Corporate Medical Policy

Hyperthermic Intraperitoneal Chemotherapy

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Origination: 5/19/2005
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Description of Procedure or Service

**Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy**

Cytoreductive surgery (CRS) comprises peritonectomy (ie, peritoneal stripping) 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 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).

**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.

**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).

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.

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 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” (eg, 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 (eg, 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.
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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

For individuals who have pseudomyxoma peritonei who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes cohort studies and a systematic review. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment-related mortality and treatment-related morbidity. Uncontrolled studies of primary treatment of pseudomyxoma peritonei with CRS and HIPEC have reported median and 5-year overall survival ranging from 47 to 156 months and 41% to 96%, respectively. One retrospective study of 26 patients who underwent CRS and HIPEC for recurrence indicated 5-year overall survival of 34%. Procedure-related morbidity and mortality have generally decreased over time. Controlled studies are needed to draw conclusions about the efficacy and safety of CRS and HIPEC compared with standard treatment (CRS alone). The evidence is insufficient to determine the effects of the technology on health outcomes.

Although no randomized trials or comparative studies have been published, uncontrolled studies data have shown consistent, long-term overall survival with use of this technique. Procedure-related morbidity and mortality have decreased over time. Because the prevalence of pseudomyxoma peritonei is very low, conducting high-quality trials is difficult. Therefore, based on the available evidence, CRS and HIPEC may be considered medically necessary for this indication.

For individuals who have peritoneal carcinomatosis of colorectal origin who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes 1 randomized controlled
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trial (RCT), a systematic review, and observational studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment-related mortality and treatment-related morbidity. A 2016 meta-analysis identified 76 studies, 15 of which were controlled. Meta-analyses of controlled studies found that CRS and HIPEC was associated with a significantly higher survival rate and was not associated with a significantly higher rate of treatment-related morbidity. The RCT, in which patients were followed for at least 6 years, demonstrated improved survival in patients with peritoneal carcinomatosis due to CRC who received CRS plus HIPEC and systemic chemotherapy compared with patients who received systemic chemotherapy alone. However, procedure-related morbidity and mortality were relatively high and systemic chemotherapy regimens did not use currently available biologic agents. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal carcinomatosis of gastric origin who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes 2 small RCTs and 2 small retrospective comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment-related mortality and treatment-related morbidity. A 2017 systematic review and meta-analysis identified 2 RCTs and 12 controlled nonrandomized studies comparing surgery plus HIPEC with standard surgical management in patients who had peritoneal carcinomatosis due to gastric cancer. A meta-analysis found significantly better survival in the surgery plus HIPEC group at 1 year but not at 2 or 3 years. One RCT, but not the other, found better survival in patients who received CRS plus HIPEC compared with an alternative treatment. Given that patients eligible for CRS and 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 only RCT that used this design reported reduced survival in the CRS and HIPEC group, although the trials was small (N=26) and statistical testing was not reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal carcinomatosis of endometrial origin who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes cohort studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment-related mortality and treatment-related morbidity. Only uncontrolled studies were available and they had small sample sizes (<25 patients). Randomized trials that compare CRS plus HIPEC to standard treatment (eg CRS alone or systemic chemotherapy alone). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal mesothelioma who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes retrospective cohort studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment related mortality and treatment-related morbidity. Uncontrolled studies have shown median and 5-year overall survival ranging from 30 to 92 months and 33% to 68%, respectively, for patients with peritoneal mesothelioma who are treated with CRS and HIPEC. Reported procedure-related morbidity and mortality were approximately 35% and 5%, respectively. Controlled studies are needed to draw conclusions about the efficacy and safety of CRS and HIPEC compared with standard treatment (CRS alone). The evidence is insufficient to determine the effects of the technology on health outcomes.

Although no RCTs or comparative studies have been published, uncontrolled studies data have shown reasonable rates of overall survival with the use of this technique. Procedure-related morbidity and mortality have remained steady over time. Because the prevalence of peritoneal mesothelioma is very low, conducting high-quality trials is difficult. Therefore, based on the available evidence, CRS and HIPEC may be considered medically necessary for this indication.

For individuals who have ovarian cancer who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes 1 RCT, systematic reviews, and uncontrolled studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment-related mortality and treatment-related morbidity. Results from 1 RCT with methodologic flaws, case-control studies, and cohort studies are inconsistent; the RCT and case-control studies showed improved
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survival with CRS plus HIPEC in the second-line setting compared with CRS without HIPEC, but retrospective cohort studies have not shown a clear survival advantage compared with current treatment in the first- or the second-line setting. Results of at least some of these studies were confounded by prognostic factors (completeness of cytoreduction, extent of peritoneal carcinomatosis, chemosensitivity to platinum). Well-designed, RCTs are needed to control for potential covariates and to demonstrate improvements in net health outcomes compared with current treatment approaches (ie, CRS with systemic chemotherapy). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have appendiceal goblet cell tumors who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment related mortality and treatment-related morbitity. One retrospective series was identified. Additional studies, preferably controlled and ideally RCTs, are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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**


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Medical Director – 12/2011


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


Policy Implementation/Update Information


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)
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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. 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 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)

4/29/16 Updated Description section. Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)
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8/11/17 Updated Policy Guidelines section. Reference added. No change to policy statement. (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.