Evidence-based medicine in the treatment of peritoneal carcinomatosis: past, present and future

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Introduction

In order to discuss the rational for the treatment of peritoneal surface malignancies it is imperative to define the problem, its magnitude, and understand its underlying biology and pathophysiology.

Peritoneal carcinomatosis (PC) is defined as the spread and implementation of cancer cells in the peritoneal cavity resulting in malignant tissue deposits involving parietal peritoneum surfaces or the visceral peritoneum lining abdominal and pelvic organs. Peritoneal carcinomatosis may be associated with accumulation of fluid in the peritoneal cavity containing cancer cells, a condition known as malignant ascitis (MA).

Primary neoplastic diseases of the peritoneum are rare and include peritoneal mesothelioma and primary peritoneal carcinoma. However, Peritoneal metastasis originating from colorectal carcinoma, ovarian carcinoma, gastric carcinoma, pancreatic carcinoma, and appendiceal carcinoma are more common [1]. Peritoneal surface malignancies (PSM) can present in the form of MA, multiple small tumor nodules, tumor masses in various sizes, layers of tumor tissue enveloping peritoneal surfaces and organs, or mucin deposits, a condition 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 PC are generally unknown. Metastatic tumor deposits spread within the peritoneal cavity by a different and unrelated mechanism compared to the hematogenous spread of malignant diseases resulting in visceral metastasis or lymphatic spread of tumor cells resulting in regional lymph node metastasis. Several theories were proposed to explain the formation of PC [2].

A "tumor rupture" physical theory was proposed by several investigators. According to the "tumor rupture" theory, a tumor of gastrointestinal or gynecological origin infiltrating the serosal layer can exfoliate neoplastic cells into the peritoneal cavity, resulting in PC; this process can be made easier by the surgical manipulation. [3,4]. Although this theory may applied to some tumors, such as ruptured gastrointestinal stromal tumors (GIST) or other large solid tumors, it is very difficult to explain how low rectal cancers with no direct communication to the peritoneal cavity can still result in PC. Also the observation that the incidence of PC following perforated adenocarcinoma of the colon is not significantly different than the incidence of PC following non-perforating tumors contradicts this theory. Exfoliation of cancer cells from a tumor would create a random pattern of PC. However, in most cases the pattern of PC spread is predictable [5].

Mucin production is the hallmark of many secondary PSMs. Extracellular or intracellular mucin secretion by cancer cells is associated with higher incidence of peritoneal spread. These observations are the basis of the "secretion theory" which suggests that the peritoneal cavity is a hostile environment for cancer cells and acts as a barrier for systemic cancer spread. However, secretion of growth factors, nutritional factors, or other substances alone or embedded in mucinous substance by the tumor
cells, should be able to turn the peritoneal surface from a hostile environment into a fertile area for the growth of tumor deposits.

Recent studies by Yonemura et al [6,7] provide new histological description of the peritoneal lymphatic system. They described lymphatic stomata, peritoneal lymphatic orifices connecting the peritoneal surface with subperitoneal lymphatic system and the "milky spots", small aggregates of lymphatic vessels, lymphocytes and macrophages present in the peritoneum and omentum. According to several independent observations [8-11], cancer cells can pass through milky spots and lymphatic stomata, to be trapped and proliferate in the subperitoneal lymphatic system.

In summary, the pathophysiology of PC is a multi step process involving cancer cells either exfoliated from tumors with direct communication to the peritoneal cavity or delivered by the lymphatic system into the peritoneal cavity and submesothelial spaces. Growth factors, angiogenic factors either embedded in mucin or secreted directly into the peritoneal cavity allow the implementation of cancer cells on the peritoneal surface. The implementation usually starts in areas rich in lymphatic stomata such as the greater omentum, diaphragm and pelvis [12].

**Epidemiology**

Primary PSMs are rare tumors and include peritoneal mesothelioma and primary peritoneal carcinoma.

Peritoneal mesothelioma is a rare tumor, more common in 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 consists about 10%-20% of all mesothelioma cases [13,14]. There are three subtypes of peritoneal mesothelioma; epithelial, multicycstic, and biphasic.

Primary peritoneal carcinoma (PPC), 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%-13.8% of ovarian carcinomas [16]. There are three types of PPC; serous papillary carcinoma, mixed epithelial carcinoma, and malignant mixed Mullerian tumor. Secondary PSMs are more common (table 1), [17].

