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Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Colorectal Carcinomatosis: If at First You Don't Succeed...

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The management and outcomes of stage IV colorectal cancer have changed significantly over the past 5–10 years. The advent of relatively effective, multimodality regimens of 5-fluorouracil and leucovorin combined with cytotoxic agents (e.g., oxaliplatin or irinotecan) and targeted therapies (e.g., bevacizumab or cetuximab) has resulted in unprecedented rates of both tumor response and patient survival.[1,2] Simultaneously the indications for surgery in the management of hepatic and pulmonary metastases from colorectal cancer continue to expand. However, for patients with carcinomatosis from colorectal cancer, the view remains generally nihilistic for a number of reasons. First, the historical life expectancy of patients with colorectal carcinomatosis was a dismal 6–7 months.[3] Second, surgery has traditionally not been shown to play any significant role other than selective palliation. Third, despite the overall results of the more efficacious chemotherapy regimens, the actual benefit to patients with carcinomatosis has yet to be determined. Consequently, while evidence-based guidelines recommending neoadjuvant chemotherapy followed by surgery for the management of patients with hepatic and pulmonary metastases are readily available, there are no management guidelines for patients with carcinomatosis.

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Despite this daunting backdrop, significant efforts are being made to improve the outcome of patients with carcinomatosis. One such effort is the use of a combined treatment approach involving cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC). Currently, this approach is gaining recognition as a treatment option for a variety of peritoneal surface-based malignancies. Significant improvements in disease-free and overall survival from CRS and PIC have been demonstrated in patients with peritoneal dissemination of appendiceal and ovarian cancers and diffuse malignant peritoneal mesothelioma.[4–6] In fact, CRS and PIC are considered by many to be the standard of care for select patients with peritoneal-based disease from these malignancies.[7,8] CRS and PIC have also been used in the treatment of carcinomatosis from colorectal cancer with some centers publishing 5-year survival rates of 30% or higher.[9–12] For such a historically hopeless clinical situation, these results seem almost miraculous. Consequently, and despite a paucity of high-level evidence, a consensus statement has been published advocating the use of CRS and PIC in select colorectal patients with carcinomatosis.[13,14]

In "Failure Analysis of Recurrent Disease Following Complete Cytoreduction and Perioperative Intraperitoneal Chemotherapy in Patients with Peritoneal Carcinomatosis from Colorectal Cancer," Bijelic et al.[15] are the first to analyze the anatomic distribution, timing, and outcomes of recurrent peritoneal disease after complete cytoreduction and PIC for peritoneal carcinomatosis from colorectal cancer. The data are derived from a single-institution experience, spanning

23 years and include 70 patients who underwent complete (CC-0) or near complete (CC-1) cytoreduction. Despite a high frequency of recurrent disease ($n = 55$, 78%), the authors achieved an overall median survival of 30 months and a 5-year survival of 17%. Twenty-six patients had at least one reoperation, including a second, complete cytoreduction in 18 patients. Fourteen patients also underwent repeat PIC. Patients who underwent a second, complete cytoreduction achieved a median survival of 42 months, and a 5-year survival approaching 30% was seen in all patients having a second surgery, regardless of the completeness of cytoreduction. In addition, the authors identified significant ''failure-related'' predictors of survival including the anatomic distribution (localized versus diffuse or distant) of the recurrence and the time to recurrence. Assuming the premise that CRS and PIC are indicated for carcinomatosis in colorectal cancer, the authors conclude that additional CRS and PIC in selected patients with recurrence may result in long-term survival. Whether this reflects the impact of the therapy, or tumor biology that lends itself to subsequent procedures, is unknown.

Before promoting the repeated use of this highly morbid treatment for recurrent disease, the appropriate role of CRS and HIPEC in the initial management of colorectal carcinomatosis remains to be determined. Whereas historically patients with colorectal carcinomatosis have had no clinically meaningful treatment options, there appears now to be two potentially efficacious options—systemic therapy and CRS and HIPEC. For a number of reasons, determining the optimal use of these evolving therapies will not be easy.

Because of the high morbidity, and potential mortality, associated with CRS and HIPEC (mortality rates of 2–5 % are common), it is not enough to simply compare the benefits of this treatment to that of systemic therapy. Rather it is the risk-benefit ratio of each treatment that must be considered and compared. Furthermore, because CRS and HIPEC employs two treatment modalities (surgery and chemotherapy), it is also necessary to consider the individual risk-benefit ratio of each modality. For example, it is possible that in the setting of the newer chemotherapy regimens, a standardized complete cytoreduction may offer the same benefit as, with significantly less morbidity than, CRS and HIPEC. Important issues such as this will only be settled through the completion of an appropriately designed and conducted clinical trial.

