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Coverage Policy

Cigna covers hyperthermic intraperitoneal chemotherapy (HIPEC) as medically necessary when used in combination with cytoreductive surgery for EITHER of the following:

- pseudomyxoma peritonei (PMP)
- peritoneal carcinomatosis from gastric or colorectal cancer without distant (i.e. extra-abdominal) metastases

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 hemicolecctomy, 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**

The evidence in the published peer-reviewed medical literature evaluating the safety and effectiveness of HIPEC combined with CS for various indications primarily consists of systematic reviews, observational studies, and comparative case series with prospective and retrospective designs 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 primarily in form of case series supports the relative safety and effectiveness of HIPEC for PMP when compared to other standard treatments (Elias, et al., 2010; 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:** Chua et al. (2013) conducted a systematic review (n=19 studies/2492 patients) of the evidence on treatment outcomes of metastatic CRC to the peritoneum. Patients underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) (n=1084) or palliative surgery and/or systemic chemotherapy (n=1408). For complete cytoreductive surgery HIPEC (n=9 studies/663 patients), the overall survival ranged between 20 and 63 (median 33) months, and five-year survival ranged between 17% and 51% (median 40%). For palliative surgery and/or systemic chemotherapy (n=10 studies/1408 patients), the overall survival ranged between five and 24 (median 12.5) months, and five-year survival ranged between 13% and 22% (median 13%).

A matched case-control study (n=32) by Cashin et al. (2012) compared perioperative (HIPEC) (n=16) and normothermic sequential postoperative intraperitoneal chemotherapy (SPIC) (n=16) with respect to overall survival, disease-free survival, morbidity, and mortality in patients with peritoneal carcinomatosis from colon cancer. Median overall survival was 36.5 months in the HIPEC group and 23.9 months in the SPIC group (p= 0.01). Median disease-free survival for these groups was 22.8 (HIPEC) and 13.0 months (SPIC; p= 0.02). Morbidity was not found to be statistically different, 19% for SPIC patients and 37% in the HIPEC group. Postoperative mortality was observed in one patient in each group. HIPEC was associated with improved overall survival and disease-free survival compared with SPIC at similar morbidity and mortality.
Hompes et al. (2012) conducted a multicentre prospective phase II clinical study (n=48) to evaluate the safety and efficacy of complete cytoreductive surgery with HIPEC/oxaliplatin for patients with peritoneal carcinomatosis from CRC. At median follow-up of 22.7 (range 3.2-55.7) months, OS was 97.9% at one year and 88.7% at two years. Disease free survival at one year was 65.8% and 45.5% at two years. Median time until recurrence was 19.8 months. After dichotomizing PC index was a significant difference in OS found between low and high PC index. Thirty-day mortality was 0% with an overall complication rate of 52.1%. Anastomotic leakage occurred in 10.4% of patients, bleeding in 6.3%, and bowel perforation in 2.1%.

Cashin et al. (2011) conducted a matched case-control study comparing perioperative HIPEC and normothermic sequential postoperative intraperitoneal chemotherapy with respect to overall survival, disease-free survival, morbidity, and mortality in patients (n=36) with peritoneal carcinomatosis from colon cancer. The median follow-up was 38 months. The median overall survival was 36.5 months in the HIPEC group and 23.9 months in the postoperative intraperitoneal chemotherapy group (p=0.01). The median disease-free survival for these groups was 22.8 (HIPEC) and 13.0 months (postoperative intraperitoneal chemotherapy) (p=0.02). Morbidity was not statistically different, 19% for postoperative intraperitoneal chemotherapy patients and 37% in the HIPEC group. Postoperative mortality was reported for one patient in each group. Study results are limited by the small sample size and lack of randomization.

Cavaliere et al. (2011) presented follow-up data on 146 consecutive patients presenting with peritoneal carcinomatosis of colorectal origin treated with CRS and HIPEC. At a minimum follow-up of 24 months, the overall morbidity rate was 27.4% with a mortality rate of 2.7%. Peritoneal cancer index, unfavorable peritoneal sites, synchronous or previously resected liver metastasis and the completeness of cytoreduction were all found to be independent prognostic factors that correlated with survival.

Franko et al. (2010) compared outcomes of patients with colorectal carcinomatosis who received chemotherapy alone (n=38) versus those who underwent CRS combined with HIPEC. Median survival measured from the diagnosis of peritoneal disease was longer with cytoreductive surgery combined with hyperthermic intraperitoneal chemoperfusion (34.7 months versus 16.8 months; p<0.001). Presence of liver metastasis was a significant negative predictor of survival.

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).

