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In brief

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Peritoneal surface malignancies (PSMs) comprise a heterogeneous group of diseases that have traditionally carried a poor prognosis. Although peritoneal dissemination is considered to be a metastatic disease, current treatment paradigms have leveraged local/regional treatments, including tumor debulking and peritonectomy, intraperitoneal chemotherapy, heated intraperitoneal chemotherapy, and immunotherapy.

This monograph summarizes recent advances in the management of PSMs. It begins with a discussion of the impact of surgical approaches to PSMs on patient-reported outcomes (PROs). The ensuing sections delineate treatment approaches for specific histologies, including colorectal, appendiceal, ovarian, gastric, and small bowel cancers, as well as diffuse peritoneal

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mesothelioma. An excellent discussion on the treatment of PSMs in the pediatric population follows. This analysis is rounded out by the consideration of immunotherapeutic approaches to PSMs.

Understanding the impact of emerging treatments for PSMs on PROs is becoming increasingly important. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is associated with significant morbidity due to the magnitude of the procedure, patients' baseline comorbidities, the effects of intraperitoneal chemotherapy on the bowel, and the systemic hematologic effects that result in anemia, leukopenia, and infectious complications. PROs, defined as health assessments reported by the patient with no intervening interpretation by another observer or source, are increasingly utilized to evaluate surgical outcomes, especially in oncology patients. Health-related quality of life (HRQOL), when acquired with appropriate instruments and methods, can enhance clinical trials by providing more data to support (or challenge) the study's primary outcome. This further complements the primary outcome by adding unique patient perspectives that may change the study's interpretation, especially in noninferiority trials. Patient-reported HRQOL helps in evaluating surgical outcomes and provides prognostic information in cancer patients, especially in the CRS-HIPEC population. Patient-reported HRQOL is generally improved following CRS-HIPEC after a brief postoperative decline but remains a significant predictor of postoperative mortality and morbidity. There is considerable heterogeneity in surgical approaches, which partly accounts for different PROs in this population. Thus, it is becoming apparent that the standardization of intraoperative practices and perioperative care in CRS-HIPEC is urgently needed, along with the establishment of evidence-based perioperative management pathways in which outcomes are regularly evaluated through clinical and patient-reported assessment tools.

Currently, there are a number of debates on the role of HIPEC in the treatment of peritoneal surface dissemination from colorectal cancer. Modern chemotherapy with targeted therapies has increased the overall median for patients with PSM and CRC from approximately 6 (in the EVOCAPE study) to 20 months. Although this is a significant achievement, outcomes are inferior compared to other metastatic sites. There is high-quality evidence, mainly limited to single-center retrospective reviews, that CRS-HIPEC provides a significant survival advantage to patients with PSD from colorectal primaries, with a 5-year overall survival (OS) in the 25% to 40% range. CRS-HIPEC can provide substantial therapeutic effects, but it is also associated with significant attendant morbidity and mortality; thus, appropriate patient selection is crucial. CRS-HIPEC is only beneficial if a complete R0/R1/CCR-0 or near-complete R2a/CCR-1 cytoreduction can be achieved. A large multi-center retrospective review determined that the survival benefit from CRS-HIPEC performed for PSD due to colorectal cancer was only present when the peritoneal carcinomatosis index (PCI) score was less than 20. Despite data on the effectiveness of CRS-HIPEC, little work to date has provided a concise review of RCTs of CRS-HIPEC for patients with PSD from CRC. Here, we address this issue by reviewing past trials and the 5 recent randomized control trials of HIPEC in colorectal cancer. Although early trials by Verwaal and colleagues and Cashin and colleagues demonstrated a survival advantage, recent trials (including the PRODIGE 7, PROPHYLOCHIP, and COLOPEC trials) have failed to demonstrate a significant difference in OS. The analysis of the data from these trials demonstrates that complete or near-complete CRS unquestionably provides a survival benefit for patients with peritoneal metastases. Furthermore, CRS and HIPEC should be conducted in conjunction with systemic chemotherapy.

