Hyperthermic Intraperitoneal Chemotherapy and Cytoreductive Surgery in the Management of Peritoneal Carcinomatosis

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Background: Malignant peritoneal disease can lead to significant debility due to bowel obstructions, ascites, and cancer cachexia. Moreover, inadequate imaging techniques can lead to the suboptimal detection of disease, and the poor vascularity of tumors can lead to a poor response to systemic chemotherapy. However, combination cytoreductive surgery/hyperthermic intraperitoneal chemotherapy (HIPEC) is a promising novel treatment for patients with this disease.

Methods: The medical literature focusing on diagnostic updates and the management of peritoneal disease was reviewed. The application principles of HIPEC for use in peritoneal disease were also summarized.

Results: Improvements in imaging and the application of laparoscopic techniques have significantly increased the rate of diagnosis of early peritoneal disease with consequently less morbid cytoreductive procedures. Appropriate patient selection based on prognostic scores along with complete cytoreduction can identify a cohort of patients likely to derive durable benefit from this combination treatment.

Conclusions: Advances in diagnostic and therapeutic techniques, including surgical cytoreductive techniques, have demonstrated significant survival gains in patients with peritoneal disease. Although HIPEC can be used for the management of various types of histologies, further development of high-level evidence is necessary to advance the field.

Introduction
Peritoneal metastases represent an advanced stage of abdominal cancers and often present with disseminated disease. The incidence of peritoneal metastases varies from 60% in ovarian cancers to 20% in gastric cancer and 8% to 17% colorectal cancer.1,2 An estimated 134,490 cases of colorectal cancer, 26,370 cases of gastric cancer, and 22,280 cases of ovarian cancer are expected to be diagnosed in 2016 in the United States alone, with estimated deaths from these cancers to reach 74,160.3

Many mechanisms of peritoneal spread have been proposed.4-7 Invasion of the luminal wall by invasive cancer or a perforation of the wall by a noninvasive tumor may lead to a direct spread to the peritoneum.4 Adherence molecules on free cancer cells may aid in peritoneal implantation.5 Iatrogenic spread during surgery, when tumor emboli are released from blood vessels and the lymphatics, is also a possible cause. When untreated, peritoneal carcinomatosis rapidly progresses to malignant ascites, acute bowel obstruction, and perforation requiring aggressive palliative chemother-
apy or surgery. Although patients with extraperitoneal metastases undergoing interventions of curative intent now have acceptable survival rates, peritoneal surface disease was historically considered an incurable entity and palliative therapy resulted in a median survival rate of a few months to less than 1 year.6,7

The magnitude of the burden of peritoneal metastasis is often underappreciated due to the low sensitivity rate of common imaging techniques for peritoneal disease.8 The rate of sensitivity of computed tomography in identifying peritoneal disease depends on the location in the abdomen, the size of individual nodules, and the morphology of the disease. The rate of sensitivity of computed tomography is 11% for visualizing peritoneal nodules less than 0.5 cm in size in the setting of colorectal disease, a rate that is unacceptable in clinical practice.9 However, use of advanced imaging for the detection of peritoneal carcinomatosis outside referral centers is infrequent, and many cases may go unreported.9 Consequently, peritoneal metastases are rarely included in clinical trials of systemic chemotherapy because the disease and its progression are often not detected by imaging standards set in the trials.2

Conventional antineoplastic strategies for visceral metastasis are not effective for peritoneal cancer. Although systemic chemotherapy has become more successful for use in visceral metastases, a secondary analysis of 2 phase 3 trials on systemic chemotherapy in metastatic colorectal cancer demonstrated that peritoneal metastases incur a 30% reduction in rate of overall survival (OS) than nonperitoneal metastases, even after adjusting for other prognostic factors (Fig 1).2 This lower rate of survival in peritoneal carcinomatosis suggests an inherent unfavorable biology.2

Cytoreductive surgeries in solid organ metastases have been useful as a curative therapy, whereas its use has been evolving over time for peritoneal disease. For patients with isolated metastasis to the peritoneum, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) yields improved rates of survival and quality of life.10,11 This multidisciplinary therapy is based on the concept of the peritoneum as an organ and hypothesizes that improved prognosis is achieved with complete removal of disease from the peritoneum.

