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Cytoreductive Surgery and HIPEC for Colorectal Cancer: Facing the Facts and Addressing the Issues to Allow for Widespread Acceptance

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Abstract

60% of colorectal cancers are diagnosed at an advanced stage. Curative strategies involving multimodality treatment with surgical resection and chemotherapy have been employed for liver and lung metastases from colorectal cancer.

Peritoneal metastases are diagnosed synchronously in 10-15% of all newly diagnosed colorectal cancer, and in 40-70% of patients who suffer a recurrence. They are the sole sites of metastases in 10-30% of these cases. An understanding of peritoneal metastases must take into consideration the following:

1. Peritoneal metastases do not respond to systemic chemotherapy in the same fashion as liver and lung metastases

2. Peritoneal disease causes many local problems, resulting in disruption of planned chemotherapy

3. CRS and HIPEC actually works for peritoneal disease and

4. Peritoneal disease is usually not detected on state-of-the-art imaging modalities.

Despite mounting evidence of the effectiveness of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC) at prolonging survival in selected patients with colorectal peritoneal carcinomatosis, there remains a reluctance to explore this combined treatment modality. This is likely to be a result of the perceived morbidity and mortality of such a procedure, with most medical oncologists and colorectal surgeons being unfamiliar with the combined treatment. As with all complex procedures, a learning curve is observed, with proficiency likely only after 25 cases and at a high volume centre, with more than 30 cases annually.

An effective management strategy employing CRS and HIPEC for selected patients with colorectal peritoneal carcinomatosis can only be achieved if a concerted effort is made to understand this disease and address the concerns regarding this treatment.

Introduction

Colorectal cancer is one of the commonest cancer in most developed countries, afflicting 1 in 20 in the United States alone[1] and has a worldwide incidence of 43.7 per 100000 men and women per year [1]. It results in close to 50000 cancer deaths per year[2] , with many patients diagnosed at a late stage. Despite the advent of screening, 60% of patients are diagnosed at stage 3 or 4, leading to significantly poorer prognosis compared to early-staged disease [1].

Stage 4 colorectal cancer often results from liver, lung, peritoneal metastases, or a combination of disease at these sites.

Traditionally, the prognoses is dismal for most stage 4 cancers, but complete cytoreduction, along with adjuvant chemotherapy has provided long-term survival of 50% and 40% in patients with liver and lung metastases [1-4]. As such, it has long been considered and accepted as standard of care for patients with metastases at such sites to be discussed at multidisciplinary tumour boards for a potentially curative approach to be taken for their disease[3,5].

Peritoneal metastases are diagnosed synchronously in 10-15% of all newly diagnosed colorectal cancer, and in 40-70% of patients who suffer a recurrence. They are the sole sites of metastases in 10-30% of these cases, but the approach to the management of colorectal cancer peritoneal metastases remains a point of debate.

The Fourth International Peritoneal Surface Malignancy Conference held in Spain, came to a consensus in 2004 that states that "cytoreductive surgery with perioperative intraperitoneal chemotherapy was considered standard of care for all cases of mucinous appendiceal neoplasms with peritoneal dissemination, in an otherwise fit patient in the absence of distant metastases [1] Subsequently, at the 59th Society of Surgical Oncology Conference in San Diego in 2006, a consensus statement was issued stating that "Better surgical techniques that include peritonectomy procedures, standardized methods to deliver intraoperative hyperthermic intraperitoneal chemotherapy and better patient selection criteria, have resulted in a significant improvement in survival and in morbidity and mortality of the surgical management of this particular group of stage IV colon cancer patients [1]. Despite increasing number of publications and mounting evidence that cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) affords long-term survival in selected patients with colorectal peritoneal metastases, this treatment modality is not universally considered standard of care, and many patients are routed to a palliative chemotherapy route. This paper describes what CRS and HIPEC entails, examines the reasons for why CRS and HIPEC should be the first consideration for fit patients with isolated peritoneal metastases and why there remains such a lack of acceptance of this treatment modality.

