

Editorial

Problems of Success and Problems of Failure: Recurrent Disease After Cytoreductive Surgery and Intraperitoneal Chemoperfusion

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Peritoneal carcinomatosis is an all-too-frequent mode of dissemination of colorectal carcinoma. Natural history studies have shown that peritoneal carcinomatosis is uniformly fatal, with median survival of approximately 6 months.¹ For more than a decade, a handful of centers have pursued aggressive cytoreductive surgery combined with intraperitoneal chemotherapy for this disease. Several phase II single institution trials showed survival of peritoneal carcinomatosis from colorectal carcinoma well in excess of a year. Although more than doubling the survival time in comparison with historical controls represents a significant accomplishment in this group of patients, the results were treated with a healthy degree of skepticism. Strict selection criteria, variation in intraperitoneal chemotherapy, and the vagueness of what represents “cytoreductive surgery” made many of our colleagues, particularly those in medical oncology, reticent to refer patients for such an aggressive therapy. To bring cytoreductive surgery and intraperitoneal chemotherapy into the mainstream, a randomized trial was sorely needed.

Conducting a randomized trial involving patients with peritoneal carcinomatosis is a difficult undertaking. However, investigators from the Netherlands Cancer Institute in Amsterdam succeeded where other institutions had failed. A report on their prospective randomized trial was published in the *Journal of Clinical Oncology* last year.² In their study, over a 3-year period, 105 patients were randomized to receive “standard treatment” with fluorouracil and leucovorin, with or without palliative

surgery, or the same chemotherapy with aggressive cytoreduction and intraperitoneal hyperthermic chemotherapy with mitomycin c. With a mean follow-up of 21.6 months, the median survival was 12.6 months in the standard therapy arm and 22.3 months in the cytoreduction and chemoperfusion arm ($P = .032$). Treatment morbidity in this study was similar to that at other centers, and the mortality rate was 8%.

Furthermore, an exciting finding of this trial was a Kaplan-Meier estimate of 5-year survival in the range of 20%, which confirmed the results of several of the single-institution phase II trials.^{3–5} This study also confirmed the universal finding that the prognosis following cytoreductive surgery and intraperitoneal hyperthermic chemotherapy is closely related to the completeness of the cytoreduction. Critics of this randomized trial could argue with the fact that this study used a fluorouracil-based chemotherapy rather than more active oxaliplatin- and irinotecan-based regimens. However, this randomized trial clearly succeeds where the previous phase II trials failed, making cytoreductive surgery and intraperitoneal hyperthermic chemotherapy a standard treatment for selected patients with peritoneal carcinomatosis from colorectal carcinoma.

Problems can arise either from success or from failure. A key problem of success related to this prospective randomized trial is how to make such therapies standardized and available to large numbers of patients. There are no registries for “perfusion centers,” but I believe that there are fewer than 25 currently active centers in the United States. Furthermore, there are only a handful with extensive experience with the technique (>100 cases). The operative procedures attendant to aggressive cytoreduction are lengthy and challenging, associated with morbidity, and utilize a great deal of hospital, blood bank, and house officer resources.

Clearly, this is not a procedure that should be undertaken by the occasional operator. Moreover, the utiliza-

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tion and safety of chemotherapy in the operating room are daunting for many centers. Additionally, great care needs to be taken in selecting patients to undergo this procedure. It is estimated that only a handful of patients who are potential candidates for this therapy actually receive it, which is underscored by the relatively small number of patients accrued to the phase II studies even at large "perfusion centers." I believe that the number of centers should be expanded with surgical oncologists who have more than a passing knowledge of systemic chemotherapy and are comfortable with the rigors of aggressive operative procedures in the abdomen.

In this issue of the *Annals of Surgical Oncology*, the same group at the Netherlands Cancer Institute report on an analysis of their problems associated with failure.⁶ That article highlights the difficulties still associated with even aggressive cytoreductive surgery in intraperitoneal hyperthermic chemotherapy. Specifically, with a median follow-up of nearly 4 years, two-thirds of patients had recurrences. As anticipated from other reports, most of the failures were intraperitoneal; two-thirds of the failures were exclusively at intra-abdominal sites. This certainly supports the contention that a subset of patients will manifest intra-abdominal disease without manifesting hematogenous metastases.

It is noteworthy that there were fewer recurrences among patients who had undergone more complete cytoreduction (called R1 in this report) than among patients with gross residual disease (R2). With R2 resections nearly 80% of the recurrences were intraperitoneal, whereas with more complete (R1) resections only 50% of the recurrences were intraperitoneal. The authors suggest surgical therapy be considered for patients with intraperitoneal failures at a single peritoneal site. When this could not be resected with a negative margin, they added adjuvant radiation therapy. Additionally, patients who had recurrent disease at more than one site or that was not deemed resectable were offered second- or third-line chemotherapy. The authors chose not to repeat cytoreduction with intraperitoneal hyperthermic chemotherapy.

The article ameliorates the paucity of data on management strategies for patients with recurrent disease after cytoreductive surgery and chemoperfusion. The median survival of the 15 patients who underwent a second surgical debulking (without chemoperfusion) was 10.3 months, which was not significantly different from the median survival (8.5 months) of those who received systemic chemotherapy for several sites of recurrence.

Despite all the aforementioned findings, we and others believe that for selected patients a second cytoreductive procedure and chemoperfusion may be of value.⁷ In

evaluating patients for a second cytoreduction, the criteria that are used to select patients for the first remain important. Specifically, the patients must remain medically fit to tolerate a major operative procedure, be free of extra-abdominal or hepatic parenchymal metastases, and have disease that seems amenable to complete cytoreduction. Additionally, as the authors point out, the time to recurrence after initial cytoreduction and the completeness of the initial cytoreduction also should be factored into the decision to proceed with an additional procedure. Patients who have bulk residual disease after an initial cytoreduction for colorectal carcinoma should not be considered candidates for second cytoreductive procedures.⁷

Although the results from "perfusion centers" represent a substantial improvement in duration and likely quality of life,⁸ the vast majority of patients undergoing these procedures will have a recurrence. Evaluating patients for second cytoreduction and additional chemoperfusion will become an ever-more-common problem as these procedures move into the mainstream. Drs. Verwaal and Zoetmulder and their team at the Netherlands Cancer Institute must be congratulated for bringing data from a prospective randomized trial to this very difficult area. However, much remains to be done, and additional randomized trials are sorely needed. It is high time that multi-institutional trials supported through surgically oriented cooperative groups such as the NSABP or the ACOSOG be initiated to evaluate many of the fundamental questions regarding cytoreduction and intraperitoneal hyperthermic chemoperfusion.

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