



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Hyperthermic Intraperitoneal
Chemotherapy (HIPEC)**

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Coverage Policy

CIGNA covers hyperthermic intraperitoneal chemotherapy (HIPEC) as medically necessary when used in combination with cytoreductive surgery for the treatment of pseudomyxoma peritonei (PMP).

CIGNA does not cover hyperthermic intraperitoneal chemotherapy (HIPEC) for any other indication because it is considered experimental, investigational or unproven.

General Background

Hyperthermic intraperitoneal chemotherapy (HIPEC), also referred to as intraperitoneal hyperthermic chemotherapy (IPHC), has been proposed as an alternative for the treatment of cancers within the peritoneal cavity, including primary peritoneal mesothelioma and gastric cancer. The HIPEC is applied during surgery, via an open or closed abdominal approach. The heated chemolytic agent is infused into the peritoneal cavity, raising the temperature of the tissues within the cavity to 106–108 °Fahrenheit (F). During traditional intraperitoneal chemotherapy (IPC), the chemolytic agents may also be infused at the time of surgery or over a course of several days. However these agents are not heated before being infused, which is the main difference between IPC and HIPEC. The effectiveness of HIPEC is based on the achievement of a hyperthermic intracavity temperature. Because various tissue thicknesses are present within the peritoneal cavity, there is a concern that the entire cavity may not be receiving an even exposure to the medication. Side effects of HIPEC include blistering, burns, tissue swelling, blood clots, and bleeding, although these are usually temporary.

Cancers that arise within the organs of the abdominal cavity can metastasize to the peritoneal surface or to adjacent organs within the cavity. Metastatic cancer cells that migrate throughout the peritoneal cavity adhere to and grow within the peritoneum, causing peritoneal carcinomatosis (PC). Primary PC (also termed serous surface papillary carcinoma) is a malignancy that arises primarily from peritoneal cells. PC is a rare tumor occurring almost exclusively in women, while primary mesotheliomas are more prominent in males. The occurrence of mesotheliomas has recently increased, with this increase being associated to asbestos exposure. Survival rates for patients who are diagnosed with PC are poor, with a median survival time being reported as 12–25 months (Efiom-Ekahn, 2003).

Pseudomyxoma peritonei (PMP) represents a rare form of metastatic PC that also originates from cells within the appendix or ovary. Seventy-five percent of the patients who develop PMP are women between the ages of 45–75. These tumorous cells form gelatinous plaque on the peritoneum; however, lymphatic or extraperitoneal spread is rare. The use of systemic chemotherapy appears to be ineffective, and recurrence usually causes bowel obstruction, malnutrition, and death. At the present time, treatment for PMP of appendiceal origin is a right hemicolectomy, aggressive tissue debulking in conjunction with hyperthermic intraperitoneal perfusion (Feldman, 2006).

Conventional treatment for PC includes extensive surgical resection and tissue debulking (i.e., cytoreduction surgery [CS]) followed by the administration of chemotherapy or radiation therapy. There are numerous chemolytic agents that can be administered according to tumor cell type, the depth of the invasion of the primary tumor and the patient's tolerance to therapy. Chemotherapy can be administered orally, systemically (i.e., intravenously) or as adjuvant treatment when radioactive implants are placed directly into the tumor. In an attempt to improve the effectiveness of chemotherapy, an intraperitoneal hyperthermic approach has been proposed for the treatment of PC.

Literature Review

In general, the bulk of the evidence evaluating the safety and effectiveness of HIPEC combined with CS consist of non-comparative case series with retrospective design and relatively small sample sizes.

Pseudomyxoma peritonei (PMP): A number of studies have evaluated the use of CS combined with HIPEC as a treatment for PMP. Although not robust, the available evidence supports the safety and effectiveness of HIPEC for PMP when compared to other standard treatments (Elias, et al., 2008; Cioppa, et al., 2008; Smeenk, et al., 2007). Cytoreductive surgery with intraperitoneal hyperthermic perfusion is an effective current treatment for PMP with acceptable morbidity and mortality rates (Houghton and Wang, 2006).

