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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

The Chicago Consensus on Peritoneal Surface Malignancies: Management of Colorectal Metastases

Chicago Consensus Working Group

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ABSTRACT The Chicago Consensus Working Group provides multidisciplinary recommendations for the management of colorectal cancer specifically as it relates to the management of peritoneal surface malignancy. These guidelines are developed with input from leading experts including surgical oncologists, medical oncologists, pathologists, radiologists, palliative care physicians, and pharmacists. These guidelines recognize and address the emerging need for increased awareness in the appropriate management of peritoneal surface disease. They are not intended to replace the quest for higher levels of evidence.

COLORECTAL CANCER WITH PERITONEAL METASTASES

This article provides multidisciplinary recommendations for the management of peritoneal surface malignancies of colorectal origin and constitutes 1 article in a series composed by the Chicago Consensus Working Group for the Management of Peritoneal Surface Malignancies.[1–10] Information regarding formation of the Chicago Consensus Group and explanation of the working group's consensus methodology is discussed elsewhere.[1,2]

The collaborators for the Chicago Consensus Working Group are listed in the acknowledgments.

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The peritoneum is a common site of metastasis of colorectal cancer, and peritoneal metastases can occur either synchronously or metachronously. The true incidence of metastasis to the peritoneum is unknown but has been reported to range from 2% to 51%.[11–13] A lack of appropriate imaging techniques and exclusion of patients with peritoneal metastases from clinical trials have contributed to this uncertainty. Autopsy studies estimate that 20% of patients with adenocarcinoma (28% of those with node-positive disease) and 48% of mucinous tumors have peritoneal metastases.[14]

In the preoperative evaluation of patients with peritoneal metastases from colorectal cancer, the peritoneal disease distribution and burden, disease biology, and other sites of metastases must be assessed. This workup includes imaging the chest, abdomen, and pelvis with cross-sectional imaging such as computed tomography (CT) of the chest, abdomen, and pelvis with intravenous contrast or CT of the chest combined with magnetic resonance imaging of the abdomen and pelvis. (See *Colorectal Cancer with Peritoneal Metastasis Management Pathways*, Figs. 1 and 2). Positron emission tomography/CT scans are useful for nonmucinous tumors. However, cross-sectional imaging often underestimates the peritoneal disease burden because the sensitivity for implants smaller than 1 cm is only 25%.[15] Use of imaging to assess radiographic response to systemic therapy has similar limitations because many peritoneal metastases are not visible. Carcinoembryonic antigen levels should be measured, and levels of CA-125 and CA 19-9 can also be elevated in patients with peritoneal metastases. Tumor markers can be also helpful to assess response to systemic therapy (Figs. 1 and 2).

Principles of Pathology

The principles of pathology for primary colorectal tumors have been described elsewhere and are not covered here. Regarding the primary tumor, it is important to

