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ORIGINAL ARTICLE

Cytoreductive surgery and HIPEC for peritoneal carcinomatosis. A review on morbidity and mortality

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Summary

Purpose: *To review morbidity and mortality of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis.*

Methods: *A literature search was conducted to identify studies from centers that perform CRS and HIPEC, and to collect and analyse data about morbidity and mortality.*

Results: *Twenty-five articles, published from 2006 to 2014 were reviewed. The studies included 241069 patients that had been treated with CRS and HIPEC for peritoneal carcinomatosis. The overall rate of severe perioperative morbidity ranged from 0 to 62% and the mortality rate varied from 0 to 10%. Major morbidity was correlated with age, peritoneal carcinomatosis index (PCI), comorbidities, number of digestive anastomoses and institution where the treatment was performed.*

Conclusion: *Although the resultant morbidity is not negligible, with good patient selection this modality appears to be overall safe and effective in experienced hands. The results indicated that this treatment should be practised by institutions with expertise in the management of peritoneal carcinomatosis.*

Key words: *cytoreductive surgery, HIPEC, hyperthermic intraperitoneal chemotherapy, morbidity, mortality, peritoneal carcinomatosis*

Introduction

Peritoneal dissemination from digestive cancers and gynecological malignancies is common. The primary peritoneal malignancies, such as peritoneal mesothelioma, are rare [1]. This condition is often associated with disease progression and poor prognosis and is traditionally regarded by the surgeon as a terminal condition.

In patients with recurrent colorectal (10-35%) and gastric cancer (50%), tumor recurrence is confined to the peritoneal cavity. These patients die from complications of locoregional tumor spread, in most cases without occurrence of metastases in other sites. Patients with peritoneal carcinomatosis from adenocarcinomas of non-gynecologic origin have an average life expectancy of 6 months [2,3]. The two main mechanisms that are believed to contribute to the intraabdominal spread of cancer cells are either preoperative as a result of full thickness invasion of an organ by the cancer or intraoperative as a result of surgical manipulations [4]. Ovarian cancer spreads through exfoliation of malignant cells into the peritoneal fluid, disseminating along the abdominal and pelvic peritoneum, resulting in peritoneal metastases [5].

The understanding of tumors' biology and pathways of dissemination with intraperitoneal spread has prompted the concept that peritoneal carcinomatosis is a locoregional disease. The role of surgery in peritoneal carcinomatosis has slowly evolved from palliation to potentially curative therapeutic approach because systemic chemotherapy is not very efficient to treat intraabdominal tumor

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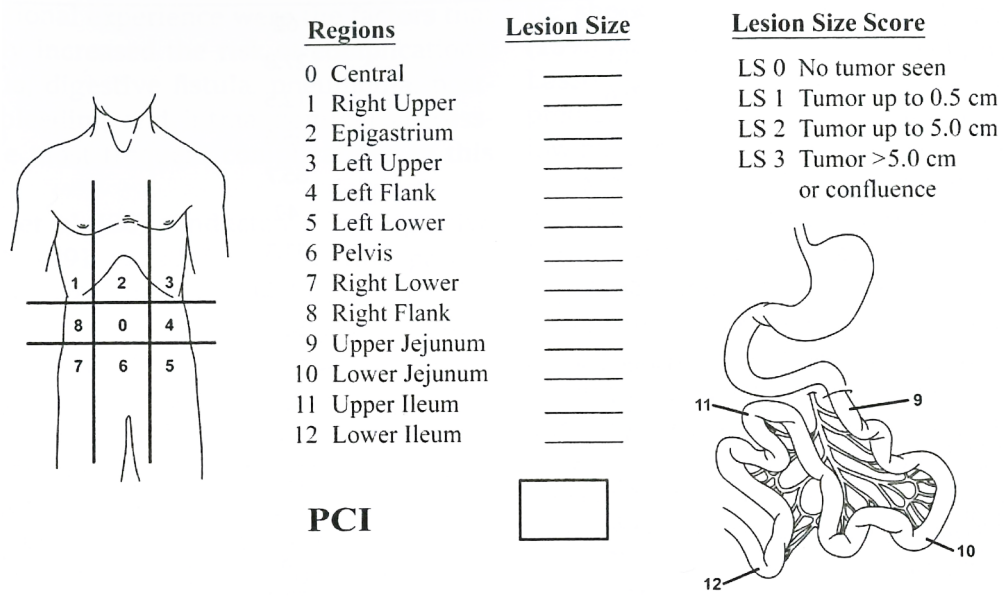

