Medical Coverage Policy

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Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

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Overview

This Coverage Policy addresses hyperthermic intraperitoneal chemotherapy (HIPEC) for a subset of cancer patients with peritoneal involvement.

Coverage Policy

Hyperthermic intraperitoneal chemotherapy (HIPEC) is considered medically necessary when used in combination with cytoreductive surgery for ANY of the following:

- pseudomyxoma peritonei (PMP)
- peritoneal carcinomatosis from gastric or colorectal cancer without distant (i.e. extra-abdominal) metastases
- malignant peritoneal mesothelioma with metastasis limited to the abdominal cavity
- stage III epithelial ovarian cancer at the time of interval debulking surgery

Hyperthermic intraperitoneal chemotherapy (HIPEC) is considered experimental, investigational or unproven for any other indication.

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 (Bleibel et al., 2016). Specific to malignant peritoneal mesothelioma, a median survival of approximately 12 months has been reported after treatment with standard therapies such as palliative surgery, systemic/intraperitoneal chemotherapy, and abdominal irradiation (Baratti, et al., 2011).

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, the optimal treatment for PMP of appendiceal origin is a right hemicolectomy with aggressive tissue debulking (Wyers, et al., 2016).

Conventional treatment for PC includes extensive surgical resection and tissue debulking (i.e., cytoreduction surgery [CRS]) followed by the administration of chemotherapy or radiation therapy. There are numerous chemolytic agents that can be administered (e.g., mitomycin C [MMC], doxorubicin, cisplatin) 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.

The evidence in the published peer-reviewed medical literature evaluating the safety and effectiveness of HIPEC combined with CRS 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 CRS 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 (Marcotte, et al., 2014; McBride, et al., 2013; Elias, et al., 2010; Elias, et al., 2009; 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 (Wyers, et al., 2016).

Peritoneal Carcinomatosis from Gastric or Colorectal Cancer

Gastric Cancer Literature Review: Desiderio et al. (2017) conducted a meta-analysis of studies comparing hyperthermic intraperitoneal chemotherapy (HIPEC) to standard oncological management for the treatment of advanced stage gastric cancer with and without peritoneal carcinomatosis. A total of 11 randomized controlled trials (RCT's) and 21 Non-RCT's (n=2520) met the inclusion criteria. The criteria included studies that clearly defined the use and the technique of HIPEC delivery following a standard gastrectomy or cytoreduction surgery (CRS). The primary outcome measures were the overall survival rate and overall recurrence rate. Secondary outcomes measured the overall complications rate, rate of complications by type and recurrence rate by site. The overall survival analysis in advanced gastric cancer (AGC) without carcinomatosis showed no significant differences in survival rates between the two groups at 1 year follow-up. A statistically significant difference was found in favor of the HIPEC procedure at the three-year (p=0.03) and five year (p=0.01) follow-up. The overall disease recurrence in patients with AGC without carcinomatosis in the HIPEC group showed a significant advantage versus the control group (p=0.002). There was no difference in the three-year overall survival (p=0.85) but there was a prolonged median survival of four months in favor of the HIPEC group with peritoneal carcinomatosis (PC) (p<0.001). HIPEC was associated with significantly higher risk of complications for both patients with peritoneal carcinomatosis (PC) (p<0.01) and without PC (p<0.01). This increased risk in the HIPEC group was related to systemic drugs toxicity. Anastomotic leakage rates were found to be similar between groups. Author noted limitations were difficulty in applying results in Asia to Western populations along with identifying the role, timing, and impact of adjuvant chemotherapy. The study demonstrated that HIPEC used as a prophylactic strategy offers a survival benefit. The patients whose disease burden is limited to positive cytology and limited nodal involvement may benefit the most from HIPEC. For patients with extensive carcinomatosis, the completeness of cytoreductive surgery is a critical prognostic factor for survival.

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.

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<0.00001). 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.

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.

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).

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).