Techniques of Peritonectomy
The oncological principles of peritonectomy surgeries were first described by Sugarbaker.12 The outcome of cytoreductive surgery is reliant on the extent of the removal of tumor deposits from visceral and parietal peritoneal surfaces, and surgical techniques vary depending on the site and volume of disease. Peritoneal staging is performed using well-established scoring systems (Peritoneal Cancer Index [PCI], Simplified PCI) that utilize tumor size and region of distribution to quantify disease burden. Techniques of peritonectomy require complete knowledge of embryology and anatomy to ensure successful extirpation of tumor.

Greater Omentectomy
The greater omentum is elevated off the transverse mesocolon by stripping the entire surface of the mesocolon. The dissection includes separation of the specimen from the gastroepiploic vessels (potential ligation) and division of the short gastric vessels. The omentum is elevated off the splenic hilum (splenectomy if necessary) and the anterior surface of the pancreas. Meticulous dissection of the omentum is essential for complete tumor removal.

Epigastric Peritonectomy
The falciform ligament is separated from the umbilicus along with the anterior peritoneum and resected flush with the liver surface to include the ligamentum teres hepatitis. The bridge of liver is often divided to access the left portal vein.

Right Hemidiaphragmatic Peritonectomy
Diaphragmatic muscle is stripped along its entirety after making a cruciate incision in the anterior peritoneum. The peritonectomy includes stripping the Gerota fascia, the right adrenal gland, and the Glisson capsule of the liver. Complete mobilization of the liver is essential and the retrohepatic inferior vena cava (IVC) is used as the medial border of the dissection.

Left Hemidiaphragmatic Peritonectomy
The upper left portion of the cruciate incision is used to initiate the left hemidiaphragmatic peritonectomy. Complete stripping of the diaphragmatic fibers with skeletonization (or ligation) of the phrenic vessels is...
undertaken. Dissection includes stripping the adrenal gland and Gerota fascia.

**Lesser Omentum Peritonectomy**
The hepatoduodenal ligament and the pars flaccida are dissected from the caudate lobe of the liver and the porta hepatitis. Careful dissection of the celiac axis branches and the right gastric arteries can elevate the tumor off of the lesser omentum. The IVC bursa is occasionally stripped, using the IVC, caudate lobe of the liver, and the left limb of the right crus as anatomical landmarks.

**Pelvic Peritonectomy**
Pelvic peritonectomy includes resection of the anterior peritoneum with the urachus and the medial umbilical ligaments. Skeletonization of the ureters, gonadal vessels, and resection of the upper rectum are often necessary to complete the peritonectomy. Visceral resections of the uterus and ovaries are performed as necessary.

**Anterior Peritonectomy**
Scar excision and resection of the anterior peritoneum is carefully undertaken with preservation of the rectus fascia at the initiation of the procedure. This becomes contiguous with the right hemidiaphragmatic peritonectomy performed in the right upper quadrant, the epigastric peritonectomy superiorly performed, the left hemidiaphragmatic peritonectomy performed in the left upper quadrant, the paracolic gutter peritonectomy laterally performed, and the pelvic peritonectomy inferiorly performed.

The completeness of cytoreduction is graded as CC-0 (no visible disease), CC-1 (< 2.5 mm residual disease), CC-2 (2.5–25 mm), and CC-3 (> 25 mm residual disease), or using the R score (R0 = complete resection, R1 = no gross disease with microscopic positive margins, R2 = macroscopic residual disease [R2a = < 5 mm, R2b = 6–20 mm, R2c = > 20 mm]).

