Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemotherapy for Colorectal Cancer: Limitations and Calls for More Research

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In Brief

Cytoreductive surgery-hyperthermic intraperitoneal chemotherapy is a complex, aggressive treatment protocol that has had limited acceptance in the mainstream oncology community. Several limitations, such as increased morbidity, a limited cohort of patients that benefit from this therapy, and technical and procedural nuances that mandate that only those who have considerable experience should perform these procedures, have caused some in the oncology community to call for continued research efforts.

The natural history of peritoneal carcinomatosis from colorectal cancer demonstrates that these patients have a dismal median survival of 5-9 months.[1] Peritoneal carcinomatosis of colorectal cancer origin is generally considered equivalent to distant metastasis but Sugarbaker has suggested that it should be labeled as regional disease and has thus championed the concept of cytoreductive surgery supplemented with hyperthermic intraperitoneal chemotherapy to eradicate microscopic residual disease.[2] Depending on the distribution and volume of the peritoneal carcinomatosis, cytoreductive surgery may involve up to 6 different peritonectomy procedures followed by formation of stomas and creation of at least 2-3 anastomoses.[3] Prior to any anastomoses, the peritoneum is treated with hyperthermic intraperitoneal chemotherapy using mitomycin C at a temperature ranging from 39-42°.

Various Phase II studies from single institutions have reported an overall two-year survival rate of 40-50 percent following aggressive cytoreductive surgery-hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin.[4-6] Investigators at Netherlands Cancer Institute in Amsterdam succeeded in completing the difficult task of performing a prospective randomized clinical trial where "standard treatment" consisting of 5-FU/leucovorin with or without palliative surgery was compared to the "experimental" cytoreductive surgery-hyperthermic intraperitoneal chemotherapy.[7] After a median follow-up of 21.6 months, the trial was closed early because the "experimental" therapy demonstrated a median survival of 22.3 months compared to 12.6 months in the standard arm. A collective experience of 506 patients from 28 different institutions that underwent cytoreductive surgery-hyperthermic intraperitoneal chemotherapy for the treatment of colorectal cancer was also reported.[8] At a median follow-up of 53 months the overall median survival achieved was 19.2 months with an associated morbidity and mortality rate of 22.9 percent and 4 percent respectively. Hence, the pioneering work of Sugarbaker in developing the concept of cytoreductive surgery-hyperthermic intraperitoneal chemotherapy and its formal testing by the Netherlands Cancer Institute prospective randomized trial has led to the evolution of a new paradigm in the approach to peritoneal carcinomatosis of colorectal origin.

Limitations of Hyperthermic Intraperitoneal Chemotherapy

Despite these encouraging results, oncologists continue to display a healthy degree of skepticism, and cytoreductive surgery-hyperthermic intraperitoneal chemotherapy has had limited acceptance in the mainstream oncology community. Potential reasons for these reservations for this locally aggressive strategy are discussed below.

Associated morbidity. The main concern with cytoreductive surgery-hyperthermic intraperitoneal chemotherapy is the associated morbidity, which has been well documented and can range from 22-39 percent. The most frequent surgical complications include anastomotic leakages, intestinal perforation, pancreatitis, prolonged ileus, bile leak, intra-abdominal bleeding/sepsis, wound dehiscence, pulmonary embolism, renal failure, and hematologic toxicities.[9,10] Intra-abdominal sepsis and enteric fistulas often necessitate re-operation. Most of these complications can be attributed to the extensive surgery performed, especially when the patient has had previous multiple operations.

Verwaal and colleagues noted that the overall toxicity was relatively high, with 65 percent of the patients exhibiting Grade 3 toxicities in one or more categories.[11] Of all patients, 35 percent needed re-intervention because of complications, fistulas resulting from bowel leakage being the most frequent. The magnitude of cytoreductive surgery directly influenced the duration of the operation, intraoperative blood loss, and the number of anastomoses. This explains the increased probability of complication with an increase in the number of regions affected by peritoneal carcinomatosis. Verwaal and colleagues also noted that when more disease is left behind, the complication rate also increased. On average, this procedure takes 10-12 hours with a median blood loss of 3-5 liters, and necessitates blood transfusion, ICU care, and re-operation, which can

