Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemotherapy for Colorectal Cancer:

A New Standard of Care

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In Brief

While patients with carcinomatosis from colon and rectal cancer have had limited survival in the past, cytoreductive surgery combined with chemotherapy in the perioperative period may improve long-term survival in 25-50 percent of colorectal cancer patients with carcinomatosis.

Clinical and laboratory research efforts over the last two decades have established a new treatment paradigm for colorectal carcinomatosis. Similar to the success that has been achieved with the surgical management of selected patients with liver metastases, the treatment of carcinomatosis by an experienced group employing knowledgeable patient selection should demonstrate long-term survival in colorectal cancer patients with carcinomatosis in 25-50 percent of patients.[1] The central components of this treatment are cytoreductive surgery that must be pursued until no visible evidence of cancer remains within the abdomen and pelvis. This treatment is then combined with chemotherapy in the perioperative period. Routinely, mitomycin C is used at approximately 42°C to wash all of the abdominal and pelvic surfaces that are at risk for cancer cell reimplantation. In selected patients not heavily pre-treated with 5-fluorouracil, early postoperative intraperitoneal chemotherapy is useful to complete the chemical cytoreduction.

Natural history studies have firmly established the limited survival of patients with carcinomatosis from colon and rectal cancer.[2] A median survival of approximately six months has been demonstrated in three different studies. Chemotherapy with 5-fluorouracil and leucovorin did not have an impact on the survival of these patients. To date, even with the most modern systemic chemotherapy regimens, no long-term survival of patients with colorectal carcinomatosis has been reported.

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The biologic rationale for a curative approach to carcinomatosis is strong. Just as in patients with between one and three liver metastases and no other evidence of disease, limited carcinomatosis can be thought of as a local/regional extension of the primary cancer. Carcinomatosis is frequently seen in the absence of liver metastases and may occur in the absence of both liver and lymph node metastases. This isolated peritoneal surface dissemination of colorectal cancer is especially prominent with the mucinous malignancies.

Also, the surgical procedures that are required have a strong rationale. Peritonectomy is a surgical innovation that allows for removal of all of the parietal peritoneum if necessary in order to eradicate carcinomatosis.[3] On the visceral peritoneum, cytoreduction from the omentums and surface of the stomach are possible. Tumor implants on the small bowel or large bowel mesentery can also be electrosurgically removed with a negative margin. Tumor nodules on the small bowel surface or large bowel surface require visceral resections for the complete cytoreduction.

The pharmacologic rationale for intraperitoneal hyperthermic chemotherapy is clear. For example, with the drug mitomycin C, approximately 25 times the exposure of the peritoneal surfaces and tumor nodules on peritoneal surfaces is achieved as compared to the systemic circulation and bone marrow.[4] The hyperthermia is used in order to augment cytotoxicity of the chemotherapy and to improve drug penetration into cancer nodules.

Using the intraperitoneal chemotherapy as a planned part of the surgical procedure also has a strong oncologic rationale. Even though the surgeon can remove all visible evidence of carcinomatosis, microscopic disease will be present in portions of the abdomen and pelvis, especially on those surfaces that have been surgically traumatized. These raw surfaces are especially vulnerable to tumor cell entrapment and then cancer progression at a later time. Using heated chemotherapy in the operating room or cell

cycle-specific drugs as a lavage for the first five postoperative days exposes these cancer cells to the full effects of the chemotherapy before they are covered by fibrinous material or entrapped within scar tissue. The perioperative timing of the intraperitoneal chemotherapy treatments is crucial to a successful management of carcinomatosis.[5]

Patient Selection

All of the clinical studies to date show that patient selection is a crucial aspect of this management strategy. Just as patients with between one and three metastases profit most from liver resection for carcinomatosis, also, patients with limited carcinomatosis profit most from these combined treatments. Selection factors that are used currently involve an absence of liver metastases, less than half of the abdominopelvic regions involved by cancer nodules, well-differentiated histology, and an absence of extensive lymph nodal disease (N0 or N1 lymph node status preferred). Perhaps, most important is that patients with carcinomatosis be referred to a peritoneal surface malignancy treatment center at the time that the diagnosis of carcinomatosis is made; this time is when complete cytoreduction may occur and therefore a possibility for cure.[6] Just as with liver metastases, an experienced surgeon should evaluate these patients with carcinomatosis before systemic chemotherapy is begun. It is our clinical impression that extensive prior treatment with systemic chemotherapy generates acquired drug resistance in these patients and makes the combined treatment of cytoreduction with intraperitoneal chemotherapy less effective.