**Hyperthermic Intraperitoneal Chemotherapy**
Early attempts at treatment for peritoneal carcinomatosis with surgery alone produced rapid rates of progression and treatment failure. The tumor cell entrapment theory proposed that intraperitoneal tumor emboli generated during surgery seeded on the peritoneal surface and aided by the growth factors associated with wound healing and peritoneal vasculature, forming metastases. Chemotherapy intraperitoneally delivered at the time of surgery can theoretically kill the tumor emboli, thus avoiding tumor progression. Chemoperfusion has continued to progress since the HIPEC delivery system was first trialed. The benefits of the intraperitoneal delivery of antineoplastic drugs are manifold; hyperthermia aids in increased cellular penetration of the drug while synergistically enhancing cytotoxicity. Moreover, vascular stasis of microcirculation occurs in neoplastic cells at temperatures produced by HIPEC, while normal cells experience increased flow. This, combined with the selective accumulation of lactic acid and the resulting lowered level of pH in neoplastic tissue, results in cell death. Drug concentrations achieved through this route cannot be replicated by intravenous chemotherapy and, to some extent, systemic toxicities are avoided.

Verwaal et al compared cytoreductive surgery/HIPEC followed by systemic chemotherapy vs systemic chemotherapy with or without palliative surgery in patients with colorectal cancer and peritoneal carcinomatosis (CRC-PC) and found that those in the HIPEC group had better survival rates than their counterparts. After 8 years of follow-up, the 5-year survival rate was 45% and significant differences in progression-free survival and disease-free survival rates between the HIPEC and control arms were also noted. A phase 3 randomized trial comparing cytoreductive surgery/HIPEC with cytoreductive surgery alone for the management of gastric cancer reported improved rates of survival and acceptable rates of morbidity with cytoreduction/HIPEC. Another trial compared cytoreductive surgery/HIPEC plus systemic chemotherapy with systemic chemotherapy alone and demonstrated that the combined modality achieved modest rates of prolonged survival in carefully selected patients with gastric cancer. The evidence continues to accumulate, with numerous observational and retrospective studies supporting the superiority of multimodality treatment with cytoreductive surgery/HIPEC in the setting of peritoneal carcinomatosis (Fig 2). Although this combination treatment began as experimental therapy, cytoreductive surgery/HIPEC is now the standard of care in peritoneal carcinomatosis, which is now being viewed as a treatable entity rather than a terminal condition. Appendiceal mucinous neoplasms, colorectal adenocarcinoma, mesothelioma, and epithelial ovarian carcinoma are histologies that most benefit from intraperitoneal chemotherapy. For patients with high-grade disease or poor prognostic factors, multidisciplinary treatment using systemic chemotherapy is often employed (Table 1). Select ongoing and recently completed trials involving cytoreductive surgery and HIPEC are described in Table 2.

**Patient Selection Prognostication Scores**
Selecting patients for a potentially morbid surgery requires careful discussion on the possible benefits of the procedure. Tumor burden determines the completion of surgery as well as the long-term outcomes. Intraoperative staging systems, such as the PCI (13 regions, with scores ranging from 0 to 3) or
Fig 2. — Selected evidence supporting use of cytoreductive surgery and HIPEC for the management of peritoneal carcinomatosis. CRS = cytoreductive surgery, DPAM = diffuse peritoneal adenomucinosis, EPIC = early postoperative intraperitoneal chemotherapy, HIPEC = hyperthermic intraperitoneal chemotherapy, OS = overall survival, PC = peritoneal carcinomatosis, PCI = Peritoneal Cancer Index, PMCA = peritoneal mucinous carcinoma, PMP = Pseudomyxoma peritonei infection, RCT = randomized controlled trial.

Information from references 18, 19, and 21 to 37.

