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REVIEW ARTICLE

Complications of Cytoreductive Surgery and HIPEC in the Treatment of Peritoneal Metastases

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Abstract The combined treatment concept of cytoreductive surgery (CRS) and Hyperthermic intraperitoneal chemotherapy (HIPEC) has shown to be an efficient therapeutic option for selected patients with primary and secondary peritoneal carcinomatosis (PC). This strategy represents the standard of care for diseases like pseudomyxoma peritonei and peritoneal mesothelioma, and offers the best long-term results for PC from colorectal cancer. Despite these results, skepticism exists regarding this therapeutic approach partly because of its perceived high toxicity. In this article, we review the current evidence on complications that can occur after CRS and HIPEC and the risk factors associated with increased incidence of morbidity and mortality.

Keywords Cytoreductive Surgery · Hyperthermic intraperitoneal chemotherapy · Complications

Introduction

The combined treatment concept consisting of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) performed in specialized centers has shown to be an efficient therapeutic option for selected patients with primary and secondary peritoneal carcinomatosis (PC). Theoretically, CRS is performed to treat macroscopic disease and HIPEC is used to treat microscopic residual disease with the intent to treat the PC by a single procedure. This strategy represents the standard of care for diseases like pseudomyxoma peritonei and peritoneal mesothelioma [1–4]. Moreover, it offers the best long-term results for PC from colorectal cancer [5–8]. Despite all of these studies suggesting a clear survival benefit, some oncologists remain skeptical regarding this therapeutic approach partly because of its perceived high toxicity.

With advances in surgical techniques and peri-operative care, the complications associated with this strategy have decreased in recent years. In a systematic review of literature, Chua et al. reported that morbidity and mortality associated with CRS and HIPEC performed in specialized centers were not significantly superior compared to morbidity and mortality of other major gastrointestinal interventions [2]. Several authors have reported reduction of morbidity and mortality over time, stressing the importance of the "learning curve" principle [9–11]. In this article, we review the complications that can occur after CRS and HIPEC and the risk factors associated with increased incidence of morbidity and mortality. For the purpose of description, these complications have been grouped into gastrointestinal, pulmonary, hematological and others.

Gastrointestinal (GI) Complications

CRS and HIPEC often involve complex and huge surgical procedures in addition to intra-peritoneal chemotherapy. The aim of the CRS is to achieve a macroscopic complete resection and may involve several peritonectomies combined with different type of digestive resections. Patients with

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metachronous peritoneal metastases treated with CRS and HIPEC have the added complexity of post-operative adhesions and distorted anatomy related to previous surgery. These have been reported as risk factors of post-operative small bowel fistulas [12]. The combination of hyperthermia and high concentration chemotherapy used in HIPEC can also alter physiological healing, which may increase the incidence of anastomotic leaks and GI complication rates [13]. Among the larger series [13–18], the reported grade III/IV GI complication rate ranges between 4.5 to 19 %. Small bowel perforations and anastomotic leaks are the most common and clinically significant GI complications after CRS and HIPEC. A possible explanation for digestive non-anastomotic perforation could be partial-thickness mechanical damage to intestinal surfaces, focal heat injury at the tip of the inflow catheters, suctioning effect of the outflow catheter, or postoperative shrinking of infiltrating metastatic nodules on the intestinal wall because of the antiblastic effect of HIPEC [19]. The risk for such complications should be minimized by careful lyses of adhesions and dissection, with a judicious use of the ball-tip electro-cautery when used for dissection of superficial peritoneal lesions.

Other GI complications include intra-peritoneal abscesses, pancreatic fistulas, biliary fistulas, chyle leak, prolonged ileus and gastric stasis. A recent study analyzing the issue of pancreatic fistula following distal pancreatectomy with or without HIPEC [20], showed a higher rate of severe pancreatic fistula according to International Study Group of Pancreatic Fistula (ISGPF) among patients undergoing HIPEC without impact in term of overall incidence (26 %). Few studies have tried to identify prognostic factors of GI complications in order to manage preoperatively surgical risk. Extent of carcinomatosis (PCI), duration of surgery, number of GI anastomoses, more than 4 peritonectomy procedures and perioperative blood loss have been associated with severe morbidity after CRS and HIPEC [13, 15, 16]. Unfortunately, preoperative imaging exploration and preoperative decisional models have failed to correctly predict resectability and extent of resection. In this context, the most accurate way to define post-operative risk of a specific patient is just represented by an exploratory laparotomy.

Pulmonary Complications

Pulmonary complications are common after standard abdominal surgery and are at the basis of a prolonged hospital stay [21]. Several studies have reported the incidence of grade 3/4 pulmonary complications to be in the range of 10–16 % [15, 22–24]. As expected, peritonectomy of abdominal diaphragmatic surfaces significantly increases post-operative pleural effusions, particularly in absence of systematic thoracic drainage [25, 26]. However, this strategy can reduce but not abolish intrinsic risk of pleural effusion, which remains the second most common pulmonary complications [22].

Patients undergoing peritonectomy procedures have a significant risk of post-operative infectious complications and pneumonia is approximately reported in 3.2–10 % of patients [14, 15, 24–29]. Several studies showed that pulmonary complications can be reduced by local experience, better peri-operative fluid and glycemic control and multi-disciplinary management of patients undergoing CRS and HIPEC [9, 30–32].

