

## linical Policy: Intraperitoneal Hyperthermic Chemotherapy for Abdominopelvic Cancers

Reference Number: HNCA.CP.MP. 346

Last Review Date: 11/21

[Coding Implications](#)  
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See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### Description

Intraperitoneal hyperthermic chemotherapy (IPHC) or chemoperfusion (HIPEC) is a highly concentrated, heated chemotherapy treatment that is delivered directly to the abdomen during surgery. This is done for both the prevention of peritoneal carcinoma as well as for the treatment of such cancers that have penetrated or metastasized into the peritoneal cavity.

### Policy/Criteria

- I. It is the policy of Health Net of California that IPHC or HIPEC may be considered medically necessary as an adjunct to aggressive cytoreductive surgery (CRS) for any of the following indications:
  - A. Treatment of appendiceal carcinoma or goblet cell carcinoid,
  - B. Prophylactic use for locally advanced gastric cancer without macroscopic peritoneal metastasis or distant metastasis,
  - C. Pseudomyxoma peritonei (PMP) and disseminated mucin-producing adenocarcinomas,
  - D. Malignant peritoneal mesothelioma,
  - E. Peritoneal carcinomatosis from colon, rectal or small bowel cancers when there are no extra-abdominal metastases
  - F. Ovarian cancer following neoadjuvant chemotherapy
  
- II. It is the policy of Health Net of California that the therapeutic use of IPHC or HIPEC as an adjunct to aggressive cytoreductive surgery is **investigational** in patients with peritoneal carcinomatosis from all other abdominopelvic malignancies. The benefit of this treatment has not been validated in randomized controlled trials.

### Background

IPHC or HIPEC is applied during surgery via an open or closed abdominal approach. The closed technique is performed to eliminate the risk of aerosolization and direct contact of the toxic chemotherapeutic agent with surgical staff. After completion of the cytoreductive procedure, peritoneal perfusion inflow and outflow catheters are placed percutaneously into the abdominal cavity. The abdominal skin incision is closed temporarily with a running cutaneous suture to prevent leakage of peritoneal fluid. The chemotherapy agent is heated and then allowed to flow into the peritoneal cavity raising the temperature of the tissues within the cavity to 106-108° Fahrenheit. The goal of IPHC is to enhance the cytotoxic effect of chemotherapeutic drugs, thereby killing circulating tumor cells and reducing the risk of tumor recurrence. The abdomen is gently massaged throughout the perfusion to improve drug distribution to all peritoneal surfaces. The increase in the patient's core body temperature during IPHC helps to offset the hypothermia associated with lengthy cytoreductive surgical procedures.

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The difference between traditional intraperitoneal chemotherapy and IPHC is that in the traditional form, the chemolytic agents may be infused at the time of surgery or over a course of several days, however, these agents are not heated before being infused. Studies suggest that outcomes are most favorable among patients who are able to undergo complete or nearly complete surgical cytoreduction prior to IPHC.

A comparative analysis of a series of 489 patients with liver metastases were treated with microscopically margin-negative resections, known as RO resections, in which no gross or microscopic tumor remains in the primary tumor bed. Another series of 60 patients with peritoneal carcinomatosis undergoing complete cytoreduction, demonstrated similar 20% survival, 8 years from treatment. In addition, intraperitoneal chemotherapy has been applied given the likely pharmacologic advantage of delivering chemotherapy within the peritoneal space as opposed to standard intravenous administration. Preclinical and clinical pharmacologic studies have demonstrated this, although penetration into tumor tissue still appears limited to a maximum of 1 to 2 mm from the surface, hence the need for radical resection of gross disease. HIPEC has been used to increase chemotherapy diffusion into peritoneal tumors.

Pseudomyxoma peritonei originating from an appendiceal mucinous neoplasm remains a biologically heterogeneous disease. An international registry study was done with the goal to evaluate outcome and long-term survival after cytoreductive surgery (CRS) and HIPEC. Two thousand two hundred ninety-eight patients from 16 specialized units underwent CRS for pseudomyxoma peritonei. The median survival rate was 16.3 years and the median progression-free survival rate was 8.2 years, with 10 and 15 year survival rates of 63% and 59%, respectively. The combined modality strategy for PMP may be performed safely with acceptable morbidity and mortality in a specialized unit setting with 63% of patients surviving beyond 10 years. Minimizing nondefinitive operative and systemic chemotherapy treatments before definitive cytoreduction may facilitate the feasibility and improve the outcome of this therapy to achieve long-term survival.