Table 1. — Therapeutic Strategies in Peritoneal Surface Malignancies

<table>
<thead>
<tr>
<th>Histological Type</th>
<th>Effectiveness of Systemic Chemotherapy</th>
<th>Preferred Intraperitoneal Therapy</th>
</tr>
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<tbody>
<tr>
<td>Appendiceal carcinoma</td>
<td></td>
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<tr>
<td>Low-grade appendiceal neoplasm with high risk of recurrence</td>
<td>–</td>
<td>HIPEC (mitomycin)</td>
</tr>
<tr>
<td>Well-differentiated appendiceal neoplasm</td>
<td>±</td>
<td>HIPEC (mitomycin)</td>
</tr>
<tr>
<td>Moderately differentiated appendiceal neoplasm</td>
<td>±</td>
<td>HIPEC (mitomycin)</td>
</tr>
<tr>
<td>High-grade appendiceal neoplasm</td>
<td>++</td>
<td>HIPEC (mitomycin)</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td>++</td>
<td>HIPEC (cisplatin/mitomycin) ± IP docetaxel/paclitaxel IP docetaxel/paclitaxel ± HIPEC (cisplatin/mitomycin)</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>++</td>
<td>HIPEC (mitomycin/oxaliplatin/irinotecan)</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>+++</td>
<td>Intrapерitoneal chemotherapy (cisplatin/paclitaxel) in optimally debulked patients</td>
</tr>
<tr>
<td>Peritoneal mesothelioma</td>
<td>+</td>
<td>HIPEC (cisplatin/doxorubicin/mitomycin)</td>
</tr>
</tbody>
</table>

Effectiveness of systemic chemotherapy is represented in an ordinal scale (–, ±, +, ++, +++), with – being least effective and +++ being maximally effective. HIPEC = hyperthermic intraperitoneal chemotherapy, IP = intraperitoneal.
Simplified PCI system (7 regions with 3 score groups), can be used to detect disease burden. Scoring systems, such as the Peritoneal Surface Disease Severity Score (PSDSS), are a noninvasive method of assigning disease burden in colon cancer. PSDSS designates weighted scores for severity of disease, extent of carcinomatosis, and aggressiveness of histology, summating the scores to stratify the disease into 4 prognostic categories. For example, moderately differentiated disease (3 points) with a PCI score of 12 (3 points) and mild symptoms (1 point) would be PSDSS stage 2 (4–7 cumulative points), whereas well-differentiated disease (1 point) with extensive intra-abdominal spread and a PCI score of 20 (7 points) and severe symptoms (6 points) would be PSDSS stage 4 (> 10 cumulative points).

PCI scores higher than 19 confer a poor prognosis despite cytoreductive surgery/HIPEC and are often a relative contraindication for peritoneal metastasis from CRC-PC. Use of the PSDSS system as a prognostic indicator for selecting patients has been validated in multiple studies.

### Diagnostic Laparoscopy

Diagnostic laparoscopy, also called staging laparoscopy, is being increasingly used in the preoperative staging of peritoneal disease to identify patients with high peritoneal burden whose disease is considered inoperable in order to avoid unnecessary intervention. The procedure is technically feasible and associated with minimal operative morbidity and mortality. Patients excluded from cytoreductive surgery/HIPEC by diagnostic laparoscopy are often candidates for conversion chemotherapy (using systemic chemotherapy to shrink tumors and convert unresectable disease to resectable) and repeat diagnostic laparoscopy. Although port-site metastases are of concern, Valle et al detected no seeding at the entry sites in their series of 351 diagnostic laparoscopy procedures. We advocate wider use of diagnostic laparoscopy, especially in tumors at risk for peritoneal spread.

