraperitoneal cisplatin (100 mg/m² every 3 weeks for six courses). A PFS benefit was demonstrated in patients receiving intraperitoneal chemotherapy (27.9 months vs. 22.2 months; P = 0.01). These studies show that multi-modality therapy in the form of cytoreduction, delayed intraperitoneal chemotherapy and systemic therapy provides a survival over cytoreduction and systemic therapy alone.

HIPEC was studied as a frontline therapy for ovarian carcinoma in small-scale clinical trials [96–97]. Large-scale Phase II and III clinical trials are lacking to define the role for HIPEC as a frontline therapy in addition to CRS in Stages III and IV ovarian carcinoma.

Neoadjuvant chemotherapy followed by interval debulking may improve results of surgically treated patients with advanced peritoneal surface disease of ovarian origin [98]. Adding HIPEC to interval

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Control arm</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery + HIPEC</td>
<td>Surgery alone</td>
<td>0.60</td>
<td>0.43–0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgery + HIPEC + EPIC</td>
<td>Surgery alone</td>
<td>0.45</td>
<td>0.29–0.68</td>
<td>0.0002</td>
</tr>
<tr>
<td>Surgery + NPIEC</td>
<td>Surgery alone</td>
<td>0.67</td>
<td>0.44–1.01</td>
<td>0.11</td>
</tr>
<tr>
<td>Surgery + EPIC</td>
<td>Surgery alone</td>
<td>0.64</td>
<td>0.37–1.10</td>
<td>0.11</td>
</tr>
<tr>
<td>Surgery + DPIC</td>
<td>Surgery alone</td>
<td>0.89</td>
<td>0.51–1.55</td>
<td>0.68</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence intervals; HIPEC, hyperthermic intraoperative intraperitoneal chemotherapy; EPIC, early post-operative intraperitoneal chemotherapy; NPIEC, normothermic intraoperative intraperitoneal chemotherapy; DPIC, delayed post-operative intraperitoneal chemotherapy.
or second look cytoreductive surgery was reported by several groups in small pilot studies [96,99]. A prospective, multi-center clinical trial is currently being conducted by the NKI. Patients are treated by three cycles of systemic therapy followed by interval debulking surgery with or without HIPEC.

A number of retrospective studies and Phase II studies reported treatment of patients with recurrent and heavily pre-treated ovarian carcinoma with HIPEC and CRS [100]. Chemotherapeutic agents that were used in these studies were mainly cisplatin varying in dose of 25–150 mg/m², and duration of perfusion ranging from 60 to 90 min, as well as intraperitoneal temperature during HIPEC, which ranged from 39 to 42.5°C. From these studies it can be concluded that HIPEC combined with CRS is feasible and can be achieved with acceptable treatment-related toxicity. Morbidity and mortality rates in these studies with heavily pre-treated patients vary, 0–17% and 0–4% respectively. In addition, factors which affect progression-free and overall survival are platinum resistance, CCR, extension of peritoneal carcinomatosis, patient age, and interval between diagnosis of disease or disease progression and CRS. Currently, there is no prospective clinical trial evaluating the effect of CRS + HIPEC in the treatment of recurrent or heavily treated patients with ovarian carcinoma. A large-scale clinical trial designed to address the role of CRS and HIPEC in recurrent ovarian carcinoma is warranted.

**SUMMARY**

Current treatment of peritoneal carcinomatosis, with the exception of a single institution Phase III trial in CRC, is based mainly on retrospective data with small prospective Phase II clinical trials. There is no doubt that in order to establish clinical treatment guidelines that will be accepted by the medical and the surgical oncology communities, large-scale clinical trials must be conducted in PSM of colorectal, gastric, and ovarian cancer origin. Smaller, Phase II clinical trials combined with international and national prospective registries will provide the data to support the treatment of diseases with lower incidence and will establish the efficacy of different HIPEC regimens. The main obstacles for conducting such clinical trials are funding and supporting organizations. Thus far, leading cooperative oncology groups have shown reluctance in supporting, much less spearheading clinical trials studying HIPEC or CRS.

Therefore, large-scale clinical trials will have to be conducted by international groups interested in improving the outcome of peritoneal carcinomatosis.

**REFERENCES**