Figure 1. The Sugarbaker peritoneal carcinomatosis index (PCI).

dissemination [6]. Over the past 2 decades, novel therapeutic approaches to peritoneal carcinomatosis have emerged that combine CRS with HIPEC and/or early postoperative intraperitoneal chemotherapy (EPIC) [7,8].

CRS was first described in the l 930s for ovarian cancer [9]. Its role was to treat macroscopic disease. Decades later, HIPEC was added for the purpose of eliminating residual microscopic disease [10]. The role of peritoneal plasma barrier in promoting a locoregional high-dose chemotherapy is very important. Indeed, the peritoneum has the capacity to limit systemic drugs diffusion in the peritoneal space. Moreover, hyperthermia enhances the efficacy and the penetration of many of the drugs employed [11].

CRS consists of numerous surgical procedures depending on the extent of peritoneal tumor dissemination. Surgery may include parietal and visceral peritonectomy, greater and lesser omentectomy, splenectomy, cholecystectomy, resection of liver capsule, small bowel resection, colonic resection, gastrectomy, pancreatic resection, hysterectomy, ovariectomy and urinary bladder resection.

Table 1. The Sugarbaker completeness of cytoreduction (CC) classification

Score	*Description*
CC0	No residual tumor nodules
CC1	Residual tumor nodules <2.5 mm
CC2	Residual tumor nodules ≥2.5 mm and ≤5 cm
CC3	Residual tumor nodules >2.5 cm

The extent of peritoneal disease is described by the PCI and the presence of residual disease is described postoperatively using the completeness of cytoreduction (CCR) score [12].

PCI combines assessment of the lesion size (lesion size: 0 for no macroscopic tumor, 1 if tumor <0.5 cm, 2 if tumor 0.5-5 cm and 3 if tumor > 5 cm) and tumor distribution (abdominopelvic region 0-12), and quantifies the disease as a numerical score 0-39 (Figure 1). The residual disease is classified intraoperatively using the CCR score (Table 1). CCR-0 indicates no visible residual tumor and CCR-1 residual tumor nodules ≤2.5 mm. CCR-2 and CCR-3 indicate residual tumor nodules between 2.5 mm and 2.5 cm and > 2.5 cm, respectively [13].

When complete macroscopic cytoreduction is achieved, CRS is followed by HIPEC. HIPEC offers the advantage of delivering high local concentration of the used agents and reduced systemic toxicity and can be performed with open or closed technique. Moreover, hyperthermia leads to direct cytotoxic effects such as protein denaturation, induction of apoptosis and inhibition of angiogenesis [14]. Various cytotoxic agents have been used for peritoneal carcinomatosis worldwide. The perfusion times range from 30 to 120 min depending on the protocol and the drug used.

