

## Carcinomatosis—Is Cure an Option?

MANY WHO read the article by Glehen et al<sup>1</sup> in this issue of the Journal will scoff at a renewed interest in intraperitoneal chemotherapy. They will likely cite two decades of work in this field that have yielded only modest benefits. Many others who have used the intraperitoneal route have concluded that the difficulties with intraperitoneal chemotherapy outweigh the established benefits. This opinion, concerning long-term intraperitoneal chemotherapy treatment plans, has come about for three reasons. First, nearly all the patients in whom these treatment plans were used had extensive intestinal fibrosis and adhesions as a result of prior surgical interventions. At best, one could expect a heterogeneous regional response because of poor drug distribution. Second, patients were treated who had gross disease with tumor nodules up to 1 cm or more in diameter; only systemic effects of intraperitoneal chemotherapy would be of help in these patients. Numerous pharmacologic studies have shown that the penetration of the intraperitoneal chemotherapy as a regional treatment is only a few cell layers. Third, these long-term intraperitoneal chemotherapy treatments required ports that caused many problems, both acute and chronic. Even if no problems occurred with insertion, after several months they resulted in pain with drug administration and became increasingly unreliable in terms of the drug distribution because of fibrosis around the infusion catheter. Most oncologists, therefore, came to the conclusion that all intraperitoneal chemotherapy was more trouble than its limited benefits might justify.

By using intraperitoneal chemotherapy as part of a surgical intervention, Glehen et al<sup>1</sup> have addressed all of these objections. First, all intestinal adhesions were divided by the surgeon before the initiation of the chemotherapy. Yes, these adhesions may reform at a later time as the wound healing occurs. However, in the operating room and for approximately the first postoperative week, no adhesions exist. Second, by proper patient selection and cytoreductive surgery, patients with large tumor nodules are not treated. A complete cytoreduction, with the resection of cancer to a status of no evidence of disease by the surgeon's unaided eye, removes all but the microscopic component of the disease. The target for the intraperitoneal chemotherapy is cancer cells or minute nodules, not gross disease. Third, there are no problems with long-term access. The infusion and the drainage tubes are placed in the operating room. They are always open with unimpeded flow, both into and out of the abdomen. The apparatus that this group used for the instillation of warm chemotherapy is safe, reliable, and as this report shows, effective. Although some new technology is necessary to provide a hyperthermic perfusion, it certainly is not overwhelming in terms of technical requirements. Not only a change in route of administration (intraperitoneal *v* intravenous) but also a change in the timing (perioperative *v* adjuvant) may point the way to a promising new treatment modality.

At my own institution, randomized phase III studies in patients with carcinomatosis have been attempted, but were not successful because of poor patient accrual. However, some courageous investigators have established through the phase III mechanism that cytoreductive surgery with intraperitoneal chemotherapy produces rather remarkable survival benefits in patients with peritoneal seeding from colon cancer. Zoetmulder et al<sup>2</sup> at the Netherlands Cancer Institute randomly assigned patients to receive standard systemic chemotherapy treatment with fluorouracil and leucovorin, versus a comprehensive management plan very similar to that used by Glehen et al.<sup>1</sup> At the first analysis of this trial, there was a 16% 2-year survival in the group treated with systemic chemotherapy. There was a highly statistically significant 43% 2-year survival in those patients who were randomly assigned to cytoreductive surgery plus chemotherapy ( $P = .0145$ ). Are these sufficient data to accept the fact that carcinomatosis from gastrointestinal cancer can be cured in selected patients? If this were true, it would be a major step forward for oncology. Natural history studies suggest a survival of approximately 6 months.<sup>3,4</sup>

Stimulated by this report, I compared the survival of patients with resected liver metastases to the survival of my own patients with complete cytoreduction of carcinomatosis.<sup>5</sup> All patients had disseminated disease from colon and rectal cancer (Fig 1). If liver resection for metastases has been accepted as standard of practice in the absence of phase III studies, perhaps this favorable comparison of treatment outcome indicates that further study of these patients needs careful thought.

If these comprehensive treatments for carcinomatosis gain wider acceptance, the work of Glehen et al<sup>1</sup> places new and heavy responsibilities on the oncology community. Chemotherapy would no longer be reserved for administration in the oncology infusion center. With the perioperative timing necessary for the destruction of residual cancer cells, chemotherapy administration needs to move to the operating theater. For early postoperative intraperitoneal chemotherapy programs, chemotherapy will need to be given on the surgical nursing unit.<sup>6</sup> The proper role of the medical oncologist and the surgeon in this new application of intraperitoneal chemotherapy will need to be defined.

Of course, one must look critically at this work, and a healthy skepticism is encouraged in its evaluation. Perhaps there was a selection bias toward the treatment of favorable patients with a small volume of nongynecologic carcinomatosis. If that were not true, this group would not have performed their study optimally. Knowledgeable selection of patients with carcinomatosis for this new management plan is absolutely essential. However, it is clear from historical control studies performed by this group and others that carcinomatosis is uniformly fatal. In the past, there was no escape from this terminal illness. To my knowledge, this

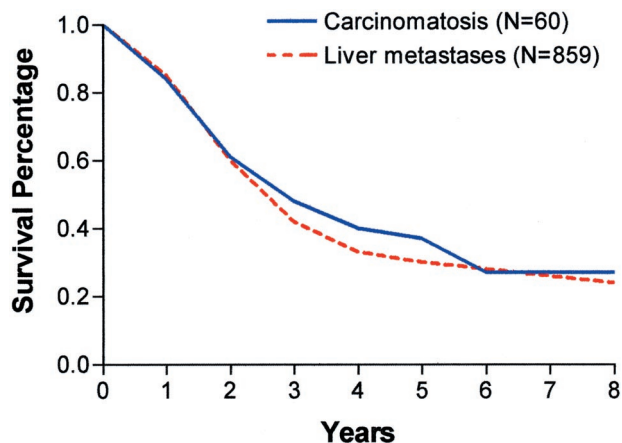


Fig 1. Comparison of survival of a group of patients with colorectal metastases to the liver and a second group with carcinomatosis. In all liver metastases patients<sup>5</sup> the liver resection was scored R0; in all the carcinomatosis patients, the cytoreduction was scored as complete.

new management plan is the only one that suggests a potentially curative option for carcinomatosis.

