MASSACHUSETTS

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Medical Policy

Hyperthermic Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies

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Policy Number: 048

BCBSA Reference Number: 2.03.07 (For Plan internal use only)
NCD/LCD: N/A

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] 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 individual has stage III disease*;
- The individual 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**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue℠	Prior authorization is **not required**.
Medicare PPO Blue℠	Prior authorization is **not required**.

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

CPT codes:	Code Description
96547	Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, including separate incision(s) and closure, when performed; first 60 minutes (List separately in addition to code for primary procedure)
96548	Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, including separate incision(s) and closure, when performed; each additional 30 minutes (List separately in addition to code for primary procedure)

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

ICD-10 Diagnosis Codes

ICD-10-CM-codes:	Code Description
C45.1	Mesothelioma of peritoneum
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary

C56.3	Malignant neoplasm of bilateral ovaries
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum

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.[1] The incidence of pseudomyxoma peritonei is estimated at 2 cases per 1 million individuals.[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, 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.[3]

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 6 to 7 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 3 months, and 5-year survival is less than 1%.[4] Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis.[5]

Treatment

Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for a cure.[6]

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 United States, 200 to 400 new cases of diffuse malignant peritoneal mesothelioma are registered every year, accounting for 10% to 30% of all-type mesothelioma.[7] Diffuse malignant peritoneal mesothelioma has traditionally been considered 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 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.

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 United States. Most ovarian cancer patients (>70%) present with widespread disease, and annual mortality is 65% of the incidence rate. In addition, African American women reportedly have a higher prevalence of presenting with more advanced tumors, being undertreated or untreated, and having shorter disease-free survival compared to other racial groups.[8,]

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.

Cytoreductive surgery 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.

Summary

Description
Cytoreductive surgery (CRS) includes peritonectomy (ie, peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination. Cytoreductive surgery may be followed 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). Cytoreductive surgery 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.

Summary of Evidence
For individuals who have pseudomyxoma peritonei who receive cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC), the evidence includes cohort studies and a systematic review. Relevant outcomes are overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related mortality and morbidity. Retrospective cohort studies and systematic reviews have reported median survival ranging from 47 to 156 months and 5-year OS ranging from 41% to 96% for patients with primary treatment for pseudomyxoma peritonei treated with CRS plus HIPEC. Two retrospective studies reported results of CRS plus HIPEC for recurrence with 5-year OS rates of 34% and 79%. Although no direct comparisons between CRS plus HIPEC and other interventions have been published, traditional surgical debulking is not curative, and complete CRS alone (without HIPEC) has been associated with a 5-year OS of approximately 50%, along with high recurrence rates (91%, with a median disease-free survival of 24 months). Median progression-free survival (PFS) with CRS plus HIPEC as primary treatment has been reported as 40 to 78 months, with 5-year PFS rates of 38% to 80%. Procedure-related morbidity and mortality have generally decreased over time. Because the prevalence of pseudomyxoma peritonei is very low, conducting comparative trials is difficult. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have peritoneal carcinomatosis of colorectal origin who receive CRS plus HIPEC, the evidence includes randomized controlled trials (RCTs), systematic reviews, and a large number of observational studies. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Meta-analyses have found that CRS plus HIPEC, compared with traditional