Colorectal Cancer: A systematic review and meta-analysis of comparative studies (n=4) and observational studies (n=43) by Cao et al. (2009) evaluated the survival outcomes of patients with colorectal PC. Results of the meta-analysis indicated that a significant improvement in survival was associated with treatment by CS and HIPEC compared with palliative approach (p< 0.0001). However, this was based on four studies comparing combined treatment involving CS and perioperative intraperitoneal chemotherapy. Only two of these four studies involved patients who underwent HIPEC, a randomized controlled trial (RCT) (n=105 patients) and a non-randomized comparative study (n=96 patients). The observational studies demonstrated that overall median survival varied greatly from 11.9 to 60.1 months. The median one-, two-, three-, four-, and five-year survival rates from these studies were 76%, 55%, 36%, 28%, and 19% respectively. Perioperative morbidity and mortality rates for all cytoreductive surgery procedures ranged from 14.8% to 76%, and 0% to 12%, respectively. Follow-up ranged from 10–113 months. It was noted that patient selection criteria differed between centers and individual trials. Also each treatment center prescribed different chemotherapy regimens and varied in the amount of detail reported.

Shen et al. (2009) presented a cohort of patients (n=55) with peritoneal surface disease from colorectal cancer who received CS and HIPEC. Follow-up occurred one month post-procedure and every six months thereafter up to five years. The median follow-up period was 86 months. The five-year overall survival rate for this cohort of patients with resection status of R 0 or R1 was 36% and 14 % respectively. The overall postoperative morbidity and mortality was 41.8% and 5.5% respectively.

A retrospective comparative study (n=96) by Elias et al. (2009) found two-year and five-year overall survival rates of 81% and 51% respectively for patients treated with HIPEC (n=48), and 65% and 13% respectively for

those treated with standard chemotherapy (n=48). The median survival was 23.9 months in the standard group versus 62.7 months in the HIPEC group (p<0.05).

Another retrospective multicenter study (n=506) by Glehen et al. (2004) reported an overall median survival of 19.2 months for patients who had CS with HIPEC for PC from colorectal cancer. The median follow-up was 53 months. The morbidity and mortality rates were 22.9% and 4%, respectively. Patients in whom cytoreductive surgery was complete had a median survival of 32.4 months, compared with 8.4 months for patients in whom complete cytoreductive surgery was not possible (p<0.001).

An RCT by Verwaal et al. (2003) reported outcomes of 105 patients with PC colorectal cancer origin who were randomized to receive either standard systemic chemotherapy (n=51) or cytoreductive surgery with HIPEC (n=54). Median survival in the standard treatment arm was 12.6 months, compared to 22.4 months in the HIPEC group. A subgroup analysis did not reveal a difference of treatment outcome between systemic chemotherapy versus CS and HIPEC, and in the first six months, survival was identical between the study groups. Adverse events included toxicity, small bowel leakage, and abdominal sepsis.

Gastric Cancer: A multicenter retrospective study (n=159) by Glehen et al. (2010) reported outcomes of patients with PC from gastric cancer who underwent CS followed by perioperative chemotherapy. A total of 150 patients were treated with HIPEC and 12 received early postoperative intraperitoneal chemotherapy (EPIC). The median follow-up was 20.4 months. Postoperative mortality and morbidity rates were 6.5% and 27.8%, respectively. The overall median survival was 9.2 months and one-, three-, and five-year survival rates were 43%, 18%, and 13%, respectively. Limitations of both studies include the retrospective, nonrandomized design.