In addition, the results presented in this manuscript highlight a number of important CRS and HIPEC-specific issues that also require resolution. The first and foremost is that of patient selection. It is notable that of 156 select patients who underwent attempted CRS by one of the world's most experienced peritoneal surgeons, complete CRS was possible in only 70 (45%), and the true denominator from which these 156 patients were culled is unknown. Furthermore, despite the accomplishment of a complete cytoreduction, 78% ultimately developed recurrent disease. Clearly better-defined criteria for patient selection are essential before embracing this approach. The authors' analysis of the types of recurrence following a complete cytoreduction provides some guidance for the development of these criteria.

By evaluating tumor recurrences based on their anatomic location, Bijelic and colleagues offer a potential rationale for these events that is insightful and provocative. First, recurrence in the form of distant metastatic disease raises important questions about the role of tumor biology (e.g., lymph node status and primary tumor histology) in patient selection. Because recovery from CRS and PIC can often delay the delivery of systemic chemotherapy, it is reasonable for patients at higher risk of developing extraperitoneal disease to receive treatment with ''neoadjuvant'' systemic therapy based on the newer chemotherapy regimens. This approach could not only help identify patients unlikely to benefit from additional treatment with either CRS or CRS and PIC, but it may also improve patient outcomes by treating micrometastatic disease up front, thereby enhancing the benefit of additional treatments.

Second, for patients with diffuse peritoneal recurrence, the authors postulate a failure of the chemotherapy. It is hard to know exactly what role the method of intraperitoneal chemotherapy played in this type of recurrence, as there was use of both hyperthermic intraoperative and normothermic perioperative chemotherapy present within the study population. The concept of a chemotherapy failure also raises questions about the role of tumor histology and the potential utility of using DNA or protein arrays to determine genetic signatures of chemoresistance. In addition, it raises concern as to the potential impact of prior chemotherapy selecting chemoresistant tumor cells. This is yet another important question that can only be answered in the context of a clinical trial.

Third, for patients with localized recurrence the authors postulate a failure of the surgery. Because all the patients in this study presumably received the same initial level of surgical effort, this concept is intriguing. Unlike unpredictable failures of chemotherapy or the progression of undetectable distant metastases, surgical failures are an opportunity to identify predictive characteristics of recurrence.

For example, the Peritoneal Carcinomatosis Index (PCI) has clearly been established as a predictor of survival after CRS and PIC for colorectal carcinomatosis.[9,16] Is there a role for PCI (or an alternate objective measure of tumor burden) in predicting the different types of recurrences defined by the authors? Similarly, prior surgical score (PSS) has been shown to impact the outcome of CRS and HIPEC and may also play a definable role in predicting recurrence.[6] Finally, the completeness of cytoreduction has clearly been shown to be one of the most important predictors of success with CRS and HIPEC for any type of malignancy.[17–19] At this time, the clinically significant definition of a complete cytoreduction for carcinomatosis from colorectal cancer is controversial. While a CC-1 may be sufficient for the less aggressive mucinous neoplasms of the appendix, it may not be adequate for carcinomatosis from colorectal cancer. Future analysis of these and other potentially predictive characteristics of recurrence with respect to patterns of recurrence and to the patients who do and do not develop recurrent disease will be essential in the pursuit of better patient selection.

The authors' results with patients who have undergone second CRS and PIC are truly laudable. However, given the new era of chemotherapy for stage IV colorectal cancer, the appropriate role of CRS, either alone or with PIC, for the initial management of carcinomatosis remains to be determined. Early referral to peritoneal surface oncology centers can facilitate achieving this goal. In addition to minimizing the number of operations suffered by an individual patient, the experience available at dedicated centers will offer patients the greatest chance at complete cytoreduction. Furthermore, concentrating the care of these complex patients in a small number of high-volume centers will allow a more scientific evaluation of the utility of CRS, with and without PIC, and their appropriate roles (e.g., primary versus adjuvant therapy) vis-à-vis systemic chemotherapy. While there is still a long way to go in the management of this devastating disease, at least there now appears to be some light on the horizon.

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