Hyperthermic Intraperitoneal Chemotherapy

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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, which bathes the peritoneal space. 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).

The rationale for HIPEC stems from the potential benefits described for intraperitoneal chemotherapy—very high drug concentrations in contact with tumor cells lining the peritoneal surfaces, with limited drug absorption and decreased systemic toxicity. The use of hyperthermia increases the intensity and penetration of therapy. Additional potential benefits of HIPEC include the possibility of avoiding multiple, postoperative sessions of standard intraperitoneal chemotherapy.

There are few formal guidelines for the selection of patients for CRS and HIPEC, and given the rarity of some of the tumors treated, well-designed controlled studies are generally lacking. In general, ideal patients will have a good performance status and disease localized to the peritoneal cavity that can be removed completely.

Pseudomyxoma peritonei

Pseudomyxoma peritonei is a clinicopathologic entity characterized by the production of mucinous ascites and mostly originates from epithelial neoplasms of the appendix. 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
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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
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sterile saline solutions when these devices are marketed for off-label use in HIPEC (eg, ThermaSolutions Inc., Minneapolis, MN; Belmont Instrument Corp., Billerica, MA).

***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 (HIPEC) 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 intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of pseudomyxoma peritonei due to low grade appendiceal mucinous neoplasms may be considered medically necessary if the disease can be optimally debulked and there are no distant metastases.

Cytoreductive surgery and intraoperative HIPEC for the treatment of diffuse malignant peritoneal mesothelioma may be considered medically necessary, if the disease can be optimally debulked and there are no distant metastases.

Cytoreductive surgery and intraoperative HIPEC for the treatment of newly diagnosed epithelial ovarian cancer may be considered medically necessary when ALL of the following criteria are met:

- The patient has stage III disease;
- The patient is not eligible for primary cytoreductive surgery but will receive neoadjuvant chemotherapy and subsequent interval cytoreductive surgery; (see Policy Guidelines)
- It is expected that complete or optimal cytoreduction can be achieved at the time of the interval cytoreductive surgery; (see Policy Guidelines)
- The cytoreductive procedure is performed by a physician trained in gynecologic oncology and it is performed in a facility staffed with specialists trained to administer HIPEC treatment.

When Intraperitoneal Hyperthermic Chemotherapy is not covered

Cytoreductive surgery and intraoperative HIPEC is considered investigational for:

- peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer;
- all other settings of ovarian cancer (including with primary cytoreductive surgery or recurrent disease);
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- all other indications, including goblet cell tumors (adenocarcinoid tumors) of the appendix.

Policy Guidelines

Policy statement guidelines

Pseudomyxoma Peritonei
The use of CRS and HIPEC for pseudomyxoma peritonei has shown benefit when it is due to low grade neoplasms of appendiceal origin (eg mucinous cystadenoma, also known as disseminated peritoneal adenomucinosis [DPAM]).

Ovarian Cancer
Eligibility for neoadjuvant chemotherapy and interval cytoreductive surgery is based on a high perioperative risk profile (ie the patient is a poor candidate to withstand an aggressive initial cytoreductive procedure) or the patient has extensive disease and a low likelihood of achieving up-front optimal cytoreduction to < 1 cm.

Complete cytoreduction is defined as no visible disease and optimal cytoreduction as one or more residual tumors measuring 10 mm or less in diameter.

Evidence summaries

Pseudomyxoma peritonei
For individuals who have pseudomyxoma peritonei who receive cytoreductive surgery and HIPEC, 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. Because the prevalence of pseudomyxoma peritonei is very low, conducting high-quality trials is difficult. Due to the lack of randomized trials, the absolute benefit of CRS and HIPEC for pseudomyxoma peritonei due to appendiceal tumors is unknown. However, given that multiple studies have shown consistent, long-term overall survival with use of this technique, HIPEC has become the standard approach for low-grade appendiceal neoplasms that have metastasized intraperitoneally and produced pseudomyxoma peritonei. Therefore, based on the available evidence, CRS and HIPEC may be considered medically necessary for this indication.

Mesothelioma
For individuals who have peritoneal mesothelioma who receive cytoreductive surgery and HIPEC, 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. Although no appropriate comparative studies have been published, multiple studies have shown consistent, long-term 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.

Ovarian Cancer
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For individuals who have ovarian cancer who receive cytoreductive surgery and HIPEC, the evidence includes RCTs, systematic reviews, and uncontrolled studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment-related mortality and treatment-related morbidity. CRS plus HIPEC has been studied in both newly diagnosed and recurrent ovarian cancer. Results of some studies have been confounded by factors such as heterogeneity of completeness of cytoreduction, extent of peritoneal carcinomatosis and chemosensitivity to platinum.