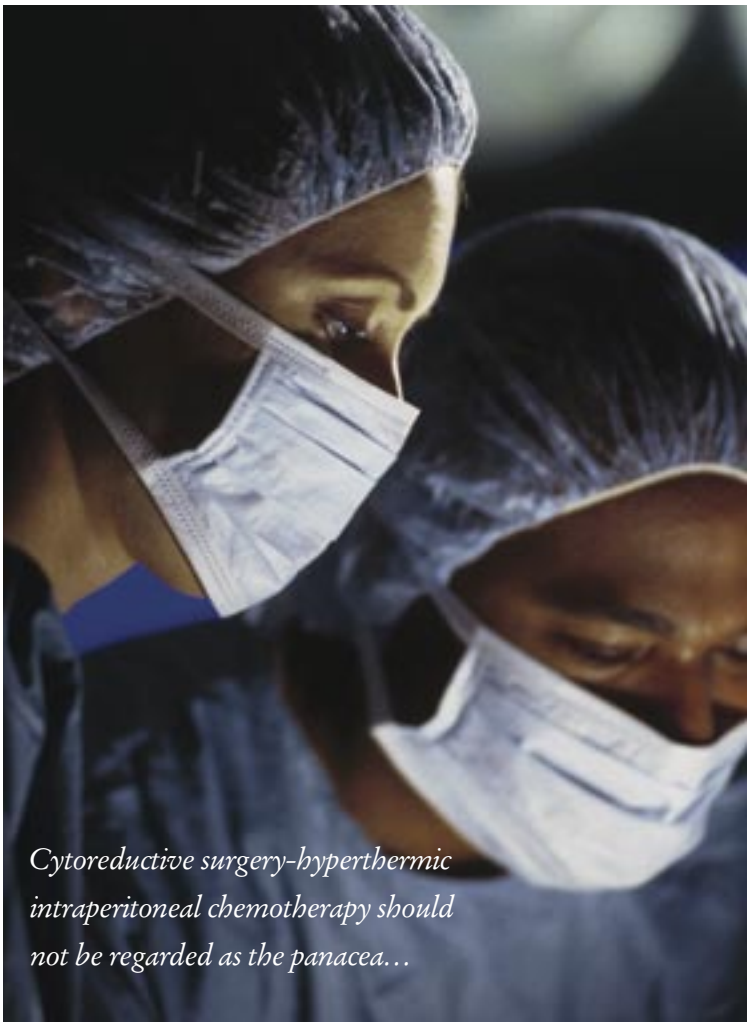
be a considerable drain on the resources of an institution in order to gain benefit for a small group of patients. In fact, previous studies have shown that patients with substantial tumor load derive little or no survival benefit from cytoreductive surgery-hyperthermic intraperitoneal chemotherapy. Moreover, progression of cancer occurs in around 30 percent of the patients, and these patients also do not derive significant benefit from this aggressive approach.

The single institutional study reported by Shen from Wake Forest reported that complete or near complete resection (R0, R1 resection) could be achieved in only 25 percent of the patients.[12] Interestingly, nearly a third of the patients in this series did not receive the full application of heat and chemotherapy as described in the protocol. Sugarbaker points out that the dosing of chemotherapy needs to be modified to keep the morbidity and mortality of this group of patients at 30 percent and 2 percent respectively. He suggests a one-third dose reduction in patients who have had prior extensive surgeries, extensive cytoreductive surgery, if multiple anastomosis needed to be performed, those who have had prior chemo or radiation therapy, and those who are over 65 years of age.[13] Therefore, several technical and procedural nuances mandate that only those who have considerable experience should perform these procedures.

Limited vs. extensive peritoneal carcinomatosis. Though the multi-institutional study demonstrated that the strongest independent prognostic factor for outcome was completeness of cytoreductive surgery, other confounding factors that could also influence outcome were lymph node involvement, age, tumor differentiation, and treatment with adjuvant systemic therapy.[8] Patients who most benefited from this approach are those with limited extent of peritoneal carcinomatosis, as they are most likely to undergo a complete resection, but they represented only 33 percent of their cohort. The remaining patients with extensive peritoneal carcinomatosis are more likely to require a complex and extensive resection, which the Netherlands Cancer Institute randomized trial demonstrated to experience an increased complication rate.[7]

Issues with the randomized studies. Several important issues are raised by the randomized study reported by Verwaal, from the Netherlands Cancer Institute.[7] First, as is true for all the reported Phase II studies, we do not have an accurate assessment of the denominator for the population of patients with peritoneal carcinomatosis. The design of this study failed to answer the question of whether the observed benefit was exclusively due to the aggressive cytoreductive surgery alone, and whether hyperthermic intraperitoneal chemotherapy had any impact on survival, or it just added unnecessary toxicity.

