

MEDICAL POLICY

POLICY TITLE	HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY FOR SELECT INTRA-ABDOMINAL AND PELVIC MALIGNANCIES
POLICY NUMBER	MP 2.021

CLINICAL BENEFIT	<input checked="" type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	12/1/2024

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I. POLICY

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Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) 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 (see Policy Guidelines);
- 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 (see Policy Guidelines); **AND**
- It is expected that complete or optimal cytoreduction can be achieved at time of the interval debulking surgery (see Policy Guidelines).

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**.

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.

There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

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The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. The National Cancer Institute's PDQ (Physician Data Query) is NCI's comprehensive source of cancer information, which includes evidence-based summaries on topics that cover adult and pediatric cancer treatment. These guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

Policy Guidelines

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.

Eligibility for neoadjuvant chemotherapy and interval debulking surgery is based on a high perioperative risk profile (i.e., the patient is a poor candidate to withstand an aggressive initial cytoreductive procedure) or a low likelihood of achieving cytoreduction to less than 1 cm (i.e., the patient has extensive disease that precludes upfront optimal cytoreduction) or surgery has been performed but was incomplete (i.e., after surgery, one or more residual tumors measuring greater than 1 cm in diameter were present).

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

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

III. DESCRIPTION/BACKGROUND

Cytoreductive surgery (CRS) includes peritonectomy (i.e., 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

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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.

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. The incidence of pseudomyxoma peritonei is estimated at 2 cases per 1 million individuals. 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.

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%. Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis.

Treatment

Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for cure.

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

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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. 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 a 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 (greater than 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.

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.

Regulatory Status

Mitomycin, oxaliplatin, carboplatin, and other drugs used for HIPEC have not been approved by the U.S. Food and Drug Administration (FDA) for this indication.

Several peritoneal lavage systems (FDA product code: LGZ) have been cleared for marketing by the FDA through the 510(k) process to provide “warmed, physiologically compatible sterile solution” (e.g., Performer® HT perfusion system; RanD; Warrior Blood and Fluid Warmer; X-

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FLO Fluid Management System). None has received marketing approval or clearance to administer chemotherapy. The FDA has issued warnings 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.

Table 1. Hyperthermic Intraperitoneal Lavage Devices Cleared by the U.S. Food and Drug Administration

Device	Manufacturer	Date Cleared	510(k) No.	Indication
FluidSmart	THERMEDX LLC	9/5/2017	K172048	For irrigation, distention, fluid warming, and fluid volume/deficit measurements in endoscopic procedures within gynecology, urology, and orthopedic disciplines.
Hang&Go PAC	RanD S.r.l.	12/28/2016	K161613	To recirculate, filtrate and perfuse physiologically compatible sterile solution (i.e., saline solution) in the thoracic or abdominal cavity
The Belmont Hyperthermia Pump	BELMONT INSTRUMENT CORPORATION	9/2/2015	K152208	To raise the temperature of the thoracic or peritoneal cavity to the desired target temperature by continuously lavaging the cavity with circulating warmed sterile solution

IV. RATIONALE

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Summary of Evidence

For individuals who have pseudomyxoma peritonei who receive CRS plus 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,

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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 RCTs, systematic reviews, and a large number of observational studies. 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, is associated with significantly higher survival rates and was 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 (e.g., CRS alone or systemic chemotherapy

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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.

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V. DEFINITIONS

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CYTOREDUCTION SURGERY involves mobilization of the liver, exploration of the diaphragm, mobilization of the stomach, exploration of the bilateral abdominal gutters, pelvic recesses, and mobilization of the large and small bowel with examination for tumor deposits along their entire length.

INTRAPERITONEAL refers to within the peritoneal cavity. The peritoneum is a serous membrane lining the abdominal cavity and reflected over the viscera.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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Procedure Codes							
96446	96547	96548	96549				

ICD-10-CM Diagnosis Codes	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
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.63	Secondary malignant neoplasm of bilateral ovaries
D12.1	Benign neoplasm of appendix

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.021	09/04/2020 Consensus Review. No changes to policy statement. References unchanged, coding reviewed.
	06/04/2021 Consensus Review. No change to policy statement. References, background, and rationale updated. Coding reviewed. Added NCCN statement
	09/07/2021 Administrative Update. New codes C56.3 and C79.63 added. Effective 10/1/2021
	10/17/2022 Consensus Review. No change to policy statement. Background, rationale, and references updated. Coding reviewed
	08/09/2023 Consensus Review. No change to policy statement. Product variation language, Background and References updated.
	12/12/2023 Administrative Update. Added New Codes 96547 & 96548. Effective 1/1/24.
	08/14/2024 Consensus Review. No change to policy statement. Rationale updated. References added and updated.

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