A systematic review and meta-analysis (n=13 RCTs) by Yan et al. (2007) evaluated the safety and effectiveness of adjuvant intraperitoneal chemotherapy for patients with locally advanced resectable gastric cancer. Studies compared patients who received surgery and intraperitoneal chemotherapy (n=873) with those who received no adjuvant intraperitoneal chemotherapy (n=775). The primary end-point was overall survival. Of the 13 RCTs, four trials from 1994 to 2001 investigated the efficacy of HIPEC, one of which was considered to be of poor quality. Based on the remaining three studies, a significant survival improvement was found in favor of HIPEC (p=0.002).

Zhu et al. (2006) conducted a prospective, unblinded controlled study of 118 patients to investigate the clinical safety of intraoperative HIPEC for advanced gastric cancer (AGC). Based on the presence of metastases patients were divided into two subgroups, the prophylactic group (n=96 patients without metastases) and the therapeutic group (n=22 patients with metastases). Within the prophylactic group, patients underwent a combination of gastrectomy and HIPEC (n=42), or gastrectomy (n=54; control group). Of the 22 patients with metastases, 10 underwent HIPEC and palliative gastrectomy, while 12 were treated with gastrectomy alone. The median follow-up period was 43 months. The prophylactic HIPEC group had 2-, 4-, and 6-year survival rates of 83.03%, 70.48%, and 67.87%, respectively. This was higher than those without HIPEC, (63.69%, 52.11% and 37.74%, respectively). Mean survival rates were statistically significant between these groups. Complications were higher in the HIPEC group versus the control group (23.08% versus 12.12%) with renal dysfunction being the most common complication.

A meta-analysis (n=11 RCTs) by Xu et al. (2004) assessed the safety and effectiveness of IPC in patients undergoing curative resection for gastric cancer. Of the 11 trials only three were reported to be of high quality, with the remaining studies reported to be of low quality. HIPEC was evaluated in total of seven studies and was found to produce more benefits to patients than normothermic IPC. It was noted that two trials from Austria showed that IPC was not beneficial to patients, while the other nine Asian studies confirmed a significant survival benefit" (Xu, et al., 2004).

Hall et al. (2004) conducted a prospective, nonrandomized controlled trial (n=74) to study the efficacy of CS and HIPEC for adenocarcinoma of the stomach. Thirty-four patients had CS and HIPEC, while 40 had standard curative surgery. For all patients, the median survival was eight months; 36% were alive at one year and 26% at two years. The researchers concluded that neither conventional surgery nor combined surgery and HIPEC were associated with improved survival. Although this study is prospective, the two groups studied varied in the degree of cancer and metastatic involvement.

Ovarian Cancer: A systematic review (n=19 studies) by Chua et al. (2009) of the evidence on CS and HIPEC as a treatment for ovarian cancer PC. All studies were observational case series. The overall rate of severe perioperative morbidity ranged from 0–40% and mortality rate varied from 0–10%. The overall median survival following treatment with HIPEC ranged from 22–64 months with a median disease-free survival range of 10–57 months. The overall three-year survival rate ranged from 35–63%, and five-year survival rate ranged from 12–66%. **Level of Evidence: 4**

Bijelic et al. (2007) performed a systematic review (n=14 studies) to evaluate the use of cytoreductive surgery combined with HIPEC in the treatment of ovarian cancer. Studies were primarily retrospective analyses. The median overall survival for primary and recurrent disease ranged from 22 to 54 months and the median disease-free survival from 10 to 26 months. The rates of significant morbidity associated with this combined treatment were low, ranging from 5% to 36%. It was noted the retrospective design and heterogeneity of studies limited the ability to make conclusive statements about the benefit of this procedure for the treatment of ovarian cancer (Bijelic, et al., 2007).

Similar survival rates have been reported in prospective and retrospective series and comparative studies with patient populations ranging from 47–155 and a follow-up range of 24–65 months (Di Giorgio, et al., 2008; Bae, et al., 2007; Cotte, et al., 2007; Gori, et al., 2005; Ryu, et al., 2004). However randomized controlled studies demonstrating improved outcomes for treatment with HIPEC versus standard chemotherapy protocols are lacking.