A number of prospective and retrospective studies (Glehen, et al., 2010; Zhu, et al., 2006; Hall, et al., 2004) with patient populations ranging from 74–159 have evaluated the use of HIPEC during CRS for the treatment of PC from gastric cancer. Outcomes included overall survival rates with morbidity and mortality rates. Follow-ups have ranged from 20–72 months, with overall median survival of 8–9.2 months. Glehen et al. (2010; n=159) reported that the overall survival rates for patients treated with HIPEC at one-, three-, and five-years were 43%, 18%, and 13%, respectively. Zhu et al. (2006; n=118) reported that the survival rates for patients who had HIPEC compared to those without HIPEC at two, four, and six years were 83.03%, 70.48%, 67.87% and 63.69%, 52.11% and 37.74%, respectively.

Colorectal Cancer Literature Review: Chua et al. (2013) conducted a systematic review (n=19 studies/2492 patients) of the evidence on treatment outcomes of metastatic colon rectal cancer (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 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 CRS and HIPEC compared with palliative approach ($p<0.0001$). However, this was based on four studies comparing combined treatment involving CRS 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.

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 CRS 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.

A number of prospective and retrospective case series (Cashin, et al., 2012; Hompes, et al., 2012; Cavaliere, et al., 2011; Franko, et al., 2010; Shen, et al., 2009) with patient populations ranging from 32–506 have evaluated the use of HIPEC during CRS for the treatment of PC from colorectal cancer. Outcomes have included overall

survival rates, median disease-free survival rates with morbidity and mortality rates. Median follow-ups ranged from 22.7–60 months with median overall and progression free survival of 34.7–36.5 months and 19.8–22.8 months, respectively. A five-year overall survival rate of 36% was reported (Shen et al. (2009); n=55). Overall, the data demonstrated that cytoreductive surgery combined with HIPEC was associated with improved overall survival and disease-free survival.

Malignant Peritoneal Mesothelioma

Literature Review: Helm et al. (2014) published their results of a systematic review and meta-analysis (n=20 studies/1047 patients) of the literature on CRS and HIPEC for treating patients with malignant peritoneal mesothelioma (MPM). Articles reviewed included retrospective studies (n=15), clinical trials (n=4), and a single prospective cohort study and were published between 1992 and 2013. The majority of patients (n=625) were from three large retrospective studies (n=405, 116, 104). Studies were also evaluated for inclusion based on the outcome data, including survival, morbidity, mortality, and adverse events. Studies including any other diagnoses in addition to MPM were excluded from the review. Studies not containing both CRS and HIPEC were also excluded. The median age was 51 years with 59% female patients. The majority of patients (n=672, 64%) had epithelioid histology, and the median peritoneal cancer score was 19 (16–23). CRS and HIPEC was performed using both closed and open techniques, and the chemotherapy agents used were most frequently a combination of cisplatin, doxorubicin, and mitomycin (n=742, 71%). Complete cytoreduction (CC0, 1) was performed in 67% (46%-93%) of patients. Meta-regression techniques were used to synthesize data. Pooled estimates of survival yielded a one-, three- and five-year survival of 84%, 59%, and 42%, respectively. Patients receiving early postoperative intraperitoneal chemotherapy (EPIC) (44%) and those receiving cisplatin intraperitoneal chemotherapy alone (48%) or in combination (44%) had an improved five-year survival. The summarized mortality rate for all studies was 0.17. Morbidity was reported between 8.3 and 90% among studies reporting this outcome (n=14/20 studies, 70%). Limitations of this systematic review and meta-analysis include the primarily retrospective design of studies and the acknowledged heterogeneity of treatment regiments used in studies potentially causing variation in outcomes.