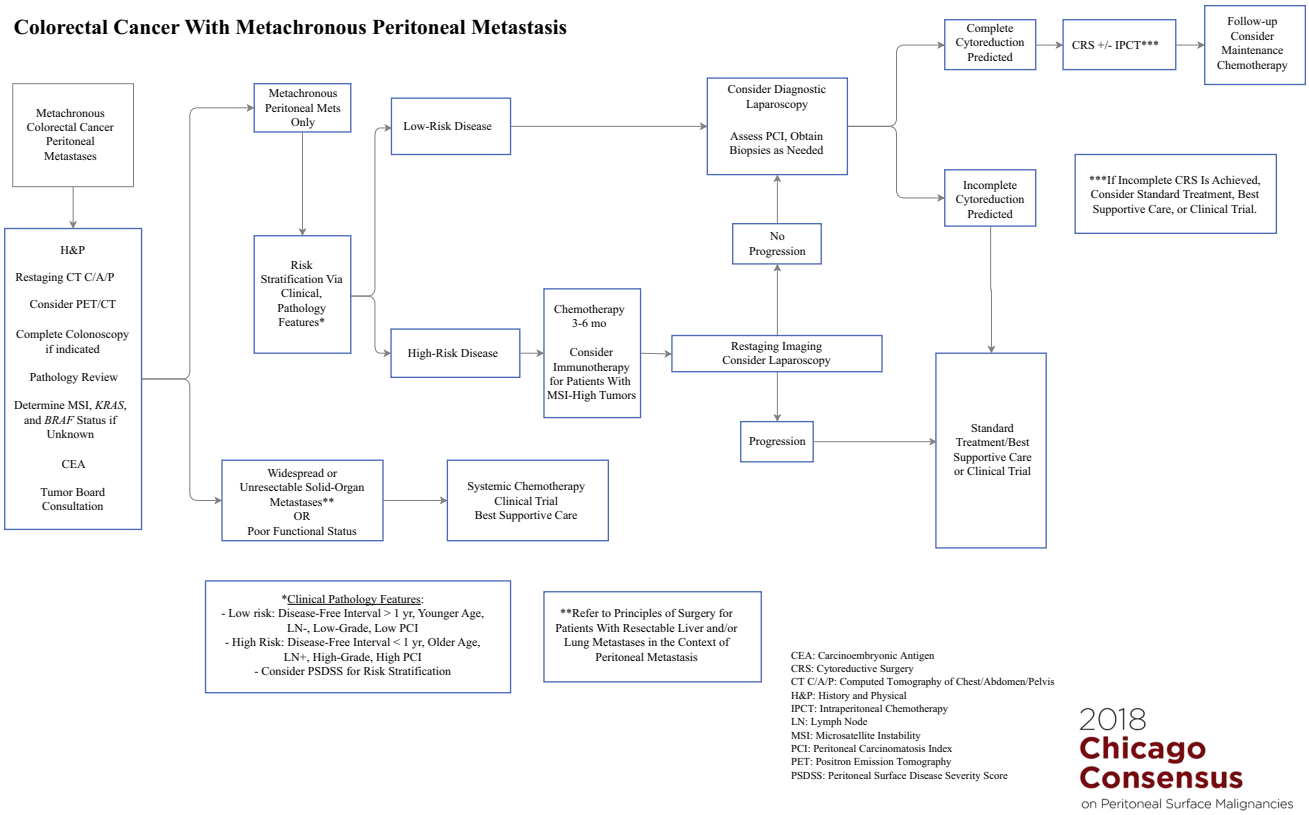

FIG. 1 Colorectal cancer with metachronous peritoneal metastasis management pathway

describe the radial and mesenteric margin status, T stage, and peritumoral deposits, which are risk factors for metachronous peritoneal metastases. Lymphovascular invasion, grade, perineural invasion, and signet ring cell histology portend an unfavorable prognosis.[16,17] It is also important to obtain the *KRAS*, *NRAS*, *BRAF*, and microsatellite instability (MSI) status of these tumors. Pathological evaluation of metastasectomy for colorectal cancer requires description of the treatment effect and completion of resection.

Principles of Systemic Chemotherapy

Limited evidence regarding the role of systemic chemotherapy in patients with peritoneal-only metastases is available. This lack of evidence is due to systematic exclusion of patients with peritoneal-only disease from several randomized trials because of imaging difficulties. Subset analysis of several first- and second-line chemotherapy trials revealed that patients with peritoneal metastases have worse overall survival than those with other visceral metastases,[18] although it may be contended that the disease burden may not be the same in both groups.

Regardless of the level of evidence, systemic chemotherapy is standard in the management of peritoneal metastases, especially as palliative or conversion chemotherapy in patients with extra-abdominal tumors, unresectable tumors, or a high burden of disease. For patients with resectable colorectal peritoneal metastases, limited evidence regarding the benefit of preoperative or postoperative systemic chemotherapy exists, but chemotherapy is often employed with an intention to define disease biology and responsiveness to therapy and possibly to limit visceral resection.

Systemic chemotherapy regimens have been described elsewhere for patients with metastatic colorectal cancer. Generally, first- and second-line therapies have a 5-fluorouracil/leucovorin (5-FU/LV) backbone, with the addition of oxaliplatin (FOLFOX), irinotecan (FOLFIRI), or both (FOLFOXIRI). Anti–epidermal growth factor receptor (EGFR) antibodies (cetuximab and panitumumab) are used to treat left-sided pan-*RAS* wild-type (*KRAS* and *NRAS*) as well as *BRAF* wild-type tumors, whereas anti–vascular endothelial growth factor antibodies like bevacizumab can be used in all patients. Robust patients can be treated with FOLFOXIRI and bevacizumab to maximize tumor response. FOLFOXIRI and anti-EGFR therapy combinations are under active investigation but should not be routinely used in clinical practice until more definitive trial