Van Driel et al (2018) reported that HIPEC reduced mortality for patients with newly diagnosed stage III epithelial ovarian cancer undergoing interval cytoreductive surgery. Patients were referred for interval cytoreductive surgery because their abdominal disease was too extensive for primary cytoreductive surgery or because surgery had been performed but was incomplete. Patients had at least stable disease after neoadjuvant systemic chemotherapy and were randomized at the time of interval cytoreductive surgery to HIPEC or no HIPEC (n=122 and n=123, respectively). At 5 year follow-up, 50% of patients treated with HIPEC had died compared with 62% treated with CRS only (p=0.02), Median OS was 45.7 months in the HIPEC group, and 33.9 months in the control group. The incidence of grade 3 or 4 adverse events was similar in the 2 groups.

Although the survival outcomes among the patients in the Van Driel study who underwent interval cytoreductive surgery with HIPEC were improved compared to the patients who underwent surgery alone, neither group had PFS results as good as the published results seen in patients who undergo up-front (primary) surgery with optimal cytoreduction (that is, patients with newly diagnosed ovarian cancer treated with up-front surgery without neoadjuvant chemotherapy). Therefore, the results of the Van Driel trial cannot be extrapolated to other clinical settings, and, based on current evidence, the use of HIPEC in the treatment of ovarian cancer should be limited to patients undergoing neoadjuvant chemotherapy and interval cytoreductive surgery.

Well-designed clinical trials which control for potential covariates and demonstrate improvements in net health outcomes compared with current treatment approaches (ie, CRS with systemic and/or intraperitoneal chemotherapy) may eventually identify other subgroups of patients with ovarian cancer who differ from those in the Van Driel study and might benefit from intraoperative administration of HIPEC.

Spiliotis et al (2015) reported on a single-center RCT of 120 women with recurrent ovarian cancer, who received CRS and postoperative systemic chemotherapy either with or without HIPEC. Although the authors reported an OS advantage in the HIPEC group, the study was flawed, including issues with study reporting, statistical analyses, study power and treatment bias, and that postoperative morbidity and mortality were not reported. Quality evidence of a benefit of HIPEC in recurrent ovarian is lacking.

Colorectal

For individuals who have peritoneal carcinomatosis of colorectal origin who receive cytoreductive surgery and HIPEC, the evidence includes 2 RCTs, a systematic review, and observational studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment-related mortality and treatment-related morbidity.

In 2018, the results of the PRODIGE 7 trial were presented at the American Society of Clinical Oncology (ASCO) meeting. PRODIGE 7 randomized 265 patients with stage IV colorectal cancer with peritoneal carcinomatosis and no distant metastases to surgery plus HIPEC or surgery alone. Most (96%) of the patients also received systemic chemotherapy before or after surgery or both. At a median follow-up of 64 months, median OS was 41.2 months in the surgery only group and 41.7 in the HIPEC group. Recurrence free survival was also similar between the two groups. At 30 days after surgery, the overall mortality rate was 1.5% in both groups, and there was no difference in the rate of side effects during the first 30 days between groups. At 60 days, however, the rate of complications in the HIPEC group was almost double that in the non-HIPEC group (24.1% vs 13.6%).

Based on the available evidence, CRS and HIPEC is considered investigational for this indication.
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Gastric
For individuals who have peritoneal carcinomatosis of gastric origin who receive cytoreductive surgery and HIPEC, 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.

Endometrial
For individuals who have peritoneal carcinomatosis of endometrial origin who receive cytoreductive surgery and HIPEC, 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 (e.g., CRS alone or systemic chemotherapy alone). The evidence is insufficient to determine the effects of the technology on health outcomes.

Appendiceal goblet cell tumors
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 morbidity. 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, 96549

“When performed using a temporary catheter or performed intraoperatively, the unlisted code 96549 (unlisted chemotherapy procedure) would be reported.”

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


Hyperthermic Intraperitoneal Chemotherapy


Senior Medical Director review 2/2018


BCBSA Medical Policy Reference Manual [Electronic version]. 2.03.07, 7/12/2018

Medical Director review 9/2018

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)


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
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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 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)


8/11/17 Updated Policy Guidelines section. Reference added. No change to policy statement. (lpr)

12/15/17 For clarity, added “hyperthermic” to the “When Covered” statements as well as the investigational statement under “When Not Covered.” Added CPT 96549 to the Billing/Coding section. No change to policy intent. Removed reference to “Hyperthermia Therapy” policy. (lpr)


Hyperthermic Intraperitoneal Chemotherapy

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.