Medical Policy
Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 048
BCBSA Reference Number: 2.03.07
NCD/LCD: NA

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Cytoreductive surgery and perioperative intraperitoneal chemotherapy may be considered MEDICALLY NECESSARY for the treatment of:
- Pseudomyxoma peritonei; and
- Diffuse malignant peritoneal mesothelioma.

Cytoreductive surgery and perioperative intraperitoneal chemotherapy is considered INVESTIGATIONAL for:
- Peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer;
- Ovarian cancer; and
- All other indications, including goblet cell tumors of the appendix.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>N/A</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>N/A</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>N/A</td>
</tr>
</tbody>
</table>
The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes
There are no specific CPT codes for this service.

ICD-10 Procedure Codes

<table>
<thead>
<tr>
<th>ICD-10-PCS procedure codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWY38ZZ</td>
<td>Hyperthermia of Abdomen</td>
</tr>
<tr>
<td>DWY68ZZ</td>
<td>Hyperthermia of Pelvic Region</td>
</tr>
</tbody>
</table>

Description

CRS and HIPEC
CRS comprises peritonectomy (ie, peritoneal stripping) procedures and multivisceral resections, depending on the extent of intraabdominal tumor dissemination.¹ The surgical procedure may be followed intraoperatively by the infusion of hyperthermic chemotherapy, most commonly mitomycin C. Inflow and outflow catheters are placed in the abdominal cavity, along with temperature probes to monitor temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours. This procedure is referred to as HIPEC.

Pseudomyxoma Peritonei
Pseudomyxoma peritonei is a clinicopathologic entity characterized by the production of mucinous ascites and mostly originates from epithelial neoplasms of the appendix. Appendix cancer is diagnosed in fewer than 1000 Americans each year; less than half are epithelial neoplasms.² As mucin-producing cells of the tumor proliferate, the narrow lumen of the appendix becomes obstructed and subsequently leads to appendiceal perforation. Neoplastic cells progressively colonize the peritoneal cavity and produce copious mucin, which collects in the peritoneal cavity. Pseudomyxoma peritonei ranges from benign (disseminated peritoneal adenomucinosis) to malignant (peritoneal mucinous carcinomatosis), with some intermediate pathologic grades. Clinically, this syndrome ranges from early pseudomyxoma peritonei, fortuitously discovered on imaging or during a laparotomy performed for another reason, to advanced cases with a distended abdomen, bowel obstruction, and starvation. The conventional treatment of pseudomyxoma peritonei is surgical debulking repeated as necessary to alleviate pressure effects. However, repeated debulking surgeries become ever more difficult due to progressively thickened intra-abdominal adhesions, and this treatment is palliative, leaving visible or occult disease in the peritoneal cavity.³ Five-year OS depends on tumor histology and ranges from 6% for high-grade (HG) tumors to 75% for low-grade (LG) tumors.⁴,⁵
Gastrointestinal Cancers (Colorectal, Gastric) and Peritoneal Carcinomatosis
Peritoneal dissemination develops in approximately 10% to 15% of patients with colon cancer and, despite the use of increasingly effective regimens of chemotherapy and biologic agents in the treatment of advanced disease, peritoneal metastases are associated with a median survival of 6 to 7 months. Peritoneal carcinomatosis is detected in more than 30% of patients with advanced gastric cancer and is a poor prognostic indicator. Median survival is 3 months, and 5-year survival is less than 1%. Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis. Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for cure.

Mesothelioma
Malignant mesothelioma is a relatively uncommon malignancy that may arise from the mesothelial cells lining the pleura, peritoneum, pericardium, and tunica vaginalis testis. In the United States, 200 to 400 new cases of diffuse malignant peritoneal mesothelioma (DMPM) are registered every year, accounting for 10% to 30% of all-type mesothelioma. DMPM has traditionally been considered as a rapidly lethal malignancy with limited and ineffective therapeutic options. The disease is usually diagnosed at an advanced stage and is characterized by multiple variably sized nodules throughout the abdominal cavity. As the disease progresses, the nodules become confluent to form plaques, masses, or uniformly cover peritoneal surfaces. In most patients, death eventually occurs as a result of locoregional progression within the abdominal cavity. In historical case series, treatment by palliative surgery, systemic/intraperitoneal chemotherapy, and abdominal irradiation resulted in a median survival of approximately 12 months.

Surgical cytoreduction (resection of visible disease) in conjunction with HIPEC is designed to remove visible tumor deposits and residual microscopic disease. By delivering chemotherapy intraperitoneally, drug exposure to the peritoneal surface is increased some 20-fold compared with systemic exposure. In addition, previous animal and in vitro studies have suggested that the cytotoxicity of mitomycin C is enhanced at temperatures greater than 39°C (102.2°F).

Ovarian Cancer
Several different types of malignancies can arise in the ovary; epithelial carcinoma is the most common type, accounting for 90% of malignant ovarian tumors. Epithelial ovarian cancer is the fifth most common cause of cancer death in women in the United States. New cases and deaths from ovarian cancer in 2014 are estimated at 21,980 and 14,270, respectively. Most ovarian cancer patients (>70%) present with widespread disease, and annual mortality is approximately 65% of the incidence rate.

Current management of advanced epithelial ovarian cancer is CRS followed by combination chemotherapy. Treatment guidelines recommend intraperitoneal chemotherapy for patients with optimally debulked (<1 cm) stage 2 disease (pelvic extension of tumor) or stage 3 disease (peritoneal extension of tumor). Estimated median OS is 66 months with and 37 to 49 months without intraperitoneal chemotherapy, respectively. However, tumor recurrences are common, and prognosis for recurrent disease is poor.