**Current management**

The current treatment of PSM is conducted according to guidelines and consensus statements based on retrospective data and very few prospective clinical trials. Since primary PSM is rare, extrapolation of data was obtained from clinical trials of related disease. For example, the data obtained from clinical trials conducted on pleural mesothelioma are used to treat peritoneal mesothelioma and the data obtained from ovarian cancer trials are used for the treatment of PPC [14,17]. These data should be interpreted with caution, the differences studied in detail and new treatment guidelines should be established accordingly. However, it is unlikely that prospective, Phase III, clinical trials will ever be conducted in such rare diseases.
As far as secondary PSM is concerned, despite the larger number of patients treated, there are very few clinical trials. In PC originating from CRC most patients are treated either by supportive care with a nihilistic approach or by palliative systemic therapy regimes obtained from clinical trials reporting the results of treatment in visceral metastasis and not PC. Surgery is performed only for palliation or emergencies such as obstruction or perforation. Because of the poor outcome and the low response rates of PC to systemic therapy, these nihilistic and palliative approaches are slowly being replaced by a combined modality therapy approach of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic therapy [18]. This approach is discussed in detail below.

The current treatment of gastric cancer is based mainly on surgery combined with either chemotherapy or chemoradiation in cases were the tumor has not been spread outside the stomach and regional lymph nodes. Peritoneal spread of gastric cancer is common and currently treated mainly by systemic therapy. Despite several clinical trials showing the efficacy of various forms of intraperitoneal (IP) chemotherapy, this form of therapy is rarely used. The topic of clinical trials comparing IP 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 PC and with poor outcome. The minority of cases are amenable to surgical resection and even in the face of R0 resection and administration of systemic adjuvant therapy, the outcome is poor. Most of the cases are diagnosed at a stage where surgical resection is futile and are treated either by systemic therapy or best supportive care [20,21]. The overall 5-year survival rate is 5% and requires novel therapeutic approaches.

Ovarian cancer is usually diagnosed in advanced stages where peritoneal dissemination is present. The current treatment varies between institutions and countries. Debulking surgery for PC originating form ovarian cancer is advocated by many [22]. However, the extent or timing of surgery is controversial and the definition of "optimal debulking" also varies between institutions [23]. The good response rates of ovarian cancer to platinum based therapy advocates neo-adjuvant administration of systemic therapy followed by debulking surgery. However, despite the good initial response rates, recurrence rates are high and platinum resistant tumors are unlikely to respond to any current form of therapy. The role of IP therapy in ovarian cancer was established by several clinical trials. In a recent report of a prospective randomized clinical trial, IP chemotherapy was found to be superior to systemic therapy [24]. This disease may be managed with better outcome by CRS+HIPEC but this approach was never tested in a large scale clinical trial.

The rational for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Surgical therapy was traditionally used for the treatment of primary, non-metastatic solid tumors. Successful treatment of epithelial tumors is highly dependent on their resection with surrounding healthy tissue without involvement of the resection margins (R0 resection). Surgical treatment of metastasis in the liver, lung or other organs was shown to be of benefit and was accepted as a standard of care mainly in colorectal cancer but also in several other kinds of tumor, always respecting the R0 resection criteria. In traditional surgical oncology the R0 resection concept is mandatory for successful treatment, but not enforceable in the treatment of PC.
The principles of a new surgical technique for resection of peritoneal surfaces and organs covered by tumor-bearing visceral peritoneum for the radical treatment of PSM were first reported by Sugarbaker et al [25], introducing the new concept of cytoreductive surgery, a new staging system of PC, and a scoring system to define the completeness of cytoreduction. (CCR) [26]. (Table 2).