CRS and HIPEC

The role of CRS and HIPEC for colorectal peritoneal metastases was established in the first randomized prospective trial in 2003 [1]. In the trial, 105 patients were assigned to either systemic chemotherapy (5-fluorouracil/lecovorin) with or without palliative surgery, or CRS and HIPEC with mitomycin C, followed by systemic chemotherapy. The preliminary results showed a median survival of 12.6 months and 22.3 months in the standard treatment and CRS and HIPEC arms, respectively (p Z 0.032), but with a mortality of 8% with the CRS arm. The study was updated in 2008 and reported disease-specific survivals of 12.6 months and 22.2 months in the control and CRS and HIPEC arms [1], respectively. The trial was criticized for its high mortality rate, and the chemotherapy regime used in the standard arm is now outdated. The largest study reporting outcomes of CRS and HIPEC for colorectal peritoneal metastases was published by Glehen et al. [1] and involved 506 patients treated at 28 institutions. Morbidity and mortality rates of 22.9% and 4%, respectively and OS of 19.2 months were attained.

CRS is performed as described by Sugarbaker [1]. The procedure aims to remove all macroscopic peritoneal disease, and resection of involved visceral organs is typically performed first followed by the removal of sections of involved peritoneum. HIPEC targets the microscopic diseases, working on lesions less than 3 mm. Owing to the peritoneal-plasma barrier, a higher dose of chemotherapy can be delivered with less systemic toxicity. The high temperature increases the drug penetration and provides a synergistic effect with the intraperitoneal chemotherapy. HIPEC is administered for 60 minutes. A dedicated anesthetist monitors the patient's parameters, including the core temperature via an esophageal temperature probe and keeps the patient adequately volume-filled.

Reasons Why CRS and HIPEC should be the First Consideration for Patients with Isolated Peritoneal Metastases

Peritoneal metastases do not respond to systemic chemotherapy in the same fashion as liver and lung metastases

Patients with colorectal metastases are usually administered chemotherapy in a bid to control the systemic disease. In patient who present with synchronous metastases, upfront chemotherapy or chemotherapy after the resection of the primary tumour but before the metastatectomy (pseudo- neoadjuvant chemotherapy), allow the biology of the tumour to be determined, with an in- vivo test of the efficacy of the chemotherapeutic agent for that particular tumour to be effected simultaneously. Patients whose tumours respond to the prescribed chemotherapy are often considered for resection of the metastases, especially if these are situated in the liver or lung, and complete resection with clear margins is deemed possible. In patients who present with metachronous lesions, often, upfront resection is considered for liver and lung metastases, especially if there has been a reasonable disease-free interval, without progression of disease whilst the patient is on adjuvant chemotherapy [3,5]. This approach has allowed improved prognosis amongst patients with resectable liver and lung metastases. However, the same cannot be said of patients with peritoneal metastases, whose disease often does not respond to the systemic chemotherapy. In many publications on survival of patients on palliative chemotherapy for colorectal metastases, the survival data is based on treatment of metastases at all sites [1]. There remain few reports of similar evidence in patients with peritoneal metastases, being treated with chemotherapy. In Jayne et al's study looking at this issue, it was found that a diagnosis of peritoneal metastases immediately confers a poorer prognosis by threefold, and the median overall survival is 7 months [2]. Hence, the often quoted prolonged survival with state of the art chemotherapy for colorectal metastases cannot possibly be extrapolated to those with peritoneal disease.

Peritoneal disease causes many local problems, resulting in disruption of planned chemotherapy

Patients with peritoneal disease are often symptomatic, with symptoms of abdominal distension and bloatedness, shortness of breath and poor oral intake. Some present with respiratory difficulties secondary to splinting of the diaphragm from massive ascites, requiring insertion of cope loops for drainage of the ascites and temporary relief. Others experience symptoms of intestinal obstruction, often requiring admission for bowel rest, and intravenous hydration, and in some instances, a palliative surgical procedure of resection or bypass of the offending obstructive lesion. In comparison, most patients with liver or lung metastases remain asymptomatic are able to complete their planned chemotherapy. On evaluation of our institution's data (to be published), it was found that only 29% of patients with peritoneal metastases from colorectal cancer were able to complete the planned courses of palliative chemotherapy [3].

CRS and HIPEC actually works for peritoneal disease

Multiple articles have been published since Verwaal's et al. randomized trial on CRs and HIPEC versus intravenous chemotherapy for peritoneal carcinomatosis from colorectal cancer [4]). The often quoted criticism has been the use of "old-fashioned" chemotherapy for the latter arm but studies like Glehen et al.'s review incorporating standard chemotherapy have shown similarly significant results with prolonged survival in the arm treated with CRS and HIPEC [5]. There remains no evidence of any long-term survival of patients with colorectal peritoneal carcinomatosis who have been administered chemotherapy.