Several studies have shown CRS and HIPEC as an integrative part of an interdisciplinary cancer treatment concept that may improve the survival of patients with peritoneal dissemination of different tumor entities. However, morbidity remains a concern as many studies report a 0-49% perioperative complication rate. To determine more

Table 2. Reviewed articles

First author [Ref]	*Number of patients*	*Morbidity (%)*	*Mortality (%)*
Ihemelandu [15]	387	62	7.7
Votanopoulos [16]	481	27.8	2.7
Desantis [17]	356	12.5	1
Cripe [18]	32	65.6	0
Robella [19]	70	35.7	7.1
Levine [20]	1000	42	3.8
Bakrin [21]	566	31.3	0.8
Dovern [23]	546	3.4-50	2.9
Kerscher [24]	109	30.2	0
Chua [25]	(19 studies)	0-40	0-10
Spiliotis [26]	39	43.5	5.1
Konstantinidis [27]	8	36	0
Deraco [28]	75	13.3	1.3
Kbnigsrainer [29]	100	15	1.1
Casado-Adam [30]	147	8	1.3
Glehen [l]	1290	33.6	4.1
Kuijpers [31]	960	34	3
Campos [22]	91	27	0
Jafari [32]	694	32.9	2.3
Chan [33]	584 (15 studies)	0-40	0-5
Coccolini [34]	54	35.2	5.6
Mizumoto [35]	284	49	3.5
Lopez-Basave [36]	24	20.8	0
Wagner [37]	282	32	1.7
Glockzin [38]	Review	25-41	0-8

contemporary rates of morbidity and mortality associated with CRS/HIPEC, we reviewed articles in the literature from 2006 to 2014 to acquire recent data regarding the safety and efficacy of performing cytoreduction and HIPEC for peritoneal carcinomatosis.

Methods

A literature search was conducted in PubMed using combinations of the search terms "intraperitoneal", "chemotherapy", "HIPEC", "morbidity", and "mortality". The search was limited to articles written in English. Data of interest included grade 3-4 morbidity and 30-day mortality rates. Minor morbidity included complications that were resolved with medical management while major morbidity included complications where urgent definitive or invasive intervention was required.

Results

Twenty-five studies were identified reporting the results of CRS followed by HIPEC (Table 2). Studies included from 8 to 1290 patients, treated in a single institution or in multiple institutions after retrospective data collection. The most frequent origin of carcinomatosis was ovarian cancer, colorectal cancer, gastric cancer, pseudomyxoma peritonei, peritoneal mesothelioma, appendiceal adenocarcinoma and other less frequent cancers. All patients underwent CRS and HIPEC with either the open or the closed abdomen technique. Mitomycin, oxaliplatin and doxorubicin were the drugs most frequently used according to national protocols.

A retrospective, multicenter cohort study was performed in French-speaking institutions, enroll-

ing 1290 patients with peritoneal carcinomatosis from non-gynecologic malignancies [1]. They all had been treated with CRS and HIPEC and/or early postoperative intraperitoneal chemotherapy. A morbidity of 33.6% was reported, while patient age, extent of peritoneal carcinomatosis, and institutional experience were the factors that significantly increased the risk of complications. Neutropenia, digestive fistula, pneumonia, postoperative bleeding and intraabdominal abscesses were the most frequent complications in this study.

Levine et al [20] conducted a retrospective study from 1991 to 2013. During this period, 1000 patients were treated with CRS and HIPEC. The 30-day postoperative morbidity and mortality were 42% and 3.8%, respectively. Wound infection, hematologic toxicity, sepsis, respiratory failure, anastomotic leak, pneumonia, and enterocutaneous fistula accounted for the majority of the postoperative complications in this cohort of patients. Complications were less common in patients undergoing R0/1 resections when compared with cases with more residuals (p=0.04). Furthermore, to evaluate their experience over time, the authors divided their experience into 5 time periods (quintiles) of 200 patients each. The rate of complications varied significantly among the quintiles, with the highest rate during the third quintile (p<0.0001). The rate of complete resection (as defined by R0, R1, or R2a) increased with each quintile while class IV and V complications decreased over time.

Kuijpers et al [31] published the results of a nationwide study with 960 patients, about CRS combined with HIPEC for peritoneal metastasis of colorectal origin in the Netherlands following a national protocol. Major complications (grade III-V) occurred in 34% of the patients and 32 patients died of a complicated procedure; the mortality rate was 3%. The most common cause of mortality was anastomotic leakage.