Confinement of disease to the parietal peritoneal surface, in absence of systemic metastasis, was the basis for surgical eradication of disease through aggressive cytoreduction. However, surgery alone has not achieved significant improvement in survival in patients with peritoneal carcinomatosis, as grossly apparent or microscopic disease inevitably remains after even aggressive cytoreduction [27]. Viable tumor cells become sequestered in avascular intra-peritoneal adhesions explaining the resistance to and the ineffectiveness of systemic chemotherapy for peritoneal carcinomatosis [28]. Since R0 resection is not feasible in PSM and the relative tissue concentration of agents delivered systemically is relatively low in peritoneal tumor deposits, better 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, the penetration of the drugs into the tissue is limited to a 2-3 mm superficial layer. The presence of an anatomic barrier, the peritoneal-plasma partition, has enabled the exposure of the peritoneal surface to high local concentrations of chemotherapy far in excess of systemically administered agents when drug delivery is intra-peritoneal [29-34]. High molecular weight drugs 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 dose-dense intra-peritoneal 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 the problem of systemic chemotherapy resistance and, with its reduced systemic toxicity, 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. Intra-peritoneal hyperthermia, shown to be technically feasible [40], was integrated into the treatment paradigm of cytoreduction and intra-peritoneal chemotherapy for peritoneal carcinomatosis in order to increase tissue penetration and cytotoxicity of the delivered anti-neoplastic agent [41,42]. Hyperthermia itself is cytotoxic mainly by inhibition of functions essential to DNA replication, transcription and repair [43,44]. However, the combined anti-tumor effect of heat and intra-peritoneal chemotherapy is the basis for the current treatment approach to peritoneal carcinomatosis [41,45]. The synergistic killing effects of hyperthermia (42°C-43°C) and cytotoxic agents can provide an effective method of eradicating residual disease up to 2.5 mm left in the abdomen after CCR0-1 cytoreductive surgery. Although hyperthermic intra-peritoneal chemotherapy allows high local drug concentrations to exposed peritoneal surface tumors, one important limiting factor is the narrow depth of tissue penetration by the delivered cytostatic agent [46]. Depth of drug peritoneal penetration is limited to ≤ 3 mm from the parietal peritoneal surface [47,48]. Hence, the efficacy of hyperthermic intra-peritoneal chemotherapy is inversely proportional to the volume of residual disease; thereby,
therapeutic benefit is maximized when all grossly apparent disease is resected (complete cytoreduction).

Optimal therapeutic efficacy is achieved when intra-peritoneal heated chemotherapy is administered immediately following maximal cytoreduction (CCR 0-1), thereby minimizing trapping of viable peritoneal tumors cells in fibrin and post-operative adhesions, and maximizing kill of tumor cells shed during resection [49]. Adhesions are lysed during cytoreduction to facilitate uniform distribution of perfusate, maximize direct contact of drug with residual peritoneal tumor cells, and harness the advantage of “thermo-chemotherapeutic” anti-tumor synergism [50-52].

Clinical trials: colorectal cancer

Despite advances in early detection of colorectal carcinoma, peritoneal disease spread continues to be a common mode of disease progression, as 8% of patients with colorectal adenocarcinoma have synchronous peritoneal spread of disease at time of primary resection, and up to 25% of patients with recurrent colorectal cancer have disease confined to the peritoneal cavity [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. 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 to 9 months [54-56].

Novel first-line 5-Fluorouracil/Leucovorin-based chemotherapeutic regimens to treat metastatic (liver and lung) colorectal carcinoma, including Oxaliplatin (FOLFOX) and Iринотекан (IFL, FOLFIRI) with or without targeted antibody therapy utilizing Bevacizumab (IFL/Bevacizumab) or Cetuximab, have increased response rates (figure 1) and median survival (12 months to 20 months) significantly over what has been the benchmark over the past four decades - 5-FU or 5-FU/LV [57-67]. However, long-term survival for patients with 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 poor 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 carcinoma reported median overall survival of 7 months in patients with peritoneal carcinomatosis [54]. The therapeutic paradigm to peritoneal carcinomatosis consisting of cytoreductive surgery followed by hyperthermic intra-peritoneal chemotherapy 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 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, similar to outcomes following complete resection of colorectal liver metastases. Treatment with adjuvant systemic chemotherapy after cytoreduction and peri-operative 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 cytoreductive surgery,
regional intra-peritoneal chemotherapy with or without adjuvant systemic therapy in patients that could otherwise expect limited survival ranging from 5-8 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 hyperthermic intra-peritoneal chemotherapy for peritoneal carcinomatosis of colonic origin [69-80]. 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 [81].

One hundred five patients with colorectal peritoneal carcinomatosis were randomly assigned to receive “standard,” 5-FU/LV, systemic chemotherapy or hyperthermic intra-peritoneal chemotherapy with Mitomycin C (HIPEC; Mitomycin C, 35 mg/m² at 41°C for 90 minutes) following aggressive cytoreduction. After a median follow up time of 22 months, median survival was increased significantly in the HIPEC arm of the study: 22.4 vs. 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 cytoreduction, 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 [81]. However, the study utilized a systemic therapy regimen in the form of 5FU (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 intra-peritoneal hyperthermic Mitomycin C, which was administered in the context of the trial. Reductions in intra-peritoneal Mitomycin doses have been recommended on that basis. Others have demonstrated significantly lesser treatment-related morbidity (23%-35%) and mortality (0-4%) with HIPEC utilizing reduced Mitomycin doses [82,83].

