Medical Policy
Hyperthermic 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: N/A

Related Policies
None

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

Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of surgery may be considered MEDICALLY NECESSARY for the treatment of:

- Pseudomyxoma peritonei; and
- Diffuse malignant peritoneal mesothelioma.

The use of HIPEC may be considered MEDICALLY NECESSARY in newly diagnosed epithelial ovarian or fallopian tube cancer at the time of interval cytoreductive surgery when ALL of the following criteria are met:

- The patient has stage III disease*;
- The patient is not eligible for primary cytoreductive surgery or surgery had been performed but was incomplete and will receive neoadjuvant chemotherapy and subsequent interval debulking surgery; and
- It is expected that complete or optimal cytoreduction can be achieved at time of the interval debulking surgery.

The use of HIPEC in all other settings to treat ovarian cancer, including but not limited to stage IIIC or IV ovarian cancer, is considered INVESTIGATIONAL.

Ovarian cancer staging is as follows:
- Stage I: The cancer is confined to the ovary or fallopian tube.
• Stage II: The cancer involves one or both ovaries with pelvic extension.
• Stage III*: The cancer has spread within the abdomen.
• Stage IV: The cancer is widely spread throughout the body.

Cytoreductive surgery plus HIPEC are considered INVESTIGATIONAL for:
• Peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer; and
• All other indications, including goblet cell tumors of the appendix.

Prior Authorization Information

Inpatient
• For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
• For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Prior authorization is not required.</th>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

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>
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<tbody>
<tr>
<td>DWY38ZZ</td>
<td>Hyperthermia of Abdomen</td>
</tr>
<tr>
<td>DWY68ZZ</td>
<td>Hyperthermia of Pelvic Region</td>
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DESCRIPTION

Pseudomyxoma Peritonei
Pseudomyxoma peritonei is a clinicopathologic disease 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. 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, usually discovered during imaging or laparotomy performed for another reason, to advanced cases with a distended abdomen, bowel obstruction, and starvation.

**Treatment**
The conventional treatment of pseudomyxoma peritonei is surgical debulking, repeated as necessary to alleviate pressure effects. However, repeated debulking surgeries become more difficult due to progressively thickened intra-abdominal adhesions, and this treatment is palliative, leaving visible or occult disease in the peritoneal cavity.²

**Peritoneal Carcinomatosis of Colorectal Origin**
Peritoneal dissemination develops in 10% to 15% of patients with colon cancer.

**Treatment**
Despite the use of increasingly effective regimens of chemotherapy and biologic agents to treat advanced disease, peritoneal metastases are associated with a median survival of six to seven months.

**Peritoneal Carcinomatosis of Gastric Origin**
Peritoneal carcinomatosis is detected in more than 30% of patients with advanced gastric cancer and is a poor prognostic indicator. The median survival is three months, and five-year survival is less than 1%.³ Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis.⁴

**Treatment**
Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for a cure.⁵

**Peritoneal 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 to 400 new cases of diffusely malignant peritoneal mesothelioma are registered every year, accounting for 10% to 30% of all-type mesothelioma.⁶ Diffuse malignant peritoneal mesothelioma has traditionally been considered a rapidly lethal malignancy with limited and ineffective therapeutic options.⁶ 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 results from locoregional progression within the abdominal cavity. In historical case series, treatment by palliative surgery, systemic or intraperitoneal chemotherapy, and abdominal irradiation has resulted in median survival of 12 months.⁶

**Treatment**
Surgical cytoreduction (resection of visible disease) in conjunction with hyperthermic intraperitoneal chemotherapy (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 ovaries; epithelial carcinoma is the most common, accounting for 90% of malignant ovarian tumors. Epithelial ovarian cancer is the fifth most common cause of cancer death in women in the U.S. Most ovarian cancer patients (>70%) present with widespread disease, and annual mortality is 65% of the incidence rate.
Treatment
Current management of advanced epithelial ovarian cancer is cytoreductive surgery (CRS) followed by combination chemotherapy. Tumor recurrences are common, and the prognosis for recurrent disease is poor.

CRS plus 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.

CRS plus HIPEC
CRS includes peritonectomy (ie, peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.\(^7\) CRS may be followed intraoperatively by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for one to two hours.

CRS plus HIPEC is being evaluated for the following conditions:
- Pseudomyxoma peritonei;
- Peritoneal carcinomatosis of colorectal, gastric, or endometrial origin;
- Peritoneal mesothelioma;
- Ovarian cancer; and
- Appendiceal goblet cell tumors.