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**Table 2. — Selected Ongoing and Recently Completed Trials on HIPEC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
</tr>
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<tbody>
<tr>
<td><strong>Colorectal Carcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02231086</td>
<td>Patients who underwent intentionally curative resection for a T4N0–2M0 or intra-abdominally perforated colon cancer</td>
<td>Control: adjuvant systemic chemotherapy</td>
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<tr>
<td></td>
<td></td>
<td>Experimental: adjuvant HIPEC followed by adjuvant systemic chemotherapy</td>
</tr>
<tr>
<td>NCT01226394</td>
<td>Patients with a high risk of developing CRC-PC after resection of primary and 6 mo of adjuvant chemotherapy</td>
<td>Control: surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental: laparotomy + HIPEC</td>
</tr>
<tr>
<td><strong>Appendiceal Carcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01580410</td>
<td>Patients with peritoneal surface malignancies from primary appendiceal tumors</td>
<td>Experimental arm 1: cytoreductive surgery + HIPEC (mitomycin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental arm 2: cytoreductive surgery + HIPEC (oxaliplatin)</td>
</tr>
<tr>
<td>NCT01815359</td>
<td>Patients with appendiceal or colorectal cancer with isolated peritoneal metastasis</td>
<td>Treatment arm 1: cytoreductive surgery + HIPEC (mitomycin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment arm 2: cytoreductive surgery + early postoperative intraperitoneal chemotherapy (leucovorin/floxuridine)</td>
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<tr>
<td><strong>Ovarian Carcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01539785</td>
<td>Patients with platinum-sensitive first recurrence of ovarian cancer</td>
<td>Control: cytoreductive surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental: cytoreductive surgery + HIPEC</td>
</tr>
<tr>
<td>NCT02124421</td>
<td>Newly diagnosed, otherwise untreated, advanced-stage (stage 3/4) epithelial ovarian, fallopian tube, and primary peritoneal cancers</td>
<td>Treatment arm 1: cytoreductive surgery with HIPEC (carboplatin) followed by IV combination chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment arm 2: cytoreductive surgery followed by adjuvant IV/ IP chemotherapy</td>
</tr>
<tr>
<td><strong>Gastric Carcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01882933</td>
<td>Patients with locally advanced gastric carcinoma</td>
<td>Control arm: curative gastrectomy with D1 to D2 lymph-node dissection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental: curative gastrectomy with D1 to D2 lymph-node dissection + HIPEC (oxaliplatin)</td>
</tr>
<tr>
<td>NCT02158988</td>
<td>Patients with peritoneally metastasized gastric cancer</td>
<td>Control: preoperative chemotherapy + cytoreductive surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental: preoperative chemotherapy + cytoreductive surgery + HIPEC</td>
</tr>
</tbody>
</table>

CRC-PC = colorectal cancer/peritoneal carcinomatosis, HIPEC = hyperthermic intraperitoneal chemotherapy, IP = intraperitoneal, IV = intravenous.
Diffusion-Weighted Magnetic Resonance Imaging

Conventional imaging with computed tomography or magnetic resonance imaging has poor rates of per-lesion sensitivity in the setting of peritoneal carcinomatosis, which varies with site and size of the tumor deposits, which can result in falsely low PCI scores. In addition, patients with low-volume disease may not be detected, and the therapeutic window before they progress into high-volume disease may be lost.

Diffusion-weighted imaging better captures the contrast between normal and tumor tissue compared with conventional cross-sectional imaging modalities. Diffusion-weighted imaging translates the restrictive effect of tissue structure on the mobility of water molecules into visible signal intensity or contrast (Fig 3A–C). Integrating diffusion-weighted imaging with conventional imaging has been shown to increase the rate of accuracy in the staging of ovarian cancer and in patients with peritoneal disease; however, the value of this modality must be balanced with the time, resource utilization, and patient discomfort associated with it.

Anesthesia and Critical Care

Use of hyperthermia puts unique demands on patient physiology, and patients undergoing HIPEC are at increased risk for cardiac complications, particularly those with existing cardiovascular disease or associated risk factors. In addition, chemoperfusion creates changes in intra-abdominal pressure that may increase systemic vascular resistance and affect cardiac output. Chemotherapeutic drugs intraperitoneally administered possess their own toxicities (eg, nephrotoxicity with cisplatin) that may be accentuated by altered fluid dynamics. Fluid loss is also high during peritoneectomy procedures due to loss from denuded areas.

Modern anesthetic techniques and stringent patient selection has made cytoreductive surgery/HIPEC feasible for patients at both extremes of age. Advances in invasive and noninvasive fluid status monitoring and management, along with analgesic control with regional anesthesia, have contributed to reduced stays in the intensive care unit and improved perioperative outcomes.

Combined Resections

Concurrent extraperitoneal metastases have long been considered a contraindication for resection, although some studies indicate the feasibility and better outcomes for the combined resection of hepatic and peritoneal metastases. Similar radical resections, including other viscera (bladder, colon, diaphragm, pancreas, small intestine, spleen, stomach), have been reported with acceptable rates of morbidity. Advances in electrosurgical techniques, including ablative technologies and hemostasis, have made such advances possible.