Chan et al [33] reviewed the two main approaches of intraperitoneal chemotherapy delivery in ovarian cancer: postoperative adjuvant intraperitoneal chemotherapy after CRS and HIPEC. Fifteen studies reported data on 584 patients with advanced ovarian cancer undergoing HIPEC. These studies reported a perioperative mortality ranging from 0 to 5%. Major morbidity ranged from 0 to 40%.

Jafari et al [32] reported the associated 30-day morbidity and mortality of CRS-HIPEC in the treatment of metastatic and primary peritoneal cancer in the American College of Surgeons National Surgical Quality Improvement Program centers. A total of 694 patients who underwent HIPEC with CRS were sampled. Overall morbidity was 32.9% and mortality 2.3%. Postoperative bleeding requiring transfusion (17%), sepsis/septic shock (16%), and respiratory complications (15%) were the most prevalent complications. The Lasso algorithm did not demonstrate any strong predictors of mortality and morbidity given the low number of patients with mortality.

Mizumoto et al [35] studied retrospectively 250 patients treated at the Kusatsu General Hospital between 2007 and 2011 with a diagnosis of peritoneal carcinomatosis. A total of 284 CRS procedures were performed on patients with peritoneal carcinomatosis: 236 procedures in 205 patients with pseudomyxoma peritonei, 32 procedures in 29 patients with peritoneal carcinomatosis that originated from colon cancer, and 16 procedures in 16 patients with peritoneal carcinomatosis that originated from gastric cancer. The morbidity rate was 49% in all procedures. The most frequent complication was surgical site infections including intraabdominal abscess, which represented 46% of the total number of postoperative complications. Gastric or small intestinal perforation, postoperative ileus, anastomotic leakage, urinary disfunction, intestinal fistula and postoperative bleeding were the other main complications after CRS and HIPEC. Gastric or small intestinal perforation, intraabdominal abscess, anastomotic leakage, and postoperative bleeding were the main severe grade III complications.

The mortality rate was 3.5%. The causes of death were anastomotic leakage, intestinal fistula, postoperative bleeding, sepsis, and disseminated intravascular coagulation. Univariate analysis showed that PCI greater than 20, operation time longer than 5 hrs, and blood loss greater than 2.5 L were significant risk factors for the occurrence of postoperative complications.

Discussion

Peritoneal carcinomatosis has long been considered a fatal clinical entity to be treated palliatively. In the last two decades, better understanding of the natural history and biology of peritoneal carcinomatosis has been acquired. Since the 1980s CRS with HIPEC have provided new hopes of a potential cure for these patients.

The management of peritoneal carcinomatosis is still the subject of ongoing debate between those who support the use of an aggressive surgical intervention with intraperitoneal chemotherapy and those who favor the use of systemic chemotherapy [32]. Extended cytoreduction combined with HIPEC can offer better results in long-term survival. On the other hand systemic chemotherapy for peri-

toneal surface dissemination has been the traditional approach, but is hampered by the limited entry into the peritoneum. Any systemic chemotherapy for intraperitoneal disease must overcome the plasma-peritoneal partition to reach molecular targets [39].

However, the oncologic community remains hesitant over the role of HIPEC because of the lack of large prospective clinical trials demonstrating improved survival compared with current systemic chemotherapeutic regimens [40]. The high rates of morbidity and mortality that have been reported [1] increase the resistance to the adoption of CRS-HIPEC in the management of peritoneal carcinomatosis.

The morbidity and mortality of CRS-HIPEC result from the combined effects of cytoreduction and the physiological insult of the intraoperative chemotherapy. A large intraabdominal dissection area combined with peritonectomy can cause massive fluid losses. Systemic hyperthermia required during HIPEC can also result in hemodynamic changes that may result in moderate blood loss, peripheral vasodilation, and massive fluid accumulation [41]. This change in the physiological demands of the patient can increase morbidity and mortality.