Summary
Cytoreductive surgery (CRS) includes peritonectomy (ie, peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination. CRS may be followed intraoperatively by infusion of intraperitoneal chemotherapy with or without heating, which is intended to improve the tissue penetration of the chemotherapy. When heated, this is referred to as hyperthermic intraperitoneal chemotherapy (HIPEC). CRS and HIPEC have been proposed for a number of intra-abdominal and pelvic malignancies such as pseudomyxoma peritonei and peritoneal carcinomatosis from colorectal, gastric, or endometrial cancer.

For individuals who have pseudomyxoma peritonei who receive CRS plus HIPEC, the evidence includes cohort studies and a systematic review. The relevant outcomes are overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related mortality and morbidity. Uncontrolled studies of primary treatment of pseudomyxoma peritonei with CRS plus HIPEC have reported a median and a 5-year OS ranging from 47 to 156 months and 41% to 96%, respectively. Two small retrospective studies, who underwent CRS plus HIPEC for recurrence, indicated 5-year OS rates ranging from 34% to 79%. Procedure-related morbidity and mortality have decreased over time. Controlled studies are needed to draw conclusions about the efficacy and safety of CRS plus 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 study data have shown consistent, long-term 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, conducting high-quality trials is difficult. For these reasons, CRS plus HIPEC may be considered medically necessary for this indication.

For individuals who have peritoneal carcinomatosis of colorectal origin who receive CRS plus HIPEC, the evidence includes a randomized controlled trial (RCT), systematic reviews, and a large number of observational studies. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. A meta-analysis of controlled studies found that CRS plus HIPEC, compared with traditional therapy without HIPEC, was associated with significantly higher survival rates.
and was not associated with significantly higher treatment-related morbidity rates. The RCT, in which patients with peritoneal carcinomatosis due to colorectal cancer were followed for at least six years, demonstrated improved survival in patients who received CRS plus HIPEC and systemic chemotherapy compared with patients who received systemic chemotherapy alone. However, procedure-related morbidity and mortality rates 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 CRS plus HIPEC, the evidence includes two small RCTs, observational studies, and a systematic review. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. A 2017 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. The meta-analysis found significantly better survival in the surgery plus HIPEC group at one year but not at two or three years. An RCT found better survival in patients who received CRS plus HIPEC compared with an alternative treatment. 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 CRS plus HIPEC, the evidence includes cohort studies. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Only uncontrolled studies with small sample sizes were available (<25 patients). Randomized trials that compare CRS plus HIPEC with standard treatment (eg, CRS alone or systemic chemotherapy alone) are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal mesothelioma who receive CRS plus HIPEC, the evidence includes retrospective cohort studies and systematic reviews. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Uncontrolled studies have shown median and 5-year OS ranging from 30 to 92 months and 33% to 68%, respectively, for patients who had peritoneal mesothelioma treated with CRS plus HIPEC. Reported procedure-related morbidity and mortality were approximately 35% and 5%, respectively. Although no RCTs or comparative studies have been published, uncontrolled study data have shown reasonable rates of OS 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. Thus, although the evidence is insufficient to determine the effects of the technology on health outcomes, for the reasons discussed above, CRS plus HIPEC may be considered medically necessary for this indication.

For individuals who have newly diagnosed stage III ovarian cancer who receive CRS plus HIPEC, the evidence includes an RCT. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. For patients with newly diagnosed stage III ovarian cancer who had received neoadjuvant chemotherapy, HIPEC increased the time to disease recurrence and reduced mortality. HIPEC did not increase serious adverse events compared with surgery alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent stage IIIC or IV ovarian cancer who receive CRS plus HIPEC, the evidence includes an RCT and systematic review. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. For recurrent stage IIIC or IV disease (second-line setting), evidence from an RCT indicated that CRS plus HIPEC improved survival compared with CRS without HIPEC. However, interpretation of this study is limited because treatment groups in this RCT were unbalanced at baseline (variation in the completeness of cytoreduction), which has been shown to be associated with survival. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have appendiceal goblet cell tumors who receive CRS plus HIPEC, the evidence includes a case series. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-
related mortality and 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.

**Policy History**

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<td>1/2018</td>
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<tr>
<td>8/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>8/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>5/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes. Effective 10/2015.</td>
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<tr>
<td>4/2014</td>
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**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**

23. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with