Overall, 8 patients (16 percent) died from the intervention with an excessively high rate of severe side effects. Such a high complication rate is hardly justifiable for a palliative treatment that yielded an overall survival benefit of 10 months for the entire patient population. In fact, subgroups of patients with advanced disease derived no clinically relevant improvement, and one-third of the patients had a median survival of less than 6 months. Judging the success of the surgical procedure, if the patients had anything less than an R1 resection, 62-70 percent died of their disease. Those patients that can undergo the "experimental procedure" are clearly highly selected; the inclusion criteria stated that the patient should be younger than 71, fit for major surgery with normal bone marrow, renal and liver function, and have an excellent performance status. Therefore, it has to be acknowledged that, perhaps, part of the outcome can be attributed to the impact of the tumor biology and careful patient selection.



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Cytoreductive surgery-hyperthermic intraperitoneal chemotherapy should not be regarded as the panacea…

There are also several critiques of the "standard treatment" arm. For example, the systemic chemotherapy consisted of 5FU-leucovorin, which is no longer considered modern standard regimen as currently patients with advanced colorectal cancer are primarily being treated with 5FU, leucovorin, and oxaliplatin with or without biologic agents such as, i.e., bevacizumab.[14] With these modern chemotherapeutic regimens, patients with advanced colorectal cancer demonstrate a median survival reaching almost 21 months. Second, the extent and distribution of the peritoneal carcinomatosis which is a strong, independent, prognostic factor remains unknown in the "standard" group, and, thus, a fair comparison is not possible. Finally, only two-thirds of patients received their proposed adjuvant systemic chemotherapy.

Size and thickness of the tumor. No patients with substantial residual tumor (thickness of 2.5 mm or more), after cytoreductive surgery have been shown to survive for long.[15] This finding appears to

confirm that hyperthermic intraperitoneal chemotherapy with mitomycin C can eliminate only very small deposits of residual tumor. Therefore, patients with 6 or 7 involved regions of peritoneal carcinomatosis and those who do not have disease that can be technically resected to a R0 or R1 level should not receive hyperthermic intraperitoneal chemotherapy. Unfortunately, this information is rarely available before laparotomy. An important factor in this respect is the low sensitivity of CT scan or MRI for detection of peritoneal carcinomatosis.

More effective treatments in the future. With the ever-increasing array of chemotherapeutic and biologic therapies, we can reasonably expect systemic therapy of colorectal cancer to continue to improve significantly in the coming years. In fact when the Netherlands group used more effective chemotherapeutic agents, i.e., irinotecan, they noted that the value of a second surgical debulking was no different than systemic chemotherapy alone (median survival of 10.3 months vs. 8.5 months).[16]

Lack of standardized assessments. One of the most important problems in the management of peritoneal carcinomatosis is the evaluation of tumor response to treatment. Currently, there are no standardized assessments to allow a reliable and statistically valuable quantification of tumor response.[17] It is difficult to evaluate the efficacy of a given therapy other than by second look laparotomy.

A Look to the Future

Given all the aforementioned limitations of this complex, aggressive treatment protocol, continued efforts should be directed to address the following issues:

1. Improved methods of selecting patients who will truly benefit from cytoreductive surgery-hyperthermic intraperitoneal chemotherapy, including evaluation of novel molecular correlates.

2. Standardization of the technique, since the extent of cytoreductive surgery-hyperthermic intraperitoneal chemotherapy procedures can vary considerably (different temperatures, drugs, doses, times, drugs administered with open or closed abdominal technique). In addition, there is no uniformity in the assessment tools, namely, for evaluating the extent of peritoneal carcinomatosis or the extent of cytoreductive surgery.

3. Hyperthermic intraperitoneal chemotherapy may be more suitable in the adjuvant setting for patients who are at high risk of developing peritoneal carcinomatosis, and this can perhaps be based on evaluation of peritoneal washings by molecular markers, using sensitive techniques such as real time-PCR.

4. Future clinical trials of cytoreductive surgery-hyperthermic intraperitoneal chemotherapy with mitomycin C have to be tested along with and against the best modern systemic chemotherapy.

5. As cytoreductive surgery-hyperthermic intraperitoneal chemotherapy is essentially a palliative procedure with most patients eventually succumbing to their disease process, the relevant endpoints ought not to be overall survival, but, perhaps quality of life.

Cytoreductive surgery-hyperthermic intraperitoneal chemotherapy should not be regarded as the panacea but as a promising step in the management of peritoneal carcinomatosis of colorectal origin. Significant contributions by Sugarbaker and the Netherlands group have provided an impetus for continued research efforts in the future.

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