Laparoscopy

Minimal-access cytoreductive surgery/HIPEC has been studied in patients with low tumor burden and with disease of less malignant potential. Diagnostic laparoscopy is performed prior to surgery and patients with a PCI score lower than 10 are enrolled into a laparoscopic strategy. With strict patient selection, laparoscopic cytoreductive surgery/HIPEC is a procedure associated with minimal morbidity and mortality and shorter operating times while achieving similar operative and oncological outcomes to the open procedure. Concerns regarding the ability to complete a thorough examination of the peritoneal cavity have precluded the widespread application of this technique until further evidence is gathered.

Perfusion Techniques

Drug delivery to the peritoneum is controlled by flow rate, temperature, dose, and duration of HIPEC. Experiments by Facy et al on animal models suggest that increasing the intraperitoneal pressure enhances the penetration of the chemotherapeutic drug into the peritoneum but not the depth of penetration. The effect is maximal when using an open technique at

Fig 3A–C. — (A) Low-attenuation material along the perihepatic, lesser sac, and perigastric regions suggestive of mucinous ascites seen in contrast-enhanced computed tomography, (B) axial, T2-weighted magnetic resonance imaging, and (C) diffusion-weighted imaging of the abdomen showing peritoneal metastases along the left lobe of the liver and anterior to the greater curvature of the stomach consistent with peritoneal implants.
25 cm H₂O more in the parietal peritoneum than visceral, and it is feasible and well tolerated. In animal and in vitro models, higher flow rates were seen to shorten the time to attain and maintain target temperatures during HIPEC, thus resulting in higher temperature gradients that may potentially enhance the rate of cytotoxicity. Ceelen et al reported that higher perfusion temperatures worsen the metabolic changes associated with oxaliplatin HIPEC but they do not affect surgical outcomes.

Despite the evolution of HIPEC as standard therapy in peritoneal carcinomatosis, standardized protocols are not yet followed in the United States. After a Dutch cancer institute implemented an HIPEC protocol in peritoneal surface malignancy centers in the Netherlands, outcomes were improved compared with the preimplementation phase. A standard protocol decreased the length of procedures, rate of blood loss, complications, and duration of hospital stay. It should be noted that, with experience, the corresponding improvement in patient selection led to fewer numbers of patients with extensive disease after the protocol was enforced. Attempts at standardizing the delivery of HIPEC in US centers specializing in peritoneal surface malignancy have resulted in a recommendation of a closed technique using a standardized dual dose of mitomycin in a 90-minute cycle in patients with CRC-PC.

**Medications**

Oxaliplatin and mitomycin are the components of common HIPEC regimens for CRC-PC and comparisons of their efficacy have yielded conflicting results. One multisite, retrospective review reported that treatment with oxaliplatin and mitomycin conferred better rates of OS than oxaliplatin alone in patients with CRC, favorable histologies, and low-tumor burden, but a separate comparison cohort trial found no difference in survival. Both of these studies were restricted to patients with complete cytoreduction. Glockzin et al compared bidirectional oxaliplatin- and irinotecan-based HIPEC and found no differences in rates of morbidity and toxicity but did suggest that oxaliplatin may have clinical superiority on the basis of a positive survival trend after 3 years of follow-up.

Studies on animal models of CRC have shown that combination irinotecan/oxaliplatin/mitomycin/panitumumab exceeds any survival benefit from any other agent, alone or in combination.

Applications of newer antineoplastic agents such as melphalan are being investigated for intraperitoneal therapy. Sardi et al reported on the successful intraperitoneal use of melphalan in patients with peritoneal carcinomatosis who failed conventional systemic chemotherapies and cytoreductive surgery/HIPEC. Their rates of OS were promising, particularly in the milieu of documented chemoresistance; however, significant postoperative myelosuppression was a noted concern. Although the peritoneal–plasma barrier prevents the systemic absorption of intraperitoneal chemotherapy, systemic accumulation does occur with peritoneal stripping in cytoreductive surgery and through other routes, such as in the hepatic metabolism of oxaliplatin and mitomycin. Rates of hematological toxicity following treatment with oxaliplatin, mitomycin, and HIPEC ranges from 27% to 40%, but grade 4 toxicity is minimal. Kemmel et al advocated the monitoring of plasma concentration with oxaliplatin and mitomycin treatment at 30 minutes after starting HIPEC to identify patients at high risk for developing neutropenia. However, neutropenia after HIPEC has not been shown to increase rates of mortality, postoperative infection, or length of hospital stay.

