Peritoneal Metastases, a Frontier for Progress

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KEYWORDS

• HIPEC • Intraperitoneal chemotherapy • Appendiceal mucinous neoplasms
• Pseudomyxoma peritonei • Colorectal cancer • Hyperthermia

KEY POINTS

- Peritoneal metastases has been an unsolved problem in oncology, causing progressive disease in a large proportion of patients with gastric, colorectal, and pancreas cancers.
- The current standard of care for success in management of peritoneal metastases from gastrointestinal cancer combines complete cytoreductive surgery, perioperative intraperitoneal chemotherapy, and intraperitoneal hyperthermia.
- Peritonectomy and visceral resections are used to surgically eliminate all visible evidence of peritoneal metastases so that hyperthermic intraperitoneal chemotherapy can eliminate microscopic disease.
- Efforts to develop treatments that show success in the cure of peritoneal surface malignancy have been combined multinational initiatives in Europe, the United States, Japan, and Australia.

INTRODUCTION

There is a glimmer of hope that a major enemy of the success in a cure of gastrointestinal and gynecologic malignancy may be brought under control. This consistent cause of treatment failure is peritoneal metastases. However, now we are learning how to use peritonectomy and visceral resections to achieve a complete visible clearing of the abdominal and pelvic space. In addition, we are learning how to use cancer chemotherapy as an integral part of this surgical intervention. There is now a combined management strategy, perhaps not perfect, but safe enough and effective enough to become a standard of care for selected patients with appendiceal peritoneal metastases, colorectal peritoneal metastases, and peritoneal mesothelioma.[1] The possibilities for prevention and treatment strategies for gastrointestinal and gynecologic malignancy may be nothing short of spectacular!

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Where did the combined treatment strategies get started? Who made them work? How has it grown so definitively to bring us all together here this evening? I hope this article can answer some of these questions. This is peritoneal metastases, a frontier for progress.

WHY STUDY PERITONEAL METASTASES?

People ask why spend so much time and effort dedicated to the study of peritoneal metastases. For Francois Gilly, that answer was easy. This is a terrible problem in oncology that, in the past, had no reasonable treatments. The French multi-institutional prospective study, EVOCAPE 1 (Evolution of Peritoneal Carcinomatosis), was designed to establish the natural history of peritoneal metastases in patients with gastric cancer, colorectal cancer, and pancreas cancer.[2] The data collected were even more shocking than previously expected. It was gathered from the time of diagnosis of the primary cancer with peritoneal seeding in 212 patients and from 158 patients when peritoneal seeding was diagnosed in follow-up. The median survival of 125 patients with gastric cancer with peritoneal seeding was 3.1 months. The median survival of 118 patients with colorectal cancer with peritoneal seeding was 5.2 months, and for patients with pancreas cancer it was only 2.1 months.

Also, the data showed that the extent of disease was an important determinant of survival. Peritoneal metastases should not be recorded, as in the past, as present versus absent but the disease should be quantitated. EVOCAPE data showed that patients with cancerous nodules less than 5 mm lived significantly longer than patients with nodules greater than 5 mm. The answer to this question, "Why study carcinomatosis?" is that this is a terrible problem in oncology—something needed to be done!

INTRAPERITONEAL CANCER CHEMOTHERAPY

Perhaps we will never know who first infused cancer chemotherapy into the peritoneal space in a patient with peritoneal metastases. However, it is clear that Dedrick and colleagues[3] at the American National Cancer Institute provided a rationale for direct intraperitoneal administration. Dedrick and coworkers discovered that the rate at which anticancer drugs leave the peritoneal space is considerably slower than the rate at which the body metabolizes or excretes the drug. This results in a marked increased concentration of cancer chemotherapy at the peritoneal surface and also at the surface of a peritoneal cancer nodule as compared with the concentration in the bloodstream and bone marrow. Dedrick and coworkers' data showed that intraperitoneal instillation would produce greater local efficacy but less systemic toxicity. Mitomycin C is a common drug now used for intraperitoneal instillation in patients with peritoneal metastases (**Fig. 1**). In this pharmacologic study, on the vertical axis the concentration of the drug is plotted. The time over a period of 90 minutes is shown on the horizontal axis. At all points in time the intraperitoneal concentration of mitomycin C is much greater than in the blood. Mathematically, the exposure of a cancer nodule is more than 27 times greater than the exposure of bone marrow cells.[4] Intraperitoneal instillation of selected cancer chemotherapy agents may cause greater efficacy within the peritoneal space and less toxicity to the body.

HEAT ALONE IN THE PERITONEAL SPACE

The use of heat to fight cancer is as old as Greek medicine. Hippocrates said, "Those diseases which medicines do not cure, the knife cures; those which the knife cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable."[5] The use of intraperitoneal heat alone to help control cancer was not described