Baratti et al. (2013) published their results of a case series (n=108) of diffuse malignant peritoneal mesothelioma (DMPM) patients undergoing complete cytoreduction and closed-abdomen HIPEC with cisplatin and doxorubicin or mitomycin-C. Eligibility criteria for combined treatment included histological diagnosis of DMPM, age < 7, no significant comorbidities or extraperitoneal metastases and peritoneal disease amenable to potentially complete cytoreduction. Primary study end-points were overall survival (OS) and progression-free survival (PFS). OS and PFS were dated from the day of cytoreduction with HIPEC to the date of death for any cause or first recurrence, respectively. A total of 49 patients received systemic chemotherapy preoperatively. In the overall series, median estimated follow-up was 48.8 months (95% confidence interval (CI) = 37.1–60.6). During the study period, disease progression occurred in 52 patients. Median calculated OS was 63.2 months (95%CI = 29.6–96.7); five- and 10-year OS were 52.4% and 44.6%, respectively. Median PFS was 25.1 months (95%CI = 5.1–45.1); five- and 10-year PFS were 38.4% and 35.9%. Statistical analysis indicated that improved OS and PFS correlated with peritoneal cancer score < 17 and epithelial histology. Operative mortality occurred in two patients (1.9%). The most common complication was anastomotic leakage/bowel perforation, which occurred in 14 patients (12.9%), followed by respiratory morbidity (n=10, 9.2%), and sepsis (n=6, 5.5%).

Alexander et al. (2013) reported an analysis of factors associated with long-term outcome in a case series of patients (n=211) with malignant peritoneal mesothelioma who underwent CRS and HIPEC between January 1992 and 2010. The primary objective of the analysis was to identify factors associated with progression free survival (PFS) and overall survival (OS). Follow-up data for five and 10 years were reported. Approximately 60% of the 211 patients were female and the median age was 52 years. The number of patients treated with cisplatin versus mitomycin C was almost equal. Approximately 50% of patients had a complete or near complete cytoreduction (CCR ≤ 1). The calculated median overall survival was 38.4 months with five- and 10-year survival rates of 41% and 26%, respectively. Of the 211 patients 30% had at least one complication. The operative mortality rate was 2.3%. An unplanned return to the surgery occurred in 9.4%.Factors found to be independently associated with favorable outcome were younger age <60 years ($p<0.01$), complete or near complete (R0-1) versus incomplete (R2-3) resection ($p<0.02$), low versus high histologic grade ($p<0.01$), and the use of cisplatin versus mitomycin-C during HIPEC ($p<0.01$). Study results are limited by the retrospective uncontrolled design and unclear reporting of patient populations over the entire follow-up period.

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 end-points 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).

Yan et al. (2009) evaluated 401 patients with diffuse malignant peritoneal mesothelioma who were treated with CRS and HIPEC between October 1989 and February 2009. The exclusion criteria were peritoneal mesothelioma secondary to pleural mesothelioma and extraabdominal metastasis preoperatively. 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 mortality rate of 2% perioperatively. Study limitations include a nonrandomized, uncontrolled design.

Yan et al. (2007a) conducted a systematic review of prospective observational studies (n=7) to access the efficacy of CRS 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 one-, two-, three-, five- and seven- 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 CRS 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 (Magge, et al., 2014; Chua, et al., 2011; Blackham, et al., 2010; Baratti et al., 2010; Deraco, et al., 2003) with patient populations ranging from 12–65 have evaluated the use of HIPEC the treatment of malignant peritoneal mesothelioma. Outcomes have included overall and progression-free survival with morbidity and mortality rates. Follow-up has ranged from 20–64 months, with overall and progression free survival of 40.8–46.2 months and 9.1–13.9 months, respectively. Five-year overall survival rates of 54% (Deraco et al. [2003]/n=61 patients) and 90% (Baratti et al. [2010]/n=12 patients) have been reported. Prognostic factors have included ability to achieve adequate surgical cytoreduction, histology and disease burden. Studies have reported major postoperative complication rates of 23%–35% and a range in mortality rate of 0%–6%.