**Other Surgical Methods**

New methods of delivering intraperitoneal chemotherapy, such as early and sequential postoperative intraperitoneal chemotherapy, have been attempted. Sequential postoperative intraperitoneal chemotherapy was shown to be inferior in terms of survival outcomes while offering comparable morbidity and mortality rates in a case-control study of patients with CRC, whereas early postoperative intraperitoneal chemotherapy was shown to have a higher rate of complications when given alone or in combination with HIPEC. HIPEC is a reliable method for administering intraperitoneal chemotherapy with acceptable complications and survival outcomes.

**Role of Systemic Chemotherapy**

The effect of perioperative chemotherapy on outcomes after cytoreductive surgery/HIPEC has been retrospectively investigated at multiple centers. A prospective, observational study of neoadjuvant chemotherapy (folinic acid/fluorouracil/oxaliplatin or capecitabine/oxaliplatin with or without bevacizumab) in mucinous appendiceal neoplasms showed low tumor burden, fewer numbers of resections, and more completed surgeries with chemotherapy. Survival rates were similar to patients without systemic chemotherapy but were better in patients who had significant histological response. By contrast, Blackham et al reported no survival advantage in preoperative chemotherapy but reported an 8% response rate (radiological/clinical) compared with a 29% rate in the former study. Adjuvant chemotherapy was associated with better rates of progression-free survival but only in high-grade disease. A retrospective review of the effect of neoadjuvant chemotherapy on high-grade appendiceal adenocarcinoma found no statistically significant differences in operative details or survival outcomes between the chemotherapy and...
nonchemotherapy groups, whereas another retrospective review showed improved prognosis in mucinous tumors with signet ring cell histology.78,79

Although it is impossible to quantify the advantage of perioperative systemic chemotherapy without a randomized controlled trial, it may be safe to assume that this therapy provides benefit in carefully selected patients without adding to postoperative complications.

A retrospective review of perioperative systemic chemotherapy in study patients with lymph-node positive colorectal cancer showed improved rates of OS and progression-free survival in a chemotherapy cohort irrespective of the timing of chemotherapy; however, a large number of these study patients did not receive chemotherapy due to major postoperative complications.80 Therefore, these results should be interpreted with caution. The effect of adding bevacizumab to a neoadjuvant chemotherapy regimen in the setting of colorectal cancer was investigated in 2 retrospective reviews.81,82 Although Eveno et al81 reported that use of bevacizumab doubled the morbidity rates and need for additional surgery even after propensity score matching, Ceeelen et al82 demonstrated that bevacizumab therapy was associated with improved rates of OS and no added morbidity.

Although response to neoadjuvant chemotherapy is an indicator of favorable tumor biology, the converse is not always true. Treatment failure, as determined by imaging, surgical data, and tumor makers, should not dissuade the surgeon from proceeding with cytoreductive surgery as clinical response does not correlate with long-term prognosis in the setting of colorectal cancer; however, use of chemotherapy does.83