How to treat a disease that cannot be detected?

In Elias et al.'s systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis, more than 50% of these patients were found to have peritoneal disease that was not detected by clinical and imaging modalities [6]. The high risk features included peritoneal nodules detected at time of primary cancer resection, presence of ovarian metastases at primary surgery, primary cancer perforation or obstruction, adjacent organ or structure invasion and fistula formation. In addition, histopathology played a significant role, with patients with positive margins, positive peritoneal fluid cytology, T3 or T4 mucinous cancer, signet ring morphology and positive nodal status having increased risk of peritoneal carcinomatosis as well. This has led to the advent of proactive management for high risk colorectal cancers, with reduced rates of peritoneal metastases and local recurrence of 4% as opposed to 22% in those managed with prophylactic CRS and HIPEC compared to those who underwent complete surgical resction only [7]. Significant differences were seen in the median overall and disease-free survivals as well. The current practice for patients with high risk colorectal cancers is adjuvant systemic chemotherapy after primary cancer resection, but with the knowledge that systemic chemotherapy does not work well for peritoneal disease, and even in the face of a recurrence in the peritoneum, up to 50% may remain undetected, it would seem prudent that the appropriate "adjuvant" treatment is administered in each situation, and that patients who stand a high risk of developing peritoneal disease should be treated with adjuvant HIPEC instead.

Reasons for why CRS and HIPEC is not Widely Accepted

The perceived morbidity and mortality of CRS and HIPEC

There is no doubt that CRS and HIPEC is a complex procedure that requires a combination of factors for minimization of morbidity and mortality. The initially reported figures of these ranged from 40-80% and 3-20% respectively. Since then, these numbers have seen a decline with figures in the range of 20-40% and 3% respectively for morbidity and mortality [8]. However, both medical and surgical oncologists who are unfamiliar with the procedure remain wary about subjecting a patient who has just undergone what is felt to be an aggressive locally ablative surgical treatment, to heated chemotherapy, which carries its own morbidity. Most would be more comfortable with either one part of the treatment alone, but cytoreductive surgery alone, without HIPEC, misses out on the advantage of delivering high concentrations of effective chemotherapy to an area that has a high chance of loco-regional recurrence, at a time when the disease load is at its smallest, immediately after resection of all macroscopic disease. Similarly, HIPEC alone, in the face of macroscopic disease is ineffective, as demonstrated by many studies that show that completeness of resection remains the most important factor in prognosis [9-11]. The approach should not be to shun the combined procedure of CRS and HIPEC altogether but to engage in discussion about methods to reduce the morbidity and mortality, which at present stands at almost similar rates of a whipple's resection, in experience centres [12]. Unfortunately, many medical oncologists and surgeons remain wary of the potential complications of CRS and HIPEC and would continue the patient on palliative chemotherapy until the course is completed, and restart a second line of chemotherapy when the disease continues to progress.

Learning curve

As with all complex procedures, there is a learning curve for CRs and HIPEC. In the many papers published on this topic, it is evident that the latter part of an institution's experience with this procedure yields better results in terms of morbidity and mortality statistics, as well as survival results [13,14]. This is often attributed to the increased familiarity of the surgical team to the procedure, and also to the maturation in the selection critieria and protocols[19,20]. There is no definite minimum number to abide by, although most have described an improvement in their results after the first eighty to 100 number of cases. In fact, Kusamura et al.'s paper describes a need to have completed 140 cases before a surgical team or institution becomes proficient at CRS and HIPEC[19]. Despite the increasing number of centres offering this procedure,

not every centre would meet the criteria of being a high-volume centre, that neccesarily must indicate a case volume of 25 cases annually as a minimum. Without easy access to a high-volume centre that reports an acceptably low morbidity and mortality level, many physicians are hesitant about referring their patients on for consideration of CRs and HIPEC, and would prefer to stick with known modality of treatment with accepted complication rates, even if the survival results are reportedly less remarkable.

Conclusion

Although peritoneal carcinomatosis is a common end-point for many abdominal cancers and CRs and HIPEC have been proven to improve survival in many of the patients with this condition, widespread acceptance and active consideration of this procedure for their patient, by the oncologic community can only be achieved when the above factors have been addressed.

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