Studies on cytoreductive surgery and intraperitoneal chemotherapy for peritoneally metastasized colorectal cancer have noted that recurrence is very common after cytoreductive surgery and intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. Published peer-reviewed literature is necessary to determine the long term efficacy of HIPC for individuals with peritoneal carcinomatosis.

Malignant mesothelioma is a rare, highly lethal malignancy of the serosal membranes of the pleura, peritoneum, pericardium, or tunica vaginalis testes. As with pseudomyxoma peritonei, combined-modality approaches using surgery and IPHC may offer substantial improvements compared to historical controls. There have been several retrospective series using this technique, with median survival rates of 30 to 60 months, and even 5-year survival rates of up to 50%.

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Emerging literature from case series and retrospective studies has demonstrated that intraoperative HIPEC can be of benefit to patients with isolated peritoneal carcinomatosis (no extra-abdominal metastases) from colorectal cancer. Several prospective, randomized trials are ongoing.

In a systematic review, Chua et al. (2013) investigated the efficacy of systemic chemotherapy and radical surgical treatments in patients with peritoneal metastases from colorectal cancer. A total of 2,492 patients from 19 studies were reviewed. Patients were treated with complete CRS and HIPEC (n=1084) or palliative surgery and/or systemic chemotherapy (n=1408). Patients with residual tumors >2.5 mm after CRS were classified as having an incomplete cytoreduction. For CRS and HIPEC, the overall survival ranged between 20 and 63 (median 33) months, and 5-year survival ranged between 17% and 51% (median 40%). For palliative surgery and/or systemic chemotherapy, the overall survival ranged between 5 and 24 (median 12.5) months, and 5-year survival ranged between 13% and 22% (median 13%).

Intraoperative HIPEC is being studied as a treatment option for ovarian cancer. Huo et al (2015) reviewed 9 comparative studies and 28 studies of the safety and efficacy of HIPEC plus cytoreduction surgery (CRS) for primary and/or recurrent ovarian cancer. Studies were selected if they included > 10 patients and used the combined CRS and HIPEC treatment with a diagnosis of primary or recurrent epithelial ovarian carcinoma (EOC). Only one study was a randomized controlled trial. Outcomes were morbidity/mortality; overall survival (OS) and disease free survival (DFS). Meta-analysis of the comparative studies showed HIPEC with CRS and chemotherapy had significantly better one year survival compared with CRS and chemotherapy alone. The authors reported that there is an emerging body of evidence supporting the use of HIPEC with CRS and systemic chemotherapy for primary (stage III) and recurrent epithelial ovarian carcinoma compared to CRS and chemotherapy alone. They note that ongoing randomized controlled trials will further clarify the role of HIPEC for patients with advanced and recurrent ovarian cancer.

A Hayes Health Technology Assessment (2019) evaluated 1 randomized controlled trial (RCTs), 1 prospective cohort study, and 8 retrospective cohort studies for the efficacy and safety of CRS plus HIPEC compared with CRS alone for PC due to ovarian cancer in patients with PM. The low quality evidence suggested that it was more effective in improving survival than CSR alone, though complications of hematological toxicity and renal insufficiency/failure, occurring in < 20% of patients.

Auer et al. (2020) evaluated two RCTs with 184 and 245 patients with newly diagnosed, primary stage III epithelial ovarian, fallopian tube or primary peritoneal carcinoma. The authors concluded that HIPEC should be considered for those with partial or complete response following neoadjuvant chemotherapy and complete or optimal interval CRS; however, there is insufficient evidence to recommend the addition of HIPEC with primary CRS when performed outside of a clinical trial.

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There are a number of clinical trials involving patients with recurrent ovarian cancer, colorectal or gastric peritoneal carcinomatosis, mesothelioma or disseminated mucinous neoplasms. Currently there is insufficient evidence to recommend CRS with HIPEC outside of a clinical trial or research protocol.

### *National Comprehensive Cancer Network (NCCN)*

NCCN clinical practice guidelines for colon and rectal cancers state that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom complete removal of all known tumor can be achieved (R0). NCCN recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities (NCCN: 2019) The guidelines also note that the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach controversial (NCCN, 2020)

NCCN clinical practice guidelines for ovarian cancer state that HIPEC with cisplatin (100 mg/m<sup>2</sup>) can be considered at the time of interval debulking surgery (IDS) following neoadjuvant chemotherapy for stage III ovarian disease (NCCN, 2019; updated 2020).