Peritoneal Cancer: A 2009 guidance issued by the National Institute for Clinical Excellence (NICE) states that the “current evidence on the efficacy of CS followed by HIPEC for PC shows some improvement in survival for selected patients with colorectal metastases, but evidence is limited for other types of cancer. The evidence on safety shows significant risks of morbidity and mortality that need to be balanced against the perceived benefit for each patient. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research” (NICE, 2009).

In a cohort study (n=67), Hagendoorn et al. (2009) reported the clinical outcomes and survival of patients treated with cytoreductive surgery and HIPEC. Patients had PC originating from primary colorectal, cecal, appendiceal, and gastric tumors. Complete cytoreduction was achieved in 49 patients. The overall morbidity was 43%, including extended gastroparesis (11%), anastomotic failure (11%) and intra-abdominal abscess (9%). The mean time to clinical recurrence was 12 months (range 4-22).

van Leeuwen et al. (2008) conducted a prospective non-randomized study (n=103) to identify factors associated with postoperative morbidity and survival after peritonectomy with HIPEC in patients with PC. Primary tumors were pseudomyxoma peritonei (n=47), colorectal cancer (n=38), gastric cancer (n=6), ovarian cancer (n=6) and mesothelioma (n=5). Postoperative morbidity was 56.3% and was reported to be significantly lower in patients treated for pseudomyxoma peritonei (p<0.05). Postoperative mortality was less than 1%. At two years follow-up, overall survival was estimated to be 72.3%, and disease-free survival was 33.5%. Factors influencing overall and disease-free survival were tumor type and optimal cytoreduction.

A prospective study (n=460) by Levine et al. (2007) reported their findings from treating patients with CS and HIPEC for peritoneal surface malignancy. The median follow-up was 55.4 months. The median overall survival was 22.2 months with a one-, three- and five-year overall survival rates were 66.8%, 40.0%, and 27.8%, respectively. The median survival (months) was considerably different by site of origin with: appendix, 63.5; colorectal, 16.4; gastric, 6.1; mesothelioma, 27.1; ovary, 28.5; and sarcoma, 28.1 (p=0.0001). The 30-day postoperative morbidity and mortality rates were 43.1% and 43.9%, respectively. Twenty-two patients died within 30 days of receiving HIPEC. Adverse events included wound infection, hematologic toxicity, sepsis, respiratory failure, anastomotic leak, pneumonia, and enterocutaneous fistula.

Yan et al. (2007) conducted a systematic review of prospective observational studies (n=7) to assess the efficacy of CS with postoperative intraperitoneal chemotherapy including HIPEC. These studies involved a total of 240 patients diagnosed with diffuse malignant peritoneal mesothelioma (DMPM). The median survival ranged from 34–92 months. The 1-, 2-, 3-, 5- and 7- year survival rates varied from 60% to 88%, 60% to 77%, 43% to 65%, 29% to 59%, and 33% to 39%, respectively. The effectiveness of CS and IPC on overall morbidity rates varied from 25% to 40%. The overall mortality rates ranged from 0% to 8%.

A number of prospective and retrospective case series (Lanuke, et al., 2008; Ceelen, et al., 2008; Elias, et al., 2007; Gusani, et al., 2007; Stewart, et al., 2006; Deraco, et al., 2006; Garofalo, et al., 2006) with sample sizes ranging from 14-122 have evaluated the use of HIPEC the treatment of PC of various origins (e.g., appendiceal, colorectal, gastric, ovarian, mesothelioma). Outcomes have included median survival, adverse events and decrease in malignant ascites. Follow-up has ranged from 1–48 months. It is difficult to draw conclusions as these studies have utilized different treatment regimen, had mixed results, and varying rates of effectiveness for outcome measures.