In addition to a new technical responsibility, there may be added intellectual responsibilities. Patients with peritoneal seeding can perhaps no longer be regarded as a group requiring just palliative systemic chemotherapy. Proper selection of patients for application of these treatments as early as possible in the natural history of carcinomatosis will likely result in the greatest benefit. The traditional management of patients with limited seeding of carcinomatosis from gastrointestinal cancer should be questioned, and early referral to a center where carcinomatosis can be expertly managed may be indicated, as delay in comprehensive management may preclude a curative approach as the cancer on peritoneal surfaces rapidly progresses. This clinical situation is made more difficult in that there is no reliable radiologic study or tumor marker follow-up that can either signal progression or monitor the disease process. It may be possible, as we have learned from liver resection for hepatic metastases from colon cancer that all patients with established carcinomatosis should be considered for cytoreductive surgery and intraperitoneal chemotherapy.

In my opinion this new treatment also places added responsibility on the surgeon. A new surgical procedure called "peritonectomy" is necessary to achieve the desired cytoreduction.<sup>7</sup> Surgeons will need to master visceral and parietal peritonectomy procedures that are demanded in the treatment of carcinomatosis. Also, knowledgeable management of cancer chemotherapy and its toxicity during the perioperative period is required.

If one accepts these treatments as valid, major changes in the management of cancer patients with peritoneal seeding must be considered. In this new approach, using peritonectomy for cytoreduction, an intact peritoneum is the first line of defense against carcinomatosis. Opening large tissue planes with extensive resections in the presence of carcinomatosis greatly interferes with subsequent comprehensive management, and cancer cells may implant within the resection site. This implantation and cancer progression will be deep to the peritoneum and inaccessible to peritonectomy. This means

that iatrogenic invasion may occur into the pelvic sidewall, along the course of the ureter, in and around the structures of the porta hepatis, and at other surgically traumatized sites. A patient with cancer progressing deep within the recesses of the abdomen and pelvis is no longer a candidate for combined treatment by complete cytoreduction with intraperitoneal chemotherapy. Therefore, overly aggressive initial surgery in patients with peritoneal seeding should be avoided. As an example, in this new approach to gastrointestinal carcinomatosis, a patient who has colon cancer who is found to have peritoneal seeding at the time of primary cancer resection should have a minimal surgical procedure. In an obstructed patient, an ostomy above the primary cancer would be appropriate. In a patient without obstructive symptoms, definitive biopsy of the carcinomatosis would be the only recommended procedure. Only the most debilitated patient, one who is not a candidate for cytoreduction with intraperitoneal chemotherapy, should be treated definitively. The optimal treatment of colon cancer with carcinomatosis requires resection of the primary cancer, peritonectomy of implants on visceral and parietal peritoneum to remove all visible evidence of disease, and perioperative intraperitoneal chemotherapy. In the absence of an adequate management plan, a minimal surgical intervention to prevent iatrogenic invasive disease is indicated. If the institution is not adequately prepared to manage carcinomatosis, referral to a peritoneal surface malignancy treatment center would be the appropriate plan.

The work of Glehen et al<sup>1</sup> should not be regarded as the only use for perioperative intraperitoneal chemotherapy. It has been used in an adjuvant setting to prevent peritoneal seeding. Phase III studies have shown benefit, and the patients who may profit most are those who are likely to develop carcinomatosis in the future. A superb example of this approach was published by Yu et al<sup>8</sup> from Taegu, Korea. In their study of 248 randomly assigned patients, they compared extended gastrectomy alone to gastrectomy plus perioperative intraperitoneal chemotherapy using mitomycin C and fluorouracil during the first 5 days after surgery. There was no additional systemic chemotherapy. Overall, a survival advantage was seen ( $P = .0278$ ). In the group of patients with serosal invasion, where one would suspect a high incidence of cancer contamination, the 5-year survival was 25% in patients having surgery only, compared with 52% in those having surgery plus the perioperative intraperitoneal chemotherapy ( $P = .0004$ ). There was some additional morbidity in the group having combined treatment, but in most instances, the problems could be dealt with by an experienced oncologic surgeon. Studies by Yonemura et al,<sup>9</sup> also in gastric cancer, show similar benefit.

At this time, the patient populations who benefit and the essential technical features of heated intraoperative intraperitoneal chemotherapy have not been clearly determined. Many questions still need to be answered. What are the appropriate selection factors required to electively pursue such an aggressive management strategy? Is hyperthermia necessary? If it is necessary, how high a temperature must one achieve in order to see optimal tumor eradication and yet maintain acceptable morbidity

and mortality? What drugs in addition to mitomycin C and cisplatin are appropriate for peritoneal dissemination of gastrointestinal cancer? Certainly, a variety of drugs can be suggested. Appropriate and compatible drug combinations need to be established. Glehen et al<sup>1</sup> have made us think about treatment options for carcinomatosis. Now, much work is necessary to

explore their plan of management and to identify the populations of patients who are likely to benefit from this approach.

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