A 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 systematic review and meta-analysis (n=16 RCTs/1906 patients) by Mi et al. (2013) assessed the safety and effectiveness of adjuvant HIPEC for patients with resectable locally advanced gastric cancer. Compared with surgery alone, combination therapy (surgery plus HIPEC) was associated with a significant improvement in survival rate at one year (p<0.00001), two years (p<0.00001), three years (p<0.00001), five years (p<0.00001), and nine years (p=0.0007). Compared with surgery alone, combination therapy was associated with a significant reduction in recurrence rate through five years (p<0.00001). HIPEC was not found to be associated with higher risks of complications such as anastomotic leakage, ileus, bowel perforation, and myelosuppression, but was associated with an increased incidence of abdominal pain (p<0.00001). It was concluded that surgery combined with HIPEC may improve survival rate and reduce recurrence rate with acceptable safety compared to surgery alone (Mi, et al., 2013).

Sun et al. (2012) performed a meta-analysis of RCTs (n=10 studies) involving patients (n=1062) with advance gastric cancer, who underwent resection for advanced gastric cancer and were randomly allocated to receive either hyperthermic intraperitoneal chemotherapy or control. In these studies patients were divided into the HIPEC group (n=518) and the control group (n=544). A significant improvement in survival was observed in the HIPEC groups compared to the control group (p=0.0001). Findings indicated that there was a lower peritoneal recurrence rate in the HIPEC group compared to the control group (RR=0.45, 95%CI 0.28-0.72; P=0.001). Results of this meta-analysis suggest that HIPEC may improve the overall survival rate for patients who receive resection for advance gastric cancer and help to prevent peritoneal local recurrence among patients with serosal invasion in gastric cancer (Sun, et al., 2012).

Yang et al. (2011) conducted an RCT (n=68) to evaluate the safety and efficacy of cytoreductive surgery plus HIPEC for the treatment of peritoneal carcinomatosis from gastric cancer. Patients were randomized to receive cytoreductive surgery alone (n=34) or cytoreductive surgery with HIPEC (n=34). The primary end point was overall survival, and the secondary end points were safety profiles. At a median follow-up of 32 months, disease-specific death occurred in 33 of 34 (97.1%) cases in the cytoreductive surgery group and 29 of 34 (85.3%) cases of the cytoreductive surgery plus HIPEC group. The median survival was 6.5 months (95% CI 4.8-8.2 months) in the cytoreductive surgery group and 11.0 months (95% CI 10.0-11.9 months) in the cytoreductive surgery with HIPEC group (p=0.046). Serious adverse events occurred in four patients (11.7%) in the cytoreductive surgery group and five (14.7%) patients in the cytoreductive surgery plus HIPEC group (p=0.839). Study results indicated that patients with metachronous peritoneal carcinomatosis had worse survival than those with synchronous peritoneal carcinomatosis. It was noted that more high quality studies are needed to clarify the value and usefulness of this treatment strategy (Yang, et al., 2011).

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.

Mesothelioma: A systematic review by Baratti et al. (2011) evaluating the clinical management of peritoneal mesothelioma included prospective non-randomized observational case series (n=14 studies/427 patients). Series including either all-type peritoneal mesothelioma or only diffuse malignant peritoneal mesothelioma were selected. All patients underwent either combined treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy or systemic chemotherapy. Perioperative intraperitoneal chemotherapy included HIPEC and/or early postoperative intraperitoneal chemotherapy within seven days from surgery. Study endpoints were patient survival, operative outcomes, or quality of life. Of the 427 patients, 397 underwent cytoreductive surgery with HIPEC (n=289), early postoperative intraperitoneal chemotherapy (n=2), or both (n=106). HIPEC protocols varied widely among the institutions in terms of technique, drugs, carriers, timing, and temperature. The median overall survival ranged from 29.5—92 months, was not reached in three series, and was longer than 100 months in one series. The one-, two-, three-, and five-year overall survival rates varied from 43%—88%, 43%—77%, 43%—70%, and 33%—68%, respectively. In four series, median progression-free survival ranged from 7.2—40 months. Morbidity varied from 20%—41%. Operative death rates ranged from 0%—10.5%. It was noted that despite the clinical results, weak scientific evidence supports cytoreductive surgery and perioperative intraperitoneal chemotherapy, due to the lack of randomized and comparative studies. The available trials differ significantly in surgical interventions and perioperative intraperitoneal chemotherapy protocols. A selection bias for treatment is a possible explanation of the superiority of comprehensive management, other than treatment efficacy, since patients with poor performance status are generally excluded from cytoreductive surgery and perioperative intraperitoneal chemotherapy (Baratti, et al., 2011).

Blackham et al. (2010) compared IPHC with mitomycin (n=19) versus cisplatin (n=15) following cytoreduction in a series of patients with malignant peritoneal mesothelioma. Overall survival was 56% and 17% at three and five years respectively, with a median survival of 40.8 months. Median survival for mitomycin and cisplatin was 10.8 and 40.8 months, respectively (p=0.22). Median disease-free survival and progression-free survival were 10.3 and 9.1 months, respectively.

Baratti et al. (2010) presented a series of patients (n=12) who with multicystic peritoneal mesothelioma who underwent cytoreduction and HIPEC. Median follow-up was 64 months (range 5-148). Five- and ten-year progression-free survival was reported to be 90% and 72% (p= 0.0001).
Chua et al. (2010) identified patients (n=26) from a multi-institutional data registry with multicystic peritoneal mesothelioma treated by cytoreductive surgery and HIPEC. No perioperative mortality was reported. After a median follow-up of 54 (range 5-129) months, all 26 patients were still alive.