The major selection factor that operates in this group of patients is the ability to perform a complete cytoreduction. All of the groups that have reported benefit emphasize the fact that complete visible removal of the peritoneal surface and visceral carcinomatosis is a requirement for a curative effort.[7] The cytoreductive surgery must resect all gross evidence of disease. Then, the hyperthermic intraoperative intraperitoneal chemotherapy and early postoperative intraperitoneal chemotherapy have the possibility to eradicate the microscopic residual disease that the surgeon cannot appreciate.

One caveat to the general surgeon must accompany these comments. In order to have success with cytoreductive surgery, which includes peritonectomy combined with perioperative intraperitoneal chemotherapy, one must recognize that patient's first line of defense in carcinomatosis is the peritoneum. Extensive dissections of the peritoneum creating a large raw surface within the abdomen and pelvis allows free cancer cells to be implanted deep to the peritoneum. These cancer cells, as they progress, are then difficult and usually impossible to eradicate by subsequent peritonectomy procedures. In patients with limited carcinomatosis found at the time of colectomy, minimal surgery to prevent perforation, obstruction, or bleeding from the primary cancer should be performed. Extensive resections in the absence of combined treatment should not occur. In this group of patients, respect for the peritoneum as the first line of defense of carcinomatosis should be foremost in the surgeon's mind. Unless the patient is old and infirm and not a candidate for more aggressive treatment plans, the essential step in the management of carcinomatosis should be referral to a carcinomatosis treatment center where a definitive combined treatment can be initiated.

Data Supports New Timing for Chemotherapy Treatments

The data that support this new effort in carcinomatosis for colorectal cancer are very clear. First of all, major cancer institutes have collected their data and five institutions (Washington, DC; Villejuif, France; Amsterdam, Netherlands; Winston-Salem, North Carolina; Lyon, France) conclude that 31 percent of patients treated for carcinomatosis will be alive at three years. This compares to a near zero three-year survival with standard treatments.[8] Also, a Phase III study performed by Verwaal and colleagues shows that the survival of patients treated by the combined management plan have doubled the median survival of those treated in a standard fashion.[7] Finally, Glehen and colleagues in a retrospective study of 503 patients established in a multi-institutional effort that patients who had complete cytoreduction had a 33 percent five-year survival.[6]

In my opinion the multiple Phase II studies from reputable institutions, the randomized controlled study, and the multi-institutional registry report establish a reasonable database to make cytoreductive surgery with perioperative intraperitoneal chemotherapy the new standard of care for selected patients with carcinomatosis.

In summary, the successful treatment of carcinomatosis means that the surgeon and medical oncologist must accept a new timing for chemotherapy treatments. The chemotherapy should be initiated in the operating room as a planned part of the surgical procedure. Secondly, the route of administration of the chemotherapy must change. It should exploit the large pharmacologic advantage of the intraperitoneal route of administration. Thirdly, the target of the chemotherapy is greatly modified. No longer is the oncologist forced to treat gross disease with the chemotherapy. Rather, he is using it in an adjuvant setting to eradicate microscopic residual disease. Limited peritoneal carcinomatosis should be managed as is limited liver metastases from this disease. A surgical evaluation at a peritoneal carcinomatosis treatment center is mandatory in that selected patients can be cured of this condition.

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References

[1]Sugarbaker PH. Carcinomatosis—is cure an option? *J Clin Oncol*. 2003;21(5):762-764.
[2]Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies. Results of the EVOCAPE 1 multicentric prospective study. *Cancer*. 2000;88:358-363.
[3]Sugarbaker PH. Peritonectomy procedures. *Ann Surg*. 1995;221:29-42.
[4]Sugarbaker PH, Mora JT, Carmignani P, et al. Update on chemotherapeutic agents utilized for perioperative intraperitoneal chemotherapy. *Oncologist*. (accepted)
[5]Cunliffe WJ, Sugarbaker PH. Gastrointestinal malignancy: Rationale for adjuvant therapy using early postoperative intraperitoneal chemotherapy (EPIC). *Br J Surg*. 1989;76:1082-1090.
[6]Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: A multi-institutional study. *J Clin Oncol*. 2004;22(16):3284-3292.
[7]Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol*. 2003;21:3737-3743.
[8]Glehen O, Gilly FN, Sugarbaker PH. New perspectives in the management of colorectal cancer: What about peritoneal carcinomatosis? *Scan J Surg*. 2003;92:178-179.