### *National Institute for Clinical Excellence (NICE)*

A 2020 National Institute for Health and Care Excellence (NICE) guideline on colorectal cancer recommended that for people with colorectal cancer metastases limited to the peritoneum, patients should offered systemic anti-cancer therapy and within a multidisciplinary team, discuss referral to a nationally commissioned specialist centre to consider CRS and HIPEC. Although the evidence on the effectiveness of CR and HIPEC was mixed, based on their clinical knowledge, the committee agreed it was important to recommend referral to a nationally commissioned specialist centre after discussion within a multidisciplinary team for consideration of cytoreductive surgery and HIPEC so that more patients can have potentially curative treatment and to avoid centres offering the treatment without having the necessary training and resources. This advice is in line with the NICE interventional procedures guidance on cytoreductive surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis [IPG 331] published in 2010.

### *National Cancer Institute (NCI):*

The NCI noted that HIPEC is another pharmacologically-based modality to enhance the antitumor effects via direct drug delivery to peritoneal surfaces. In clinical trials, HIPEC is being applied to ovarian cancers, with considerable variation in patient selection, drugs administered, and time at target temperatures, but remains experimental in the treatment of patients with high-grade serous ovarian cancers (NCI, 2018, 2019). They also mention other clinical trials on hyperthermia in combination with radiation therapy and/or chemotherapy for various types of cancer such as rectum, liver, appendix, cervix, peritoneal lining (mesothelioma) but results are varied and further study is needed.

### *Professional Societies*

**American Society of Colon and Rectal Surgeons (ASCRS)**

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ASCRS practice parameters (Chang et al., 2012) for the management of colon cancer state that the treatment of patients with peritoneal carcinomatosis should be multidisciplinary and individualized and may include surgical cytoreduction. The role of perioperative intraperitoneal chemotherapy, with or without hyperthermia, remains insufficiently defined. Grade of recommendation: 2C – weak recommendation based on low- or very low-quality evidence. In 2017, the ASCRS published guidelines on colon cancer, including peritoneal carcinomatosis noting that the surgical approach to colorectal cancer-associated peritoneal carcinomatosis includes the combination of cytoreductive surgery in conjunction with perioperative intraperitoneal mitomycin-C or oxaliplatin with or without hyperthermia.

### Society of Surgical Oncology

A society consensus statement presents a clinical pathway for the management of peritoneal surface malignancies of colonic origin. CRS combined with HIPEC and postoperative systemic chemotherapy should be considered when complete cytoreduction can be achieved, and there is no evidence of distant disease (Esquivel et al., 2007).

### Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2015, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT® Codes	Description
77605	Hyperthermia, externally generated; deep (i.e., heating to depths)
96446	Chemotherapy administration into the peritoneal cavity via indwelling port or catheter

HCPCS Codes	Description
N/A	

### ICD-10-CM Diagnosis Codes that Support Coverage Criteria

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ICD-10-CM Code	Description
C16.0-C16.8	Malignant neoplasm of stomach
C18.0-C18.8	Malignant neoplasm of the colon
C19	Malignant neoplasm of rectosigmoid junction
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
D37.1	Neoplasm of uncertain behavior of stomach
D37.2	Neoplasm of uncertain behavior of small intestine
D37.4	Neoplasm of uncertain behavior of colon
D37.5	Neoplasm of uncertain behavior of rectum
D48.3	Neoplasm of uncertain behavior of retroperitoneum
D48.4	Neoplasm of uncertain behavior of peritoneum

Reviews, Revisions, and Approvals	Date	Approval Date
Policy adopted from Health Net NMP# 346, Intraperitoneal Chemotherapy for Abdominopelvic Cancers	11/16	
Added to indications peritoneal carcinomatosis resulting from the following colon, rectal or small bowel cancer when there are no extra-abdominal metastases. Added references	11/17	11/17
Added disseminated mucin-producing adenocarcinomas	11/18	11/18
Updated references	11/19	11/19
Added ovarian cancer, updated background and references	11/20	11/20
Updated references. In background, updated practice guidelines and society recommendation sections	11/21	11/21

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### **Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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