Preemptive Approaches
Repeat Combination Treatment for Peritoneal Recurrences
Recurrences are not uncommon after initial intervention in peritoneal cancers, so iterative rounds of HIPEC have been reported.84–89 Iterative cytoreductive surgery/HiPEC offers reasonable rates of survival when compared with conservative treatment using palliative chemotherapy, particularly in appendiceal neoplasms and malignant peritoneal mesotheliomas.84–86 However, effectiveness of a second round of HIPEC in the setting of CRC-PC is questionable. Careful patient selection using factors such as performance status, tumor volume, and symptom severity may improve outcomes.87 Some authors advocate using rates of progression-free survival to determine outcomes, but it is rational to select those patients for whom a second complete resection is feasible as survival after a second procedure is based on the completeness of the resection.85,87 Certain presentations, such as peritoneal mucinous carcinoma of the appendix with positive lymph nodes, incur poor survival rates even after additional procedures.88 Morbidity and mortality rates do not differ between initial and subsequent procedures; however, attempts to ensure complete cytoreduction using intensive surgery may result in undesirable complications.89 We recommend a second round of HIPEC in patients with recurrent disease for whom complete cytoreduction is feasible and histology is favorable.

Prophylactic Combination Treatment vs Routine Second-Look Surgery
Patients with known risk factors for peritoneal recurrence present a clinical quandary, as current diagnostic techniques for peritoneal carcinomatosis can be inaccurate. The choice between watchful waiting vs early intervention can be difficult to resolve on current evidence. Two approaches being tested are second-look surgery and prophylactic HIPEC, both of which involve selecting patients without detectable peritoneal metastases or those with low-volume peritoneal disease but who harbor risk factors.90,91 In the former, patients without clinically or radiologically detectable disease undergo a second-look surgery at the end of a fixed period of follow-up. HIPEC is systemically performed in all patients, with cytoreductive surgery performed in those with macroscopic peritoneal disease alone. In a prospective trial of 41 patients with CRC, more than one-half of study patients had detectable peritoneal disease and the reported 5-year OS rate was 90%.90 In a similar study looking at routine second-look surgery in patients with CRC-PC who underwent complete initial resection, rates of peritoneal recurrence and 2-year OS were 71% and 91%, respectively, after the second intervention was reported.91 The morbidity and mortality rates were 7% to 9.7% and 0% to 2.4%, respectively.91

Prophylactic HIPEC is offered to patients with advanced disease who are at high risk for peritoneal spread at the time of diagnosis. Risk is determined on the basis of histology and pathological stage. A prospective study of 25 patients with nonmetastatic CRC reported morbidity rates comparable to standard surgery.92 After 4 years of follow-up, the aggressive group exhibited significantly lower rates of peritoneal metastasis and higher rates of OS and disease-free survival.92 A similar study of gastric cancer in patients with either locally advanced disease or with positive peritoneal washings identified a potential role for prophylactic HIPEC.93 However, the sample sizes were small, so future research is warranted before definitive conclusions can be reached.93 Sloothaak et al94 reported the feasibility of delayed laparoscopic HIPEC in patients with CRC who had a high risk for peritoneal carcinomatosis.

Selection criteria vary across studies, so the advantage of one approach over another cannot be compared and quantified. In addition, adjuvant chemotherapy was administered in some of the studies,
confounding the interpretation of the results. Despite the successes of both techniques, the dilemma lies in identifying patients at high risk for peritoneal recurrence.

Future Directions
Improving methods for appropriate patient selection and advancing surgical techniques are disruptive changes that will alter the treatment landscape for peritoneal carcinoma. Use of telemedicine, robotic assistance, and immersive simulations for training and interventions are likely to optimize the field of surgery.

Dynamic techniques for accurate, intraoperative, pathological diagnoses can prevent unnecessary interventions. Robotic-assisted cytoreductive surgery for peritoneal disease has already been successfully used in metastatic ovarian cancers. In addition, with the advent of telesurgery, HIPEC can be introduced to areas that lack trained surgical oncologists.

Conclusions
Advances in diagnostic and therapeutic techniques, including surgical cytoreductive techniques, have demonstrated significant survival gains in patients with peritoneal disease. Such improvements must happen within the changing landscape of cancer care. In addition, advances in immunotherapy and personalized therapies hold significant promise, as do techniques in genetic sequencing that may predict and potentially prevent disease rather than treat it. Collaboration and partnerships with the community and our patients are critically important for significant strides to be made. Although hyperthermic intraperitoneal chemotherapy can be used for the management of various types of histologies, high-level evidence is still lacking for its use in patients with peritoneal carcinomatosis.

References