The NKI trial demonstrated benefit of cytoreductive surgery with HIPEC for patients with colorectal carcinomatosis, and it challenged the predominant therapeutic nihilism that has been the norm for patients with this disease [81]. 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 intra-peritoneal Mitomycin without apparent compromise in treatment efficacy.

Modern systemic therapy with combination cytotoxic and biological agents resulted in a 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 (CCR0) cytoreduction and HIPEC showed median survival exceeding 40 months (range 28-60 months) [50]. The benefit of modern systemic chemotherapy incorporating combinations of 5-FU,
Leucovorin, Oxaliplatin, Irinotecan, Capecitabine, 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 peritoneal surface malignancy from 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 and survival is imperative. The NKI trial, although not perfect, has provided the basis and impetus for further study utilizing a new reference study arm for future randomized trials of appropriately selected patients with potentially curable regionally advanced colorectal carcinoma confined to the pariетal peritoneal surface.

Based on the consensus statement of the Peritoneal Surface Oncology Group (PSOG) published in 2007 [84], a prospective randomized clinical trial was designed by the PSOG and the United States Military Cancer Institute (USMCI). This, multicenter clinical trial will start accruing patients in 2009. Included will be patients with PC of colorectal origin with a PCI<20 and a good performance status. Patients will be randomly assigned to either best available systemic therapy or cytoreductive surgery + HIPEC followed by systemic therapy. Patients that will fail systemic therapy will be allowed to cross over to the surgical arm (figure 2).

Main endpoint of this multicenter trial is overall survival with secondary endpoints of progression-free survival, peritoneal progression-free survival and quality of life. This study will define the role of CRS+HIPEC in the management of PC of colorectal 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 [85].

Peritoneal dissemination of adenocarcinoma of the stomach is common. Either at presentation, in the form of MA, macroscopic tumor deposits or microscopic dissemination detected by peritoneal washings or as a manifestation of recurrent disease. A large portion of recurrent disease will be either locoregional or peritoneal [86,87].

Peritoneal cancer cells detected by intra-operative washings are associated with higher rates of recurrence of gastric cancer [88]. Tumor cells spread by the mechanisms described above are entrapped within fibrin exudates, which protect them from host defences. These events are referred to as the “tumor cell entrapment" [89]. Not only is it important in understanding of the pathogenesis of both resection site and peritoneal surface recurrence, but also in an appreciation of the beneficial effects of adjuvant perioperative intraperitoneal chemotherapy.

As mentioned, peritoneal dissemination is a major pattern of therapeutic failure, and its recurrence rate ranges from 38% to 60%, being 53,3% in a recent large cohort of patients [90,91]. Serosal invasion, scirrhous-type stromal reaction and female gender were three independent factors found to be associated with peritoneal dissemination. In a study conducted in resected gastric cancer patients, the detection
of free tumor cells in peritoneal washings was proven to be an independent unfavourable prognostic factor [92].

Surgical treatment is the mainstay of gastric cancer treatment. Outcome after complete resection is mainly related to serosal penetration and the extent of regional lymph node involvement. The extended lymphadenectomy (D2 resection) is accepted as standard of care in East Asia. However it is still controversial in western countries where D2 dissection is considered an appropriate option where surgeons can demonstrate low operative mortality.

Adjuvant systemic chemotherapy following surgery with curative intent is a viable option for the reduction of disease recurrence and disease related mortality. In a meta-analysis of 14 randomised trials evaluating the role of adjuvant chemotherapy, only a small survival advantage was found compared to surgery alone [93].

A neo-adjuvant regimen of epirubicin, cisplatin, and infused fluorouracil (ECF) was shown in a prospective randomized trial (MAGIC trial) to increase 5-year overall survival by 13% (36% Vs. 23%) as compared to surgery alone [94]. This approach of neoadjuvant therapy was adopted by many medical centres 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 [95]. Despite the criticism on 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-postoperative combined modality therapy was widely adopted, 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 regimens showed good response rates. However, the median survival remains in the range of 6-16 months [96]. Since the most common site to harbour metastasis of gastric origin is the peritoneal cavity combined with locoregional disease-recurrence, most patients with advanced gastric cancer may benefit from intra-peritoneal therapy.

