



Management of peritoneal surface malignancies in laparoscopic era: a concise review

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Abstract

Peritoneal carcinomatosis is seldom curable. Maximal cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy has been used in efforts to improve survival. There has been a recent explosion of interest in this modality of treatment with various centers employing its use throughout the world. This is a complex procedure associated with significant morbidity and mortality. This makes patient selection very critical and hence there has been immense interest in the evaluation of various prognostic indicators being evaluated. In addition, with the advent of minimally invasive surgery, laparoscopy is being increasingly utilized in different capacity. Newer indications for treatment and possible prevention of peritoneal carcinomatosis are being evaluated especially in colorectal cancer. The aim of this brief review is to synthesize and present the recent data available regarding the outcomes and evolving trends associated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Keywords: Peritoneal carcinomatosis, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy (HIPEC), Colorectal cancer, Laparoscopic

1. Introduction

Peritoneal carcinomatosis (PC) represents the involvement of the peritoneal surface with neoplastic process. Mostly this results from intracavitary dissemination of tumor that may arise from variety of primary sites like gastrointestinal, gynecologic primary peritoneal, or mesothelioma. Historically this has been thought to have poor prognosis with the few treatment options^[1]. Although the natural history of this disease is not well documented, the overall prognosis is believed to be extremely poor with survival <6 months^[2]. Cytoreductive surgery (CS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has been utilized successfully for the treatment of this challenging condition and its role has been evolving. This paper reviews the rationale, evidence, and surgical technical updates in the current era of minimally invasive surgery.

2. Rationale for CS and HIPEC

In the past, PC was considered as advanced metastatic spread of the tumor. The only treatment options considered for patients were systemic chemotherapy, supportive care with the surgery reserved only for palliation. Although surgery could achieve gross reduction in tumor burden, there was still a need to address the micro-metastases as well as the invisible cells in the peritoneal cavity. Addition of intraperitoneal chemotherapy was thought to address this with the significantly higher concentration of selected agent in the local regional area. The effects of chemotherapy drugs are further enhanced by addition of hyperthermia (ideally to 42°C–43°C), which is understood to have synergistic effects^[3].

Professor Paul Sugarbaker pioneered the use of aggressive surgery to achieve complete cytoreduction and combined it with hyperthermic intraperitoneal chemotherapy for treatment of selected patients with the peritoneal spread^[4]. Phase III randomized control trials by Verwaal et al^[5,6] showed improvement in long-term survival in selected group of patients with colorectal cancer. This led adoption of CS with HIPEC for other peritoneal malignancies including gastric, ovarian, mesothelioma, and pseudomyxoma^[7–10]. Over the past 2 decades there has been a tremendous interest and increase of use of CS with HIPEC all over the world^[11,12].

3. Patient selection and quantification of disease

CS and HIPEC is a complex surgical procedure with the potential for high morbidity and mortality. A review of the ACS NSQIP database reporting on 695 patients showed the average operative time was 7.6 hours, with 15% of patients requiring intraoperative transfusions^[13]. The average length of stay was 13 days, with a 30-day readmission rate of 11%. Postoperative bleeding (17%), septic shock (16%), pulmonary complications (15%), and organ-space infections (9%) were the most prevalent postoperative

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery Oncology (2016) 1:e05

Received 10 October 2016; Accepted 10 October 2016

Published online 5 December 2016

<http://dx.doi.org/10.1097/IJ9.0000000000000005>

complications. Hence, patient selection is the key. Age, poor nutritional status (hypoalbuminemia), and Eastern Cooperative Oncology Group (ECOG) performance status are the pre-operative factors having a strong association with perioperative morbidity and mortality^[14].

Regarding preoperative imaging, a consensus was reached at the Fifth International Workshop on Peritoneal Surface Malignancy, stating that contrast-enhanced multisliced computed tomography remains the fundamental imaging modality, whereas magnetic resonance imaging, positron emission tomography, laparoscopy, and serum tumor markers were helpful but nonessential^[15]. Although combined imaging modalities can assess the extent of peritoneal disease, the exact quantification of the disease is best done at surgery. With recent advancements in the minimally invasive surgery, laparoscopy has been increasingly used to accomplish staging^[16].

Various measures are used to quantify the disease burden including the commonly used PC index score as well as the Dutch simplified peritoneal cancer index and the Gilly PC staging system^[17]. More critical is the completeness of cytoreduction (CC) score that is used to quantify the residual disease left at completion of surgery with the aim to achieve CC of < 1. Of all the perioperative factors, this CC score is the most important predictor of survival and recurrence^[18].