Yan et al. (2009) evaluated 401 patients with diffuse malignant peritoneal mesothelioma who were treated with CRS and HIPEC. Of the 401 patients, 372 received HIPEC. The median follow-up period for the patients who were alive was 33 months. The overall median survival was 53 months, with three- and five-year survival rates of 60% and 47%, respectively. Grades three and four complications were reported in 127 patients (31%) with a mortality rate of 2% perioperatively.

Yan et al. (2007) conducted a systematic review of prospective observational studies (n=7) to access 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%.

**Ovarian Cancer:** A retrospective study by Deraco et al. (2012) was conducted evaluating the efficacy of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients (n=56) with recurrent epithelial ovarian cancer. Major complications occurred in 15 patients (26.3%), and procedure-related mortality occurred in three patients (5.3%). The median follow-up time was 23.1 months. The median overall survival and progression-free survival were 25.7 (95% CI 20.3-31.0) and 10.8 (95% CI 5.4-16.2) months, respectively. The five-year overall survival and progression-free survival were 23% and 7%, respectively.

Independent prognostic factors affecting overall survival included preoperative serum albumin and completeness of cytoreduction.

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%.

Bijelic et al. (2007) performed of 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 retrospective, multicenter cohort study (n=1290) by Glehen et al. (2010) evaluated patients with peritoneal carcinomatosis from nonovarian malignancies who were treated with HIPEC and/or early postoperative intraperitoneal chemotherapy. HIPEC was performed in 1154 procedures. The principal origins of disease were colorectal adenocarcinoma (n= 23), pseudomyxoma peritonei (n=301), gastric adenocarcinoma (n= 159), peritoneal mesothelioma (n= 88), and appendiceal adenocarcinoma (n=50). The overall morbidity and mortality rates were 33.6% and 4.1%, respectively. The overall median survival was 34 months. The median survival was 30 months for patients with colorectal peritoneal carcinomatosis, not reached for patients with pseudomyxoma peritonei, nine months for patients with gastric PC, 41 months for patients with peritoneal mesothelioma, and 77 months for patients with PC from appendiceal adenocarcinoma.

A retrospective case series (n=440) by Elias et al. (2010) reported on patients with peritoneal carcinomatosis treated with CRS plus intraperitoneal chemotherapy. Peritoneal dissemination originated from colon (n=341),
rectum (n=27), small bowel (n=31), and nonpseudomyxoma appendix (n=41). The mean follow-up was 60 months. The five-year overall survival rates were not statistically different for the colon (29.7%), rectum (37.9%), nor the small bowel (33.8%), but was higher (p=0.01) for appendix adenocarcinoma (63.2%). Postoperative mortality was 3.9% with a morbidity rate of 31%, and did not differ according to the origin of the primary tumor.

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.

A number of prospective and retrospective case series (Vaira, et al., 2010; Glehen, et al., 2010; 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

According to the National Comprehensive Cancer Network (NCCN) practice guidelines for colon and rectal cancers (i.e., discussion updates in progress), 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, 2014a; 2014b).

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. For advanced malignant mesothelioma, intrapleural or intraperitoneal administration of chemotherapeutic agents (e.g., cisplatin, mitomycin, and cytarabine) has been reported to produce transient reduction in the size of tumor masses and temporary control of effusions in small clinical studies. Additional studies are needed to define the role of intracavitary therapy. The NCI does not address the use of hyperthermic intraperitoneal chemotherapy for the treatment of mesothelioma (NCI [c], 2012).
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

Although not robust, there is some evidence in the published scientific literature supportive of the safety and effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) for a subset of cancer patients with peritoneal involvement. The results of limited randomized controlled trials and multiple systematic reviews, cohort, and matched case-control studies indicate that patients diagnosed with pseudomyxoma peritonei (PMP), or metastatic gastric and colorectal cancers confined to the abdomen demonstrate improved survival outcomes when treated with complete cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) compared to the treatment with traditional systemic chemotherapy alone. Studies on the efficacy of HIPEC as an adjunctive treatment for other types of cancer (e.g., breast, ovarian, primary peritoneal carcinoma) have failed to provide guidance for patient selection, dosage, perfusion protocols or timing regimens that could be standardized and safely applied. The safety and effectiveness of HIPEC for these indications has not been proven, as the available studies have not demonstrated improved 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: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary when used to report hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of pseudomyxoma peritonei (PMP):

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>77605</td>
<td>Hyperthermia, externally generated; deep (i.e., heating to depths greater than 4cm)</td>
</tr>
<tr>
<td>96446</td>
<td>Chemotherapy administration into the peritoneal cavity via indwelling port or catheter</td>
</tr>
<tr>
<td>96549</td>
<td>Unlisted chemotherapy procedure</td>
</tr>
</tbody>
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