Most studies comparing IP chemotherapy to systemic therapy or surgery alone were conducted in the adjuvant setting. Yan et al [19] recently reviewed all clinical trials studying IP chemotherapy in its different forms in resectable gastric cancer. Searching all public domains, they found 106 reports, of which 14 prospective randomized clinical trials were identified. One trial was excluded from the analysis because it compared hyperthermic IP chemotherapy to normothermic IP chemotherapy. In the 13 clinical trials analysed, 1648 patients were randomly assigned to receive either IP chemotherapy (n=873) or no IP therapy (n=775). Results of this analysis are summarized in table 3. All but one clinical trial evaluating the role of HIPEC in gastric cancer compared Surgery + HIPEC to surgery alone. Therefore, the next step is the design of a clinical trial comparing the addition of HIPEC to surgery with adjuvant or neoadjuvant systemic chemotherapy. Based on the data accumulated so far from Phase II and small Phase III trials, a multicenter prospective randomized clinical trial is currently designed 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 set 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 set by the principals of the MAGIC trial (Figure 3), followed by D2 resection. Patients will be then randomized either 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 for OC is dependent on the stage of diagnosis. Most of the cases are diagnosed at advanced stage of disease [97]. Therefore, therapy for newly many diagnosed OC cases (frontline therapy) includes SRC followed by systemic therapy combining platinum compound and taxens [98-102]. For those patients for whom primary surgery is not feasible, primary chemotherapy is given, followed by interval debulking after 3 cycles of therapy. However, 60-70% of patients will suffer disease recurrence [98-99]. The two most frequent recurrence patterns are locoregional (lymph node) recurrence or peritoneal dissemination. Cytoreductive surgery may be applied as frontline therapy, interval debulking or at the time of recurrence. The principal goal of cytoreductive surgery is to remove all of the primary disease and, if possible, all metastatic disease since the size of the remaining disease is related to survival [103,104]. The high percentage of recurrent disease despite optimal treatment can be explained by residual tumor nodules remain following CRS resistant to systemic chemotherapy.

Intraperitoneal chemotherapy is attractive for the treatment of ovarian carcinoma, which 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] IP chemotherapy combined with intra-venous therapy was shown to be superior to systemic chemotherapy alone. Catheter related problems remain the highest obstacle for EPIC or DPIC as shown by another report of the same clinical trial [105]. Fifty-eight percent of the patients did not complete six cycles of IP therapy. Thirty-four percent of these patients discontinued IP treatment due to catheter related complications. Altogether, postoperative intraperitoneal chemotherapy was shown by three randomized controlled trials, to result in an overall and progression-free survival benefit when cisplatin is administered by the IP route in patients with stage III, optimally resected disease [24,100,101]. In the study reported by Alberts et al [100] optimally debulked patients (n=546) with stage III ovarian carcinoma were randomized between intra-venous cyclophosphamide and cisplatin versus intra-venous cyclophosphamide and IP cisplatin (100 mg/m2). An estimated median survival of 41 vs. 49 months was achieved in favor of the IP treated group. In the study reported by Markman et al [101], patients (n=462), with optimally debulking surgery, were randomized between either IV paclitaxel followed by IV cisplatin, or IV carboplatin, then IV paclitaxel followed by IP cisplatin 100 mg/m2 every 3 weeks for 6 courses. A progression free survival of 22.2 vs. 27.9 months was seen in favor of the IP treated group (p=0.01). These studies show that a combination of CRS, DPIC, and systemic therapy has an advantage over CRS and systemic therapy alone.

Hyperthermic intraperitoneal chemotherapy (HIPEC) was reported as a frontline therapy for OC only in small scale trials [106-109]. Large scale Phase II and III clinical trials are mandatory to establish a role for HIPEC as a frontline therapy in addition to CRS in stage III and IV OC.