Appendiceal cancer is a rare malignancy and accounts for fewer than 1% of colorectal cancers. Peritoneal dissemination occurs as a result of appendiceal wall invasion, luminal obstruction, and subsequent perforation. The understanding of appendical histology is critical in the design of treatment schemes for these patients. Tumors of the appendix are divided into mucinous and neuroendocrine tumors (NETs). The Peritoneal Surface Oncology Group International published a consensus for the classification and pathologic reporting of appendiceal neoplasms that divided appendiceal mucinous malignancies into 5 groups: low-grade appendiceal neoplasm, high-grade appendiceal mucinous neoplasm, mucinous adenocarcinoma, mucinous adenocarcinoma with signet ring cells, and mucinous signet ring cell carcinoma. Accordingly, the clinical presentation of pseudomyxoma peritonei (PMP) is divided into the following groups: acellular mucin, low-

grade PMP or disseminated peritoneal adenomucinosis, high-grade PMP or peritoneal mucinous carcinomatosis, and signet ring PMP or peritoneal mucinous carcinomatosis signet ring cells. The evidence for the management of appendiceal cancers with peritoneal carcinomatosis mainly relies on retrospective data and extrapolation from randomized clinical trials on colorectal cancer. Experienced high-volume centers recommend CRS-HIPEC as the backbone of treatment for selected appendiceal cancers with peritoneal carcinomatosis as CRS-HIPEC, with few exceptions, does not confer a significant survival benefit for high-grade nonmucinous appendiceal cancers, including adenocarcinoma, NETs, and goblet cell carcinoma. Appropriate patient selection based upon patient performance, nutritional status, and tumor factors is crucial to improve outcomes and maximize the benefits of CRS-HIPEC. Randomized clinical trials are required to help standardize the treatment paradigm for appendiceal cancers.

Approximately 10% to 20% of mesotheliomas occur in the peritoneum, and CRS-HIPEC has been the primary intervention for achieving long-term remission and survival. Given that complete cytoreduction portends a superior prognosis after CRS-HIPEC, a PCI score of 15 to 20 has been the threshold for proceeding with CRS-HIPEC in mesothelioma. Still, the procedure can be performed for higher scores if the disease can be completely resected. Other factors can influence this decision, too, such as symptomatic disease and response to neoadjuvant therapy. Patient age and sex have been shown to have prognostic value in patients undergoing CRS-HIPEC for diffuse peritoneal mesothelioma. Patients 60 years or older at diagnosis experience shorter survival, while female patients have been found to have favorable survival after CRS-HIPEC. Novel approaches offer promise, including the repeated application of intraperitoneal therapy in patients with high-volume disease. Increased understanding of the molecular and immunologic pathways is critical in expanding and developing new therapies for diffuse peritoneal mesothelioma. Recent advances in molecular and genetic testing to identify mutations in BAP-1, EGFR, NF2, and CDKN2 genes may be integral to mesothelioma survival and may predict tumor behavior.

Ovarian cancer is the leading cause of gynecologic cancer deaths worldwide and the fifth leading cause of cancer deaths for women in the United States. Given that epithelial histology accounts for 90% of ovarian cancers, the discussion of HIPEC is most relevant in this group of patients. Although the management of advanced epithelial ovarian cancer is centered around CRS and platinum-based chemotherapy, the recurrence rate remains high, and these patients have limited therapeutic options. As such, interest has grown regarding the applicability of HIPEC in this setting, and 2 randomized controlled trials of HIPEC in primary epithelial ovarian cancer were presented at the 2017 American Society of Clinical Oncology meeting. Interestingly, these trials came to opposite conclusions. Interestingly, a meta-analysis of 11 trials found that HIPEC improved OS in patients with primary, advanced, and recurrent ovarian cancers.