In general, there are limitations to the evidence for CRS and HIPEC treatment of peritoneal mesothelioma. However, the results of available studies indicate that complete CRS with HIPEC may improve survival rates for malignant peritoneal mesothelioma patients without extra-abdominal metastasis.

Ovarian Cancer

Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies, it is the fifth most frequent cause of cancer death in women. Ovarian, fallopian tube, or peritoneal cancer may not cause early signs or symptoms. When signs or symptoms do appear, the cancer is often advanced. Treatment options for all stages of ovarian epithelial cancer, fallopian tube cancer (FTC), and primary peritoneal cancer (PPC) are surgery

followed by platinum-based chemotherapy. Surgery is used to adequately stage the disease and includes total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy and debulking of as much gross tumor as can safely be performed (National Cancer Institute [NCI], 2019). Primary debulking surgery (PDS) is the recommended approach for advanced-stage disease if the patient is a surgical candidate, optimal cytoreduction appears feasible, and fertility is not a concern.

For patients with advanced stage ovarian cancer who are not good candidates for PDS due to advanced age, frailty, poor performance status, comorbidities, or disease that is unlikely to be optimally cytoreduced, neoadjuvant chemotherapy (NACT) with interval debulking surgery (IDS) can be considered. If the patient has stage III ovarian cancer, HIPEC can be considered as an option at the time of interval debulking surgery (National Comprehensive Cancer Network [NCCN], 2019d).

Literature Review: A Hayes Medical Technology Assessment evaluated the evidence (n=11 studies) on the efficacy and safety of cytoreductive surgery (CRS) plus HIPC compared with cytoreductive surgery (CRS) alone for peritoneal carcinomatosis (PC) due to ovarian cancer (OC). The review included two randomized controlled trials (RCTs), one prospective cohort study, and eight retrospective cohort studies. Study sample sizes ranged from 42–245 patients with follow-up ranging from 18–58.7 months. The measured outcomes were overall survival (nine studies), disease-free survival (seven studies), quality of life (one study) and complications (seven studies). A low-quality body of evidence suggests that CRS plus HIPC may be more effective than CRS alone in improving OS in patients with OC (eight of nine studies). The evidence regarding the impact of CRS plus HIPC on PFS generally suggests more favorable outcomes for patients who received HIPC plus CRS than those who received CRS alone; however, some studies did not report the statistical significance of the findings and some studies may have been statistically underpowered to detect differences. Only one study assessed QOL. Hayes reported that the current evidence suggests that the rate of major complications is high (up to 34.5%); however, these rates are likely due to CRS rather than HIPC. The most common major complications attributable to HIPC include hematological toxicity and renal insufficiency/failure, occurring in ≤ 20% of patients. Hayes concluded that HIPC plus CRS appears to provide additional benefit with respect to overall survival, and possibly progression-free survival, compared with CRS alone. There is potential benefit of this treatment relative to the risk of harm, given the high likelihood of disease-related mortality in this patient population (Hayes, 2019).

van Driel et al. (2018) conducted a randomized, multicenter, open-label, phase three trial (OVHIPEC), assessing the efficacy and safety of interval cytoreductive surgery with HIPEC compared to interval cytoreductive surgery without HIPEC. The study included patients (n=245) with newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer and were referred for neoadjuvant chemotherapy because their abdominal disease was too extensive for primary cytoreductive surgery or because previous surgery had been performed but was incomplete. At the time of surgery, patients were randomized into two groups using a 1:1 ratio into the surgery-plus-HIPEC group (n=122) or the surgery group (n=123). The primary end point was recurrence-free survival, which was the time from randomization to disease recurrence/progression or death from any cause, whichever occurred first. Secondary end points included overall survival, the side-effect profile, and health-related quality of life. Physical examinations and measurement of the serum cancer antigen 125 (CA-125) level were repeated every three months for two years and then every six months until five years after the completion of chemotherapy. Computed tomography was performed at one, six, 12, and 24 months after the last cycle of chemotherapy. Patients completed health-related quality-of-life questionnaires within the two weeks before