Complications are derived from the surgical procedure and from toxicity caused by the cytotoxic agent used during HIPEC [42]. The overall rate of severe perioperative morbidity ranged from 0 to 62% and mortality rate varied from 0 to 10% in our study.

Many variables have been reported in the literature to be related with the occurrence of postoperative morbidity after cytoreductive surgery and HIPEC, such as the extent of surgery, the number of peritonectomy procedures, diaphragmatic peritoneal resections, the number of visceral resections, perioperative blood transfusion, incomplete cytoreduction, number and type of gastrointestinal anastomoses, age, dose of cytotoxic agent used, gender, intraabdominal temperature reached during the HIPEC and a long operation time [22].

Gastrointestinal complications (Table 3) include anastomotic failure, bleeding, fistula, pancreatitis, pancreatic fistula, bile leak, prolonged ileus, small bowel obstruction, ascites, vomiting and diarrhea [30]. Casado-Adam et al concluded that PCI was shown to be the only independent risk factor for gastrointestinal complications [30]. Digestive anastomosis is an important factor related to postoperative morbidity. By itself, heat does not alter normal healing of the anastomosis, although alterations have been described in the healing thereof, at the expense of a lower density in the formation of collagen after the application of HIPEC with mitomycin C and cisplatin [22]. Carrying out protective ostomy after a colorectal anastomosis is actually a controversial issue.

Table 3. Gastrointestinal and pulmonary complications (from Sugarbaker et al. [30,43])

Organ system	*Complications*
Gastrointestinal system	Anastomotic failure, Fistula, Pancreatic fistula, Pancreatitis, Bile leak, Chyle leak, Prolonged ileus, Small bowel obstruction, Nausea/vomiting, Diarrhea, Ascites
Respiratory system	Pleural effusion, Respiratory distress, Pneumonia

Pulmonary complications (Table 3) include respiratory distress, pleural effusion and pneumonia. Pleural effusion is a relatively common event described in many reports and it could be due to several factors. The stripping of the diaphragmatic peritoneum elicits a mechanical and thermal injury to the muscle. This trauma would promote fluid entrance into the thorax from the abdomen of the chemotherapy solution during HIPEC [43]. Pleural drainage is usually routine in all patients in an attempt to avoid pleural effusion. Among the infectious adverse effects, pneumonia ranged from 3.5 to 6.6% in recent series [44].

The main cause of death after CRS-HIPEC is attributed to sepsis, followed by respiratory complications [1].

Complications specific to HIPEC are mainly hematologic, as well as the risk of renal failure related to the predominant use of cisplatin. The specific morbidity of HIPEC is linked to the passage of the chemotherapeutic agents into the systemic circulation resulting in hematologic toxicity; the use of oxaliplatin increases the risk of bleeding complications. The use of cisplatin is associated with a risk of renal failure that requires optimal perioperative hydration [45].

Elias et al [47] and Glehen et al [1] reported that the risk of morbidity and mortality after CRS and HIPEC is significantly related to the institution where the treatment was performed and concluded that this procedure should be centralized to institutions with expertise in the management of peritoneal carcinomatosis. Moreover, it has been demonstrated that the learning curve is an important factor to reduce the occurrence of post-operative complications. Approximately, 130-140 cases are reported to be necessary to minimize the morbidity and mortality of the procedure [47].

Conclusions

Up until recently, peritoneal carcinomatosis has been considered a locoregional metastatic condition with extremely poor prognosis and no standard therapy. CRS, in combination with HIPEC, has been shown to offer patients a chance for long-term survival. This article confirms that overall morbidity and mortality rates associated with HIPEC-CRS are acceptable. The eligibility of patients for this type of treatment requires rigorous selection, and management should be carried out by well-trained multidisciplinary teams practising in a specialized center.

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