Gastric cancer is the fifth most common cancer worldwide, and 14% of patients diagnosed with gastric cancer in the United States present with peritoneal carcinomatosis. Despite the advances in systemic therapies for gastric cancer, patients with peritoneal dissemination from gastric primaries face dismal outcomes. Early studies, although small, demonstrated feasibility and promise for this technique in patients with few other options. Although current guidelines in the West do not recognize CRS-HIPEC as a recommended therapy for patients with advanced gastric cancer, small early studies have demonstrated feasibility for CRS-HIPEC in this population of patients. Furthermore, multiple single-institution studies and international registries have provided a framework for common treatment considerations that suggest which patients may benefit from aggressive cytoreduction and intraperitoneal chemotherapy; these considerations include the PCI, the completeness of cytoreduction, and the choice of the intraperitoneal chemotherapy agent. Despite the lessons learned about patient selection, the role of CRS-HIPEC in gastric cancer remains controversial. Interestingly, HIPEC may offer a modest survival benefit in patients with a low burden of disease; more substantial, well-conducted trials with standardized patient selection criteria and treatment approaches are needed. As novel systemic therapies emerge, the role of CRS-HIPEC must continue to be studied and challenged.

In the United States, small bowel malignancies accounted for approximately 0.6% of all estimated new cancer cases and approximately 0.3% of cancer-related mortality in 2019. Although

there are several pathological types of primary small bowel tumors (SBTs), small bowel adenocarcinoma (SBA), neuroendocrine tumors (NETs), lymphoma, and sarcoma are the most commonly encountered, with SBA and NET each accounting for approximately 40% of cases. Unfortunately, the peritoneum remains one of the most common SBT metastases sites, as approximately 5,000 patients are diagnosed with SBA annually in the United States. Conventionally, patients with metastatic disease have been treated with systemic chemotherapy. Its benefits are limited since the peritoneum acts as a barrier, preventing effective drug penetration. Therefore, interest has increased in the surgical treatment of select patients with CRS-HIPEC. Some studies have demonstrated improvement in survival and other benefits in select patients, including those with SBA and NETs.

There has been significant progress in the characterization, staging, and treatment of adult patients with common PSM tumors, including those of colorectal, appendiceal, ovarian, gastric, and mesothelial origin. Similar progress in the characterization and treatment of children with PSM has been limited by the low incidence of pediatric PSM, which is estimated to be in the range of 50 to 250 cases per year in the United States. However, as viable treatment options that prolong survival have emerged, greater focus has been placed on optimizing care for children with this rare condition. Several factors have compounded to create unique challenges for treating children with PSM, including the rarity of these tumors. Here, we review the results with desmoplastic small round cell tumors, sarcoma, pediatric ovarian malignancies, colon malignancies, and mesothelioma. Progress in the treatment of these diseases has only developed recently as care of these patients has been concentrated in a few centers where principles of PSM therapy have been adapted from adult experience and refined for the care of children. The safety and feasibility of establishing new centers with proper mentorship have been demonstrated, and this contributes to the body of literature regarding the management of PSM in the pediatric population.

Because only a minority of patients with PSM are eligible for CRS-HIPEC, novel approaches to PSM are warranted, and the recent explosion of immunotherapies for cancer provides an appropriate platform for investigation. This volume includes current work on the intraperitoneal oncolytic virus and adoptive cell transfer approaches to PSM. It was observed at the turn of the 20th century that patients with cancer went into brief periods of clinical remission upon contracting an infectious disease. Subsequent interest in viral therapy for cancer reached a fever pitch in the 1950s and 1960s, followed by near-abandonment in the 1970s and 1980s. Its resurgence over the past 4 decades has culminated in the current era of oncolytic virus investigation. Oncolytic viral agents are particularly attractive for the treatment for PSM given that iterative viral replication within permissive tumor tissue results in lytic cell destruction and local release of progeny virus, as well as of tumor cell antigens. We review current trials of intraperitoneal oncolytic viral agents and include reovirus as well as measles, vaccinia, and herpes viruses. Adaptive cell therapy has received significant recent attention, and chimeric antigen receptor T (CAR T) cells have come to the forefront as an adaptive approach to antitumor immunity. The identification of specific tumor-associated antigens, including CA-125 (MUC16), carcinogenic antigen, FRα, and mesothelin, has led to the development of the CAR T trials for a variety of PSM. Emerging targets for ongoing research on immunotherapy for PSM include modulation of the peritoneal tumor microenvironment and the development of novel cellular approaches, including CAR-NK cells.