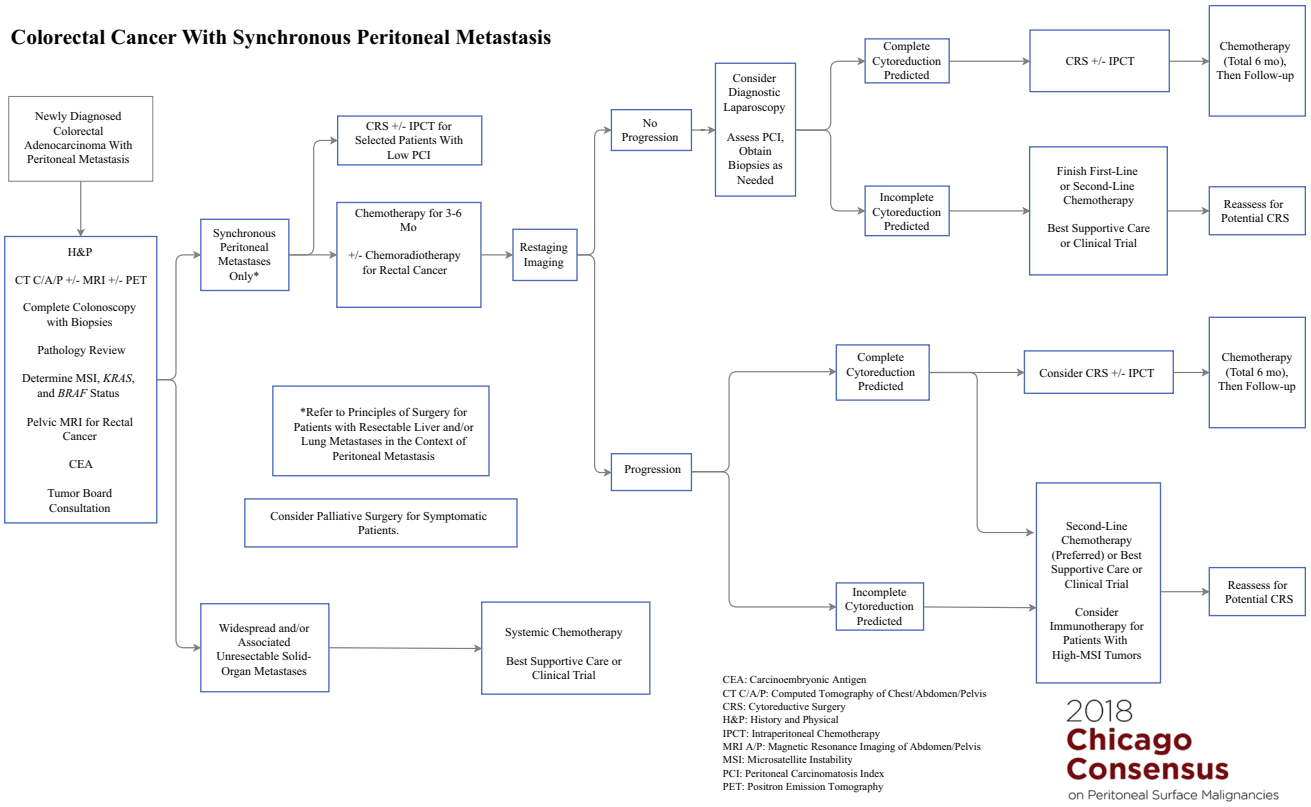

FIG. 2 Colorectal cancer with synchronous peritoneal metastasis management pathway

data are produced and the toxicity profiles are better defined.

Immunotherapy in MSI-high tumors in which first-line chemotherapy has failed is currently approved by the Food and Drug Administration, but the response of peritoneal-only disease to immunotherapy has not been well studied.

Principles of Surgery

Cytoreductive surgery (CRS) with a curative intent is best performed in patients with a low burden of metastases and favorable tumor biology. The presence of malignant ascites, large-burden tumors, or multifocal bowel obstructions usually precludes successful curative-intent surgery. Risk stratification can be performed by using clinical factors that have been combined in a predictive scoring system, the Peritoneal Surface Disease Severity Score (Table 1).[19]

Surgeons performing cytoreductive surgery must be expert in visceral resections and in standard peritonectomy techniques. The burden of disease must be clearly documented with a standard scoring system such as the peritoneal cancer index (PCI), and completion of cytoreduction should be documented with a CC or R score. The primary tumor should be resected along with the peritoneal disease if not previously done. The extent of nodal harvest and high ligation of vessels during the metastasectomy remain unsettled topics. The intent of a surgical cytoreduction is complete cytoreduction (CC0/CC1). Although resection of all gross peritoneal metastases (CC0) is optimal, a CC1 cytoreduction down to 2.5-mm or smaller residual peritoneal metastases has been shown to offer a survival benefit to patients as compared with no surgery and is acceptable when a CC0 cytoreduction is not technically or safely feasible.[20] Palliative debulking procedures (or incomplete cytoreductions/ablations) are discouraged for this population of patients.

