

Editorial

Peritoneal Carcinomatosis: A Final Frontier

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Until recent years, a diagnosis of peritoneal carcinomatosis (PC) from intra-abdominal solid tumors carried a uniformly fatal prognosis, often within weeks or months. Even though PC is common in digestive tract cancers aggressive management of PC is often viewed pessimistically. This aspect of intra-abdominal malignancy constitutes one of the remaining “frontiers” in oncology where the benefits of locoregional therapy are not well accepted or proven. The use of systemic chemotherapy has not been shown to be effective in the management of PC, due to poor penetration of the cytotoxic agents into the peritoneal cavity. Therefore other treatment options are necessary. In this issue of the *Annals of Surgical Oncology* the article from Pilati et al.¹ demonstrates an overall 2-year survival of 31% for PC due to colorectal cancer, when managed with cytoreductive surgery (CS) and hyperthermic intraoperative intraperitoneal chemotherapy (HIIC), an aggressive locoregional therapy with many theoretical and practical advantages.

The natural history of PC has been well documented in the prospective multicenter Evolution of Peritoneal Carcinomatosis 1 trial from France.² This study demonstrated the dismal prognosis of PC with a median overall survival of 3.1 months for PC arising from all tumor types and 5.2 months for PC arising from colorectal carcinoma. Significant advancements in the management of PC have been made in the past two decades in part because of the pioneering work of Sugarbaker and colleagues.³ With aggressive CS and HIIC there have been long-term survivors and significant improvement in median survival time reported in this study and several others.^{4–6} Compared with the natural history of this

disease these results represent an advance in the treatment of this relatively common condition, akin to the management of liver metastasis with hepatectomy and regional (intrahepatic) chemotherapy. Unfortunately many surgeons and oncologists remain skeptical of CS and HIIC, failing to recognize the increasing volume of literature demonstrating its benefits, therefore relegating their patients with peritoneal carcinomatosis to palliative care measures only.

PC without distant metastasis represents locoregional disease and consideration to aggressive locoregional therapy should be given, as is the case with many other solid tumors. Current surgical oncology trends and evidence support aggressive CS combined with systemic therapy for recurrent locoregional disease as well as distant metastasis in some cases.^{7,8} As with most solid tumors the ultimate outcome of the patient with PC depends on the potential for distant dissemination, which varies with the site of origination of the primary tumor, the grade of the tumor, and acquired genetic mutations resulting in the malignant phenotype. Since this potential is not known when PC is present without distant metastasis, an aggressive approach may be justified. In cases where metastatic disease eventually develops, significant improvement in long-term survival will depend on the development and efficacy of systemic therapies to eradicate micrometastatic tumor deposits, which are not apparent at the time of treatment of PC. The efficacy of CS and HIIC as a locoregional treatment is well documented in low-grade peritoneal malignancies (such as pseudomyxoma peritonei) where the incidence of dissemination outside of the peritoneal cavity is minimal. CS and HIIC now represent the standard of care in these low-grade malignancies, converting a once uniformly fatal condition to a readily curable disease (greater than 75% long-term survival in some series).

Although PC from colorectal cancer is certainly a different situation and this type of therapy is not applicable in all cases, it is probable that there is a subset of patients whose tumors exhibit the tendency for peritoneal

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spread without the ability for distant metastasis. Currently there is no way to differentiate these patients, therefore, the option for aggressive therapy with CS and HIIC should be considered when only PC is present. A recent report from Zoetmulder et al.⁹ showed a statistically significant improvement in survival in a prospective randomized study for PC in colorectal cancer. This study randomized patients to standard therapies or CS and HIIC and demonstrated a statistically significant (43% vs. 16%; $P = .0145$) 2-year survival advantage in the HIIC arm. While currently only in abstract form, this study represents the only prospective randomized study of HIIC in the management of PC.

The benefits of HIIC which have been described in detail,³ include the potentiation and increased penetration of chemotherapy agents due to hyperthermia, the direct cytotoxic effects of hyperthermia, significantly higher concentrations of chemotherapy agents in direct contact with the tumor with low systemic absorption, better contact of cytotoxic agents with tumor, and avoidance of some of the immediate side effects of chemotherapy. This study as well as others has documented that this procedure can be done safely with acceptable morbidity and mortality rates. Additional benefits include improved quality of life and ability to continue alimentation.

The authors' conclusions in this study are accurate and warrant further consideration. Despite the increasing numbers of references documenting some degree of efficacy for this treatment many questions remain to be answered. As the authors suggest, the optimal techniques for HIIC remain to be proven. Pertinent questions include the relative efficacy and staff safety of open or closed perfusion, optimal temperature and time of perfusion, most effective chemotherapy agents and doses, and treatment related morbidity and mortality. An accurate documentation of survival benefits for CS and HIIC in the treatment of PC from tumors originating in different organs would allow better patient selection and the use of this therapy in appropriate subsets of patients. The role of early postoperative intraperitoneal chemotherapy as well as adjuvant systemic therapy in combination with these treatments also needs to be better defined. These

and many other questions should be answered in large prospective multi-institutional trials, preferably under the auspices of a national clinical trials research base. There are now many cancer programs offering this type of locoregional treatment for PC, which should facilitate the accrual of patients to these potential trials in a timely fashion. I certainly agree with the authors' final conclusion that the proper assessment of this therapy can only occur when the technique has been standardized and phase III clinical trials are performed to define the clinical conditions where its use is appropriate. The time has arrived for this therapy to be validated with prospective clinical trials so that there will be more widespread acceptance and use of this therapeutic modality, with the ultimate benefit being realized by patients afflicted with this terrible manifestation of intra-abdominal malignancies.

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