Neoadjuvant chemotherapy followed by interval debulking surgery may improve results of CRS in patients presenting with advanced peritoneal disease [110].
This approach of adding HIPEC to interval or second look surgery was reported by several groups in small numbers of patients [107, 111-112]. A prospective, multicenter clinical trial is currently conducted by the Netherlands Kanker Institute (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 [113-. Chemotherapeutic agents that were used are mainly cisplatin varying in dose from 25-150 mg/m2; duration of perfusion ranged from 60 to 90 minutes and temperature of the abdominal cavity was maintained at 39 to 42.5oC. From these studies it can be concluded that this treatment regimen is feasible with acceptable toxicity. Morbidity and mortality rates in these studies with heavily pre-treated patients vary between 0-17% and 0-4% respectively. In addition, factors which affect the outcome in terms of overall survival or median time to progression, are platinum resistance, completeness of cytoreduction, extension of peritoneal carcinomatosis, patient age, and interval between diagnosis of and CRS.

Currently, there is no prospective clinical trial evaluating the effect of CRS+HIPEC in the treatment of recurrent or heavily-treated OC patients. A large scale clinical trial designed to address the role of CRS and HIPEC in recurrent OC is warranted.

Summary
Current treatment of PC, 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 guidelines that will be accepted by the medical and the surgical oncology communities, large scale clinical trials should be conducted in PC originating from colorectal, gastric, and ovarian cancer. Smaller, phase II clinical trials combined with international and national prospective registries will provide the data for 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. So far, the main oncology groups showed reluctance in organizing or even supporting 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


Table 1: 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>*<em>Primary PSM</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary peritoneal carcinoma</td>
<td>20,000</td>
<td>100%</td>
<td>20,000</td>
</tr>
<tr>
<td>Peritoneal mesothelioma</td>
<td>2000</td>
<td>100%</td>
<td>2000</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>100</td>
<td>100%</td>
<td>100</td>
</tr>
<tr>
<td><strong>Secondary PSM†</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Colorectal cancer¶</td>
<td>1023152</td>
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<td>153,472</td>
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<td>Gastric Cancer</td>
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<td>Ovarian Cancer</td>
<td>204499</td>
<td>60%</td>
<td>122,699</td>
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<td>Pancreatic cancer</td>
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<td>58,076</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>709,941</td>
</tr>
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</table>

* Incidence estimation form literature reports
†† peritoneal dissemination at diagnosis and at disease recurrence
¶ Including appendecial cancers and pseudomyxoma peritonei
PSM = peritoneal surface malignancies
Table 2: Completeness of cytoreduction (CCR) score

<table>
<thead>
<tr>
<th>CCR category</th>
<th>Tumor remaining following resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visible residual tumor present</td>
</tr>
<tr>
<td>1</td>
<td>Residual tumor of $\leq 2.5$ mm is present</td>
</tr>
<tr>
<td>2</td>
<td>Residual tumor of $&gt;2.5$ mm $\leq 2.5$cm is present</td>
</tr>
<tr>
<td>3</td>
<td>Residual tumor of $&gt;2.5$ cm is present</td>
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Table 3: Results of prospective randomized clinical trials evaluating adjuvant intraperitoneal chemotherapy for gastric cancer (Yan et al Ref. 19).

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Control arm</th>
<th>HR</th>
<th>95% C.I.</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+NIPEC</td>
<td>Surgery alone</td>
<td>0.67</td>
<td>0.44-1.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Surgery+EPI</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  
C.I= Confidence intervals  
HIPEC=hyperthermic intraoperative intraperitoneal chemotherapy  
EPIC= early postoperative intraperitoneal chemotherapy  
NIPEC= normothermic intraoperative intraperitoneal chemotherapy  
DPIC= delayed postoperative intraperitoneal chemotherapy
Figure 1: The improvement in response rates of stage IV colorectal cancer to systemic therapy.

Figure 1 legend: This bar graph represents a summary of clinical trials reporting response rate to systemic therapy in adenocarcinoma of the colon and rectum. Study subjects included mainly patients with liver and lung metastasis.
Figure 2: Study design of the PSOG-USMCI clinical trial.

Primary Outcome
- Overall Survival

Secondary Outcomes
- PFS
- Toxicity burden
- QOL appraisal
- CTC during Rx

Randomization
- Limited Peritoneal Surface Malignancy of Colonic Origin with No prior Cytoreduction
- Sync Vs Met
- Measurable Vs Not meas.

Best Systemic Therapy
- Cytoreduction + HIPEC (MMC) + Best Systemic Rx
- Cross Over At Progression

N=155
- Cytoreduction + HIPEC (MMC)
- Best Systemic Rx

N=155
- Best Systemic Therapy
Figure 3: Study design of the EUNE clinical trial.