therapy without HIPEC, is associated with significantly higher survival rates and not associated with significantly higher treatment-related morbidity rates. One RCT, in which patients with peritoneal carcinomatosis due to colorectal cancer were followed for at least 6 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. A more recent RCT found no survival benefit with CRS plus HIPEC over CRS alone, and a higher rate of adverse events 31 to 60 days post-procedure in the CRS plus HIPEC group. The lack of benefit seen with HIPEC in this trial may have been due to several factors, including the short duration of HIPEC treatment, the extensive use of preprocedural systemic chemotherapy, and the high rates of complete cytoreduction achieved in both groups. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have peritoneal carcinomatosis of gastric origin who receive CRS plus HIPEC, the evidence includes 2 small RCTs, observational studies, and 2 systematic reviews. 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. One meta-analysis found significantly better survival in the surgery plus HIPEC group at 1 year but not at 2 or 3 years. Another meta-analysis found survival benefit was reported in the CRS plus HIPEC groups at 1, 2, and 3 years. A 2024 meta-analysis identified 16 RCTS evaluating CRS plus HIPEC and found it to be a promising prophylactic and treatment therapy option, however the scarcity of large cohort studies and the heterogeneity of the included studies prevented authors from making a definitive recommendation for use. A phase 3 RCT (N=105) found no difference in OS between CRS plus HIPEC or CRS alone. One small (N=17) preliminary RCT showed improved survival in patients with peritoneal carcinomatosis due to gastric cancer who received CRS plus HIPEC compared with patients who received chemotherapy alone. Another (N=68) RCT showed improved survival in patients who received CRS plus HIPEC compared with CRS alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have peritoneal carcinomatosis of endometrial origin who receive CRS plus HIPEC, the evidence includes cohort studies. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Only uncontrolled retrospective cohort studies were available, with the largest including only 43 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 that the technology results in an improvement in the net health outcome.
For individuals who have peritoneal mesothelioma who receive CRS plus HIPEC, the evidence includes retrospective cohort studies and systematic reviews. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Retrospective cohort studies have shown median and 5-year OS ranging from 30 to 92 months and from 33% to 68%, respectively, for patients with peritoneal mesothelioma treated with CRS plus HIPEC. Although no RCTs or comparative studies have been published, historical case series have reported a median survival of 12 months with treatment by palliative surgery, systemic or intraperitoneal chemotherapy, and abdominal irradiation. Procedure-related morbidity and mortality rates with CRS plus HIPEC have remained relatively steady over time, at approximately 35% and 5%, respectively. Because the prevalence of peritoneal mesothelioma is very low, conducting comparative trials is difficult. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have newly diagnosed stage III ovarian cancer who receive CRS plus HIPEC, the evidence includes systematic reviews and RCTs. 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. It did not increase serious adverse events compared with surgery alone. The evidence is sufficient to determine that the technology results in an 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 RCTs and systematic reviews. 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. Another RCT reported that CRS plus HIPEC did not result in superior outcomes compared to CRS without HIPEC for patients with platinum-sensitive recurrent disease. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have appendiceal goblet cell tumors who receive CRS plus HIPEC, the evidence includes retrospective cohort studies. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. A propensity score-matched analysis found that CRS plus HIPEC was associated with improved median survival compared to surgery alone. However, this analysis was limited by the retrospective nature of the data and small sample size (N=44). Rates of complete cytoreduction were not reported or accounted for in this study, so between-group differences in this or other variables may have influenced the observed outcomes. Additional studies- are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
9/2024	Annual policy review. Policy updated with literature review through June 5, 2024; references added; guideline references updated. Policy statements unchanged.
6/2024	Clarified coding information.
1/2024	Clarified coding information.
9/2023	Annual policy review. References added and updated. Policy statements unchanged.
9/2022	Annual policy review. References added and updated. Minor editorial refinements to policy statements; intent unchanged.
8/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
12/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
11/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
3/2019	Annual policy review. Policy statement updated to include hyperthermic intraperitoneal chemotherapy for the treatment of newly diagnosed stage III ovarian cancer. Policy title changed. Effective 3/1/2019.
1/2018	Clarified coding information.
8/2017	Annual policy review. New references added
8/2016	Annual policy review. New references added
6/2015	Annual policy review. New investigational indications described. Clarified coding information. Title changed to “Select Intra-Abdominal and Pelvic Malignancies.” Effective 6/1/2015.
5/2014	Updated Coding section with ICD10 procedure and diagnosis codes. Effective 10/2015.
4/2014	Clarified coding information.
1/2014	Annual policy review. New references added.
11/2011-4/2012	Medical policy ICD10 remediation: Formatting, editing and coding updates. No changes to policy statements.
7/2011	Reviewed - Medical Policy Group – Hematology and Oncology. No changes to policy statements.

9/2010	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2009	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
10/2008	Reviewed - Medical Policy Group – Hematology and Oncology. No changes to policy statements.
3/2008	Medical policy #048 describing covered and non-covered indications. Effective 3/1/2008.

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

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