Hematological Complications

The incidence of hematological toxicity reported with CRS and HIPEC ranges between 4 and 39 %. This variability is probably related to the marked heterogeneity in the agent, duration, temperature and dilution used during HIPEC. In a multi-institutional French study including 1290 patients from 25 centres, hematological toxicity represented the commonest cause of complications in 13 % of patients [18]. There is limited data on the incidence of hematological complications after CRS and HIPEC. Mitomycin-C (MMC), representing the historical drug administered during HIPEC surgery, is classically associated with neutropenia (4 %-39 %) [33, 34] with an associated mortality ranging from 0 to 66 %. Factors associated with a higher incidence of neutropenia following HIPEC are anemia, obesity, prior toxicity to IV chemotherapy, female sex and dose of MMC in HIPEC. Role of splenectomy during CRS has been reported as protective toward hematologic complications by Becher et al. [35], but other studies have not confirmed this association [34]. Hematological toxicity profile in function of drug used during HIPEC has been largely investigated. Votanopoulos K et al. [36] compared hematological toxicity of MMC and Oxaliplatin and found that oxaliplatin had similar white blood cell toxicity and higher platelet and neutrophil toxicity compared to MMC-based HIPEC. Interestingly, this difference in the platelet and neutrophil toxicity was only observed in patients who had undergone a splenectomy. However, this study had used a much longer duration of oxaliplatin HIPEC (2 hours) compared to the most commonly used oxaliplatin based HIPEC protocol (30 min chemoperfusion), described by Elias et al. [37]. In fact, in a French multi-centric study [38] evaluating the role of HIPEC in GI origin peritoneal metastases, the incidence of hematological toxicity from oxaliplatin or MMC based HIPEC regimens was not different.

Other Complications

Other less frequent grade 3/4 complications can occur after CRS and HIPEC such as renal insufficiency [39, 40] (2–4 %), venous thromboembolism [5, 41] (4–4.4 %), urinary tract

infections, vascular access infections, etc. The marked variability may be related to several factors including institutional practices, heterogeneity in data collection and reporting, experience of centers and heterogeneity of HIPEC protocols.

Risk Factors for Complications

Several factors have been analyzed as predictive factors of moderate to severe morbidity following CRS and HIPEC such as sex [35], age, primary colonic anastomosis, number of peritonectomy procedures [10, 14, 15, 28, 42], number of visceral resections [10, 14, 28], number of anastomosis [10], incomplete cytoreduction, disruption of the umbilical fissure [43], dose of chemotherapeutic agent [15], intra-abdominal HIPEC temperature and histopathologic grade [42].

Most studies have shown a direct relationship between the extent of disease expressed by peritoneal cancer index (PCI) and grade 3/4 morbidity and mortality. Extended PC necessarily requires more extensive surgery, longer OT time, greater blood loss and consequently is associated with higher complication rates. In certain disease types like peritoneal metastases of colorectal and gastric origin, a high PCI (PCI > 17 for colorectal and PCI > 12 for gastric) is associated with a poorer overall survival as well [43, 44]. In these settings, intraoperative assessment of the PCI and experience of surgeon probably represent the better way to select patients for CRS and HIPEC and limiting post-operative mortality and morbidity. In the pre-operative setting, Jeroen L A van Vugt et al. [45] showed that skeletal muscle depletion (sarcopenia) was associated with an increased rate and severity of complications. These concepts are not likely to be applicable in case of PMP, where PCI is usually higher and does not impact morbidity and long-term results. Elias and colleagues analyzed [43] 105 PMP patients and showed that perioperative morbidity and mortality was significantly associated with PCI > 24. In a large retrospective multi-institutional registry (Peritoneal Surface Oncology Group International), three independent factors were associated with major complications in PMP patients treated with CRS and HIPEC: prior surgical score of 3 ($P = .006$), at least two prior operations ($P = .019$), and PCI more than 20 ($P = .001$) [2]. Saxena et al. [46] have identified ASA > 3 ($P = .006$) and an operation length > 10 h ($P = .001$) as independent risk factors for grade 3/4 complications in PMP patients.

Importance of "Learning Curve"

The importance of learning curve in the context of CRS and HIPEC has been studied. The authors [9, 10] concluded that the improvement in the perioperative outcome of patients over time was the result of improved surgical techniques, increased experience and other intuitive factors that are difficult to quantify. Over the years, reduction of post-operative mortality has been reported from tertiary centres worldwide. Moran reported a decreased mortality rate from 18 % down to 3 % [11, 30], The Netherlands Cancer Institute reported a decrease in mortality from 8 % to 4 % [9], and Yan et al. reported a decrease from 7 % to 1 % [10], all of which point towards the strong influence of the learning curve.

In French multicentric experience, Glehen and colleagues [18] identified the level of institutional experience as one of the strongest factors influencing the morbidity and mortality with better outcomes for centers with more than 7 years of activity in peritoneal surgery. It is reasonable to assume that experience may provide better patient selection, surgical expertise, and postoperative management. All complex interventional procedures have an inherent risk, and experience undoubtedly reduces but can never abolish this risk [30].

In conclusion, given the inherent aggressive nature of the treatment, the combined modality treatment of CRS and HIPEC is consistently associated with variable rates of perioperative mortality between 0 % and 18 % and morbidity between 30 % and 70 %. An understanding of the safety profile of this treatment modality and the risk factors associated with poor perioperative outcomes is essential. Current results indicate that this treatment should be centralized to high-volume institutions specialized in the management of peritoneal metastases.

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