CRS/HIPEC in combination with systemic chemotherapy is being studied for primary and recurrent disease. Because HIPEC is administered at the time of surgery, treatment-related morbidity may be reduced compared with intraperitoneal chemotherapy administered postoperatively.

Summary
Pseudomyxoma peritonei describes extensive mucus accumulation within the peritoneum due to mucin-secreting tumor cells. Peritoneal carcinomatosis from nonovarian malignancies has long been regarded as a terminal disease with limited survival. Mesotheliomas arise from the mesothelium lining potential spaces of the body, such as the peritoneum. In an attempt to prolong survival in these diseases, aggressive locoregional therapy, such as combining cytoreductive surgery (CRS) with perioperative intraperitoneal chemotherapy, has been used.
Pseudomyxoma Peritonei
Several case studies and a systematic review on the use of CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) have been published. Although no randomized trials or comparative studies have been published, data have shown consistent, long-term disease-free survival (DFS) and overall survival (OS) with the use of this technique. Procedure-related morbidity and mortality have decreased over time. Because the prevalence of pseudomyxoma peritonei is very low, the conduct of high-quality trials is difficult. Therefore, based on the available evidence, CRS and HIPEC may be considered medically necessary for this indication.

Peritoneal Carcinomatosis of Gastrointestinal Origin (Colorectal, Gastric)
In patients with peritoneal carcinomatosis from colorectal cancer (CRC), numerous studies with different levels of evidence support the safety and feasibility of CRS and HIPEC, and existing data suggest a possible improvement in long-term survival of select patients. However, peritoneal carcinomatosis from CRC is not uncommon (occurring in 10%-15% of patients with CRC), and systemic chemotherapy treatments are available. Therefore, prospective randomized trials are needed to compare best available systemic therapy with and without CRS and HIPEC to determine optimal regimens and the exact effects of each step, which are currently unknown; an ongoing Phase 3 trial (PRODIGE-7) addresses the question of how much survival benefit is derived from cytoreduction and how much from HIPEC, as patients will be randomly assigned to HIPEC or no HIPEC after CRS. Additionally, quality-of-life data do not provide a clear picture of patient benefit. Therefore, CRS and HIPEC are considered investigational for this indication.

In patients with peritoneal carcinomatosis from gastric cancer, 2 small randomized controlled trials (RCTs) and 2 small retrospective comparative studies reported inconsistent results, due primarily to differing interventions in the comparator group. Given that patients eligible for CRS/HIPEC must be surgical candidates, the most appropriate comparator would be gastric resection with or without systemic chemotherapy administered to both treatment groups in a comparative study. The RCT that used this design reported reduced survival in the CRS/HIPEC group, although the trial was small (N=26) and statistical testing was not reported. Evidence is therefore insufficient to support the use of CRS/HIPEC in patients with peritoneal carcinomatosis due to gastric cancer.

Peritoneal Carcinomatosis of Endometrial Origin
Three small cohort studies in patients with peritoneal carcinomatosis due to endometrial cancer provide insufficient evidence to assess net health outcome with CRS/HIPEC in comparison with standard treatment (surgery, systemic chemotherapy, radiotherapy, and/or hormone therapy). CRS/HIPEC is therefore investigational for this indication.

Peritoneal Mesothelioma
The conventional treatment of peritoneal mesothelioma (diffuse malignant type) has resulted in a median survival of approximately 12 months. Although data on the use of CRS and HIPEC comprises nonrandomized case series without control groups, these have shown a significant prolongation of median survival ranging from 29.5 to 92 months. Procedure-related morbidity and mortality has remained relatively steady over time at approximately 35% and 5%, respectively. Because the prevalence of peritoneal mesothelioma is low, the conduct of high-quality trials is difficult. Therefore, based on the available evidence, CRS and HIPEC may be considered medically necessary for this indication.

Ovarian Cancer
Evidence for CRS/HIPEC in primary advanced and recurrent ovarian cancer is accumulating. Currently, results from 1 RCT with methodologic flaws, case control studies, and cohort studies are inconsistent; the RCT and case-control studies show improved survival with CRS/HIPEC in the second-line setting compared with CRS without HIPEC, but retrospective cohort studies do not indicate a clear survival advantage compared with current treatment in the first- or second-line setting. Results of at least some of these studies are confounded by prognostic factors (completeness of cytoreduction, extent of peritoneal carcinomatosis, chemosensitivity to platinum). Well-designed, randomized trials are needed to control for potential covariates and to demonstrate improvements in net health outcomes compared with current treatment approaches (CRS with systemic chemotherapy). Such trials are currently in progress.
Ongoing and Unpublished Trials.) CRS/HIPEC is therefore investigational for the treatment of ovarian cancer.

Miscellaneous Tumors
Evidence for CRS/HIPEC in patients with goblet cell carcinoid tumors of the appendix comprises a single retrospective cohort study that did not show increased survival compared with published survival estimates. CRS/HIPEC is therefore investigational for this indication.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2018</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>8/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>8/2016</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>5/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
</tr>
<tr>
<td>4/2014</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>1/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
</tbody>
</table>

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References
systematic review and meta-analysis of current evidence. Oncotarget. Apr 27 2017. PMID 28514739


8