4. Choice of chemotherapeutic agent

Although over a dozen of drugs could be used, the heat-augmented drugs that are most effective are mitomycin C, Oxaliplatin, Cisplatin, and doxorubicin^[3]. The agent of choice of chemotherapeutic drug depends upon various factors including the primary cancer to be treated and preference of the team. For example the majority of the surgical oncologists in North America favored the closed method of delivery with a standardized dual dose of mitomycin for a 90-minute chemoperfusion for patients undergoing CS for PC of colorectal origin^[19].

5. Role of laparoscopy

Laparoscopy can logically have an inherent benefit in visualization of peritoneal disease including evaluation of small bowel and ability to perform biopsy^[3]. Several studies have reported success in the use of laparoscopy for staging peritoneal metastasis in colorectal, mesothelioma, and appendiceal cancer^[20,21]. A recent multicenter trial reported accuracy for laparoscopy of 80% for staging peritoneal metastasis from ovarian origin^[22].

In patients with disease limited to 1 part of the peritoneal cavity CS can be accomplished laparoscopically. Among them, in a select subgroup of patients, HIPEC can also be successfully administered by laparoscopic approach and has been found to be safe^[23]. Several studies have been reported with the indications for laparoscopic HIPEC having ranged from neoadjuvant to adjuvant (most common) to palliative. When performed to treat refractory malignant ascites, the laparoscopic HIPEC was effective in 95% of cases^[23].

More interesting is the proactive use of HIPEC along with “second look” surgery in patients with advanced local disease with or without tumor perforation^[24]. An interesting trial comparing simple follow-up to exploratory laparotomy plus “in

Principle” HIPEC in Colorectal Patients (“PROPHYLOCHIP” study) is underway.

6. Interdisciplinary concept

As with all cancer care, CS with HIPEC is best offered to patients by a dedicated multidisciplinary team. Here a group of individuals including surgeons, radiologist, anesthesiologists, nurses, HIPEC technicians, and oncologists can be involved in setting up the program and delivering it starting from patient selection to perioperative care and long-term follow-up^[25].

7. Literature overview for CS and HIPEC in various cancers

7.1. Colorectal cancer

A phase III randomized controlled trial by Verwaal et al^[5,6], initially reported in 2003 and recently updated with an 8-year follow-up, showed the median disease-specific survival of 22.2 months in the HIPEC arm compared with 12.6 months in the control arm ($P=0.028$). Additional multi-institutional studies have confirmed the benefit of HIPEC with median survival from 29.4 to 62.7 months especially when complete CS is achieved^[8,9].

Recently the focus has been to make CS with HIPEC when available to be the standard of care for PC from colorectal cancer in addition to systemic chemotherapy^[26]. Also the roles of second look surgery and adjuvant HIPEC following a curative resection of a locally advanced or intra-abdominally perforated colon cancer in preventing the development of PC in addition to the standard adjuvant systemic treatment is being investigated (NCT02231086).

7.2. Gastric cancer

Evidence is not as robust for improved survival in patients with gastric cancer especially since the outcomes for adjuvant treatments for gastric cancer remain poor^[7,27]. However, a recently reported first randomized controlled trial for CS with HIPEC showed improvement in survival to 11.2 months compared with 5.6 months^[28]. A recent novel approach has been the use of bidirectional (intra-peritoneal and systemic) chemotherapy where in a Japanese center with 194 patients, median survival was 15.8 months^[29].

7.3. Ovarian cancer

Advanced stage ovarian, primary peritoneal, and fallopian tube cancers are very challenging to treat as demonstrated by a 70%–80% recurrence rate. A recent Cochrane review showed women were less likely to die if they received an intraperitoneal component to chemotherapy (8 studies, 2026 women). Intraperitoneal component chemotherapy prolonged the disease-free interval (5 studies, 1311 women; hazard ratio=0.78; 95% confidence interval, 0.70–0.86)^[30].

8. Pseudomyxoma peritonii (PMP)

PMP results from rupture of mucinous neoplasms commonly from appendix or ovary and sometimes primary peritoneal origin. This has traditionally had a poor prognosis with median

survival of 3 years. CS with HIPEC has been extensively applied at the significant improvement in overall survival 70% at 20 years^[31]. A retrospective multi-institutional registry looking at 2298 patients from 16 specialized centers who underwent CRS with HIPEC for PMP, showed a median survival rate of 196 months (16.3 y) and a median progression-free survival rate of 98 months (8.2 y), with a 10- and 15-year survival rates of 63% and 59%, respectively^[32].

9. Conclusions

CS and HIPEC have now evolved to being a promising treatment for patients with PC. This complex procedure is associated with significant mortality and morbidity and patient selection remains the key. Minimally invasive approaches have been successfully used in delivery of CS and HIPEC and their future role in treatment and prevention of peritoneal metastasis continues to evolve.

Conflict of interest statement

The author declares that there is no financial conflict of interest with regard to the content of this report.

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