Professional Societies/Organizations

The National Cancer Institute (NCI) states that intracavitary (intrapleural, intraperitoneal) chemotherapy following resection for the treatment of localized malignant mesothelioma is a treatment option that is currently under evaluation. Additional studies are needed to define the role of intracavitary chemotherapy for the treatment of advanced malignant mesothelioma. The NCI does not address the use of hyperthermic intraperitoneal chemotherapy for the treatment of mesothelioma (NCI [d], 2009).

According to the National Comprehensive Cancer Network (NCCN) practice guidelines for colon and rectal cancers, the treatment of disseminated carcinomatosis with cytoreductive surgery and perioperative hyperthermic intraperitoneal chemotherapy is considered investigational and is not endorsed by the NCCN outside of a clinical trial (NCCN, 2010a; 2010c).

In 2007, the Peritoneal Surface Malignancy Group issued a consensus statement on the use of CS and HIPEC in the management of peritoneal surface malignancies of colonic origin. According to this statement, in a subset of stage IV colon cancer patients with metastatic disease confined to the abdomen and no evidence of hematogenous spread, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy and post-operative systemic chemotherapy has resulted in a median survival of up to 42 months when a complete cytoreduction is achieved. The report further stated that systemic treatment alone is no longer appropriate for patients with limited peritoneal dissemination from a primary or recurrent colon cancer (Esquivel, et al., 2007). This consensus opinion was based on a review of nine observational studies, an international registry and a single phase III randomized study. A 2008 update to this position on the regional treatment of colorectal cancer with peritoneal dissemination states that although some published studies have shown that good long-term results can be achieved with a complete cytoreduction and HIPEC, most of the data are from phase II studies from single institutions. There is also a wide range of inclusion/exclusion criteria, drugs, temperatures and methods of delivering the heated chemotherapy (Esquivel, et al., 2008).

Summary

Studies within the evidence-based peer-reviewed literature have shown that patients diagnosed with pseudomyxoma peritonei (PMP) confined to the abdomen when treated with total cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) demonstrate improved survival outcomes over the use of traditional systemic chemotherapy. Studies on the efficacy of HIPEC as an adjunctive treatment for various types of cancer (e.g., breast, ovarian, gastric, primary peritoneal carcinoma and peritoneal carcinomatosis) have failed to provide guidance for patient selection, dosage, perfusion protocols or timing regimens that could be standardized and safely applied. The effectiveness of intraperitoneal hyperthermic chemotherapy (HIPEC) for these uses has not been shown to improve patient morbidity and mortality rates in comparison to standard surgical resection and debulking, the administration of systemic chemotherapy and adjuvant radiation therapy.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT ^{®*} Codes	Description
77605 [†]	Hyperthermia, externally generated; deep (i.e., heating to depths greater than 4cm)
77620 [†]	Hyperthermia generated by intracavitary probe(s)

96445 [†]	Chemotherapy administration into peritoneal cavity, requiring and including peritoneocentesis
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†Note: Covered when medically necessary when used to report hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of pseudomyxoma peritonei (PMP). This policy does not address the use of hyperthermia when used as an adjunct to radiation therapy. Refer to CIGNA Coverage Policy Hyperthermia for Cancer Treatment for additional information.

ICD-9-CM Diagnosis Codes	Description
197.6 [†]	Secondary malignant neoplasm of retroperitoneum and peritoneum
199.0 [†]	Disseminated malignant neoplasm

†Note: Covered when medically necessary and used to report pseudomyxoma peritonei (PMP)

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
151.0-151.9	Malignant neoplasm of stomach
153.0-153.9	Malignant neoplasm of intestine
158.0- 158.9	Malignant neoplasm of retroperitoneum and peritoneum
159.0	Malignant neoplasm of intestinal tract, part unspecified
159.9	Malignant neoplasm of gastrointestinal tract unspecified
183.0-183.8	Malignant neoplasm of ovary
198.6	Secondary malignant neoplasm of ovary
	All other codes

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	9/15/2008	0396	Intraperitoneal Hyperthermic Chemotherapy (IPHC)

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