Pseudomyxoma peritonei describes extensive mucus accumulation within the peritoneum resulting from 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 with perioperative intraperitoneal chemotherapy, has been used.

**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. As mucin-producing cells of the tumor proliferate, the narrow lumen of the appendix becomes obstructed and subsequently leads to appendiceal perforation. The neoplastic cells progressively colonize the peritoneal cavity and copious mucin production builds up in the peritoneal cavity. Appendix tumors causing pseudomyxoma peritonei range from a benign pathologic appearance (disseminated peritoneal adenomucinosis) to malignant pathologic findings (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. Five-year OS depends on tumor histology and ranges from 6% for high-grade tumors to 75% for low-grade tumors.

**Gastrointestinal Cancers (Colorectal and Gastric) and Peritoneal Carcinomatosis**

Peritoneal dissemination develops in approximately 10–15% 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.
Hyperthermic Intraperitoneal Chemotherapy

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 U.S., 200-400 new cases of diffuse malignant peritoneal mesothelioma (DMPM) are registered every year, accounting for 10-30% 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 results in a median survival of approximately 12 months.

Surgical cytoreduction in conjunction with hyperthermic intraperitoneal chemotherapy 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 to 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 degrees Celsius (102.2 degrees Fahrenheit).

Cytoreductive surgery (CRS) consists of peritonectomy procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination. 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 the 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 hyperthermic intraperitoneal chemotherapy (HIPEC). Other methods of intraperitoneal chemotherapy include early postoperative intraperitoneal chemotherapy (EPIC).

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.10 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).11 Estimated median OS is 66 months with and 37 to 49 months without intraperitoneal chemotherapy, respectively.12,13 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.

Regulatory Status

Mitomycin, carboplatin, and other drugs used for HIPEC have not been U.S. Food and Drug Administration (FDA)–approved for this indication. Cyclophosphamide and nitrogen mustard are
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FDA approved for intraperitoneal administration, but neither drug is used regularly for this purpose. Several peritoneal lavage systems (Product Code LGZ) have been FDA-cleared to provide “warmed, physiologically compatible sterile solution” (e.g., Performer® HT perfusion system; RanD S.R.L., Medolla, Italy). None has received marketing approval or clearance to administer chemotherapy. FDA has issued warning letters to manufacturers of devices that are FDA-cleared for peritoneal lavage using sterile saline solutions when these devices are marketed for off-label use in HIPEC (e.g., ThermaSolutions Inc., Minneapolis, MN; Belmont Instrument Corp., Billerica, MA).

Related policies:
Hyperthermia Therapy

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for hyperthermic intraperitoneal chemotherapy when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Intraperitoneal Hyperthermic Chemotherapy is covered

Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei may be considered medically necessary.

Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of diffuse malignant peritoneal mesothelioma may be considered medically necessary.

When Intraperitoneal Hyperthermic Chemotherapy is not covered

Cytoreductive surgery and perioperative intraperitoneal chemotherapy is considered investigational for:
- peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer;
- ovarian cancer, including fallopian tube and peritoneal cancer;
- all other indications, including goblet cell tumors of the appendix.
Policy Guidelines

Pseudomyxoma peritonei

Several case studies and a systematic review on the use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been published. Although no randomized trials or comparative studies have been published, the 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. This evidence is sufficient for rare diseases that have limited treatment options, such as pseudomyxoma peritoneal.

Peritoneal carcinomatosis of Gastrointestinal Origin

In patients with peritoneal carcinomatosis from colorectal cancer (CRC), numerous studies with different levels of evidence support the safety and feasibility of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, and existing data suggest a possible improvement in long-term survival of select patients. However, peritoneal carcinomatosis from CRC is not rare (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 cytoreductive surgery and hyperthermic intraperitoneal chemotherapy to determine optimal regimens and the exact effects of each step, which are currently unknown. An ongoing Phase III trial (PRODIGE-7) addresses the question of how much of the survival benefit is derived from the cytoreduction and how much from hyperthermic intraperitoneal chemotherapy, as patients will be randomly assigned to hyperthermic intraperitoneal chemotherapy or no hyperthermic intraperitoneal chemotherapy after complete cytoreductive surgery. Additionally, quality-of-life data do not provide a clear picture of patient benefit.

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 from Endometrial Cancer

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 the data on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy consists of non-randomized case series without control groups, these have shown a significant prolongation of 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
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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, chemo sensitivity 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 (see Ongoing and Unpublished Trials section). 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.

When the service requested does not meet the criteria and guidelines set forth in this policy, the service components related to Hyperthermic Intraperitoneal Chemotherapy are also considered investigational. These components would include the intraperitoneal chemotherapy, the externally generated hyperthermia (deep) and the placement and removal of catheters for the administration of the chemotherapy. Surgical procedures directly relating to the removal of the tumor will be reimbursed based on the member’s benefit language.

The National Comprehensive Cancer Network (NCCN) does not recommend the use of this technology in the treatment of colon cancer guidelines outside the clinical trial setting.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 77605, 96446*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**
Hyperthermic Intraperitoneal Chemotherapy


Medical Director – 12/2011


BCBSA Medical Policy Reference Manual [Electronic version]. 2.03.07, 10/10/2013


Policy Implementation/Update Information
Hyperthermic Intraperitoneal Chemotherapy


10/12/09 Specialty Matched Consultant Advisory Panel review 8/28/09. "Description" section revised. No change to policy statement. Updated rationale in "Policy Guidelines" section. References added. (btw)

6/22/10 Policy Number(s) removed (amw)


4/26/11 Specialty Matched Consultant Advisory Panel review March 30, 2011. “Description: revised. New indication for “When Covered” states the following: “Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei may be considered medically necessary.” The “When Not Covered” section was revised to indicate; “Cytoreduction and hyperthermic intraperitoneal chemotherapy is considered investigational for peritoneal carcinomatosis from colorectal cancer.” “Policy Guidelines” updated. References added. (btw)

5/24/11 Corrected policy to include information related to 1/4/11 code update. (btw)

1/24/12 “Description” section updated to include information related to Mesothelioma. The “When Covered” section updated to indicate; “Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei may be considered medically necessary. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of diffuse malignant peritoneal mesothelioma may be considered medically necessary.” The “When Not Covered” section updated to indicate; “Cytoreductive surgery and perioperative intraperitoneal chemotherapy is considered investigational for peritoneal carcinomatosis from colorectal cancer.” “Policy Guidelines” updated. Medical Director review 12/24/11 References added. (btw)

4/17/12 Specialty Matched Consultant Advisory Panel review 3/21/2012. No change to policy intent. (btw)

10/30/12 Removed deleted code, 96445, from Billing/Coding section. (btw)

10/27/12 Reference added. (btw)

4/16/13 Specialty Matched Consultant Advisory Panel review 3/20/2013. No change to policy statement. (btw)

11/26/13 Description and Policy Guidelines sections updated. No change to policy intent. Reference added. (btw)


4/28/15 “Description” section updated to include information related to ovarian cancer. The “When Not Covered “ section updated to indicate: “Cytoreductive surgery and perioperative intraperitoneal chemotherapy is considered investigational for gastric cancer or
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endometrial cancer; ovarian cancer, including fallopian tube and peritoneal cancer; and all other indications, including goblet cell tumors of the appendix.” Policy Guidelines updated. Medical director review 1/23/2015. References added. Specialty matched consultant advisory panel review 3/25/2015. Notification given 4/28/15 for effective date 6/30/15. (lpr)

7/1/15 Date of web update changed to 7/1/15 from 6/30/15. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.