The term *low metastatic burden* is currently undefined. To date, there is no standard upper PCI score cutoff to consider CRS. However, early work suggested using a PCI score cutoff of less than 20 to determine which patients may benefit from CRS.[21] This proposal was then refined to suggest that patients with a PCI score of less than 12 should be considered for resection and that patients with a PCI score of greater than 17 are unlikely to benefit from cytoreduction.[22] For patients with a high PCI score, the decision to proceed with cytoreduction should be taken in light of the patient's overall health, the tumor biology, and the ability to achieve a CC0 resection (Figs. 1 and 2).

Liver or lung oligometastases are a relative contraindication to cytoreduction. These metastatic lesions should be considered individually with the assistance of an

TABLE 1 Modified PSDSS for peritoneal carcinomatosis of colorectal and appendiceal origins (PSDSS I < 4; PSDSS II = 4–7; PSDSS III = 8–10; PSDSS IV > 10)

Clinical symptoms (both origins)	Extent of carcinomatosis (both origins)	Primary tumor pathology (colonic origin; appendiceal origin)
No symptoms (0 point)	PCI < 10 (1 point)	Well or moderately differentiated, N0; *Low-grade mucinous neoplasm* (1 point)
Mild (1 point)	PCI 10–20 (3 points)	Moderately differentiated, N1 or N2; *Mucinous adenocarcinoma* (3 points)
Severe (6 points)	PCI > 20 (7 points)	Poorly differentiated or signet ring; *High-grade mixed adenocarcinoma and goblet cell carcinoid* (9 points)

PCI Peritoneal Cancer Index, *PSDSS* Peritoneal Surface Disease Severity Score

experienced multidisciplinary tumor board. In evaluating peritoneal disease, diagnostic laparoscopy may be used to determine the extent of peritoneal disease and to determine candidates for a complete cytoreduction.

Principles of Intraperitoneal Chemotherapy

Intraperitoneal chemotherapy has been applied in several studies for patients with peritoneal-only metastases from colorectal cancer. A small randomized trial demonstrated a survival benefit for patients treated with intraperitoneal mitomycin (hyperthermic intraperitoneal chemotherapy [HIPEC]) compared with those receiving 5-FU/LV alone, despite an 8% mortality rate.[23] Long-term follow-up of this study showed a demonstrable survival benefit only in patients with completely resected disease.[20]

An inadequately powered single randomized study comparing cytoreductive surgery with CRS plus intraperitoneal chemotherapy (normothermic) failed to accrue and failed to reveal a survival difference in the patients studied.[24] Several large observational studies have demonstrated improved survival in patients undergoing HIPEC with oxaliplatin and mitomycin C compared with matched patients receiving modern systemic chemotherapy.[25]

Recent data from a French multi-institutional trial comparing CRS with CRS/HIPEC (oxaliplatin 300 mg/m^2 for 30 min) in patients with peritoneal metastases (PCI score < 25) from colorectal cancer failed to meet its primary study end point of overall survival. The median overall survival in the 2 arms was 41.7 and 41.2 months, respectively, which is substantially longer than previously reported in any trials of systemic therapy alone. However, there was no demonstrable survival benefit of HIPEC over CRS alone. Patients received 6 months of perioperative systemic therapy, and most underwent complete cytoreduction during surgery. The study had a 16% crossover rate. Although the results have not been published, this study is important to consider in the decision to use intraperitoneal chemotherapy.[26] In a subset analysis, patients with a PCI score of 11–15 had an improvement in overall survival with HIPEC (41.6 months vs 32.7 months for CRS alone). Inpatient morbidity was equivalent in both groups, although the 60-day serious morbidity rate was higher in the CRS/HIPEC arm than with CRS alone (24.1% vs 13.6%, respectively). The comparative effect of intraperitoneal chemotherapy with or without hyperthermia has not been studied in this population, although the benefit of adding normothermic intraperitoneal chemotherapy to HIPEC is likely limited.

Proponents of intraperitoneal chemotherapy claim that perfusion with oxaliplatin is not identical to perfusion with mitomycin C and that 30-min perfusion is too short to demonstrate any benefit. Oxaliplatin and mitomycin C have never been compared head to head in the same population, but retrospective studies have had different results, with 1 study demonstrating mitomycin C to be better and another small study showing no difference between the drugs.[27,28]

Opponents of intraperitoneal chemotherapy claim the lack of standardization, lack of understanding of the mechanism of intraperitoneal therapy, and the high morbidity of the therapy as some of the reasons for not supporting it.

Current regimens that are used for intraperitoneal chemotherapy include the following:

- Mitomycin 30 mg at time 0, followed by mitomycin 10 mg beginning at 60 min and continuing for 90 min
- Mitomycin 30 mg/m^2 for 90–110 min
- Oxaliplatin 300 mg/m^2 for 30 min for patients with PCI scores of 11–15

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