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EDITORIAL – COLORECTAL CANCER

"Adjuvant" Hyperthermic Intraperitoneal Chemotherapy: A Call to Action

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The highly experienced team of Baratti et al. used hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colorectal cancer at high risk for peritoneal metastases.[1] The literature reports an overall median survival of only 1–2 years for this patient population, even in the setting of contemporary systemic chemotherapy. Furthermore, disease progression is characterized by significant morbidity from malnutrition and bowel obstruction. In an effort to improve outcomes, regional therapy, including cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC), has been used with mixed success. It appears that the best outcomes occur in patients with minimal peritoneal disease. Treatments for occult disease may be more effective than treatments for established disease.

The authors sought to define the efficacy, feasibility, and safety of CRS and HIPEC in a prospective cohort of 22 patients with colorectal cancer thought to be at high risk for peritoneal metastasis compared to a retrospectively matched group of 44 patients treated with standard surgery. The primary end point was peritoneal recurrence rate—an appropriate end point. Secondary end points were overall survival, progression-free survival, morbidity, and mortality. With a long median follow-up, the authors report that the combination of CRS and adjuvant HIPEC was associated with 33 and 11 % lower rates of peritoneal recurrence and death, respectively, without increased morbidity. These attention-getting numbers suggest that regional therapy may provide a benefit to patients in the adjuvant setting. However, we think that caution is warranted in interpreting the study's findings, as multiple important issues must be taken into account.

As mentioned in the article's introduction, patient selection and the optimal timing and treatment are not well defined for locoregional colorectal cancer. Not surprisingly, the inclusion criteria for the study were loosely defined. Moreover, the study's approach to the identification of "high-risk" features before and during surgery has not been validated, and without final pathologic evaluation, comprehensive evaluation of risk is imprecise. Furthermore, the study included eight patients with established ovarian or low-volume peritoneal metastasis, which is not truly an adjuvant setting. Additional heterogeneity was introduced by the variable use of systemic chemotherapy. Some patients were treated in the neoadjuvant setting, and more than three different adjuvant systemic regimens were described, with only two-thirds of patients receiving standard FOLFOX.

The extent of the benefit of HIPEC suggested by this study is difficult to understand, given the incremental benefit of FOLFOX for patients with microscopic metastatic disease after surgery and the lack of benefit of biologics in that setting.[2,3] In the context of the limited efficacy of contemporary systemic therapies, we should remain dubious that a single treatment of intraoperative chemotherapy would provide such a profound effect.

The authors state that this was a study of the feasibility of HIPEC at the time of curative surgery. However, only 22 patients were accrued over a 6.5-year period, and the authors do not report how many patients were initially enrolled without meeting final eligibility criteria. This limitation will impact a power analysis required to develop a feasible phase 3 study. At Memorial Sloan Kettering Cancer Center, only 2 % of patients with nonmetastatic colorectal cancer experience an isolated peritoneal recurrence. We remain concerned that the population that would benefit from adjuvant regional therapy remains small.

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To date, no study has definitively shown that HIPEC, in combination with CRS, is effective for peritoneal metastasis of colorectal origin. Thus, HIPEC is not universally accepted, despite many promising retrospective and uncontrolled studies. The existing literature shows that patients with peritoneal metastasis of colon cancer have poor long-term outcomes and a 5-year survival rate of approximately 10 %, indicating that CRS/HIPEC remains a palliative rather than curative therapy.[4]

The peritoneal cancer index, completeness of cytoreduction, histology, and grade remain key prognostic factors for colorectal cancer, and despite researchers' best efforts, patient selection will confound the results of any retrospective study. The disparate natural history of this unique cancer phenotype is a major obstacle for drawing definitive conclusions regarding the efficacy of CRS and HIPEC. The authors acknowledge their study's small number of patients and heterogeneous patient population. Two possible conclusions can therefore be drawn from the study's findings: either the cohorts were not well matched, or the authors have defined a patient cohort that will significantly benefit from CRS and HIPEC.

Despite the study's limitations, the findings demonstrate that adjuvant HIPEC appears to be safe in experienced hands, with a low risk of perioperative morbidity and mortality. The data provide a compelling rationale for a prospective randomized controlled trial of adjuvant IPC. This publication can also be viewed as sounding a call to action for physicians caring for colorectal cancer patients at high risk for peritoneal metastasis. As can be seen from the study, even at the Istituto Nazionale dei Tumori, a center specializing in the treatment of high-risk colon cancer, patient accrual is low. International leaders in this field must therefore combine their resources in order to overcome the heterogeneous tumor biology and standardize definitions and treatment strategies so that a prospective randomized trial can determine whether regional therapy can be effective for high-risk colon cancer.

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REFERENCES

1. Baratti DH, Kusamura S, Iusco, D, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of primary curative surgery in patients with colorectal cancer at high risk for metachronous peritoneal metastases. *Ann Surg Oncol.* In press.
2. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol.* 2009;27:3109–16.
3. Maillet M, Glehen O, Lambert J, et al. Early postoperative chemotherapy after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for isolated peritoneal carcinomatosis of colon cancer: a multicenter study. *Ann Surg Oncol.* 2016;23:863–9.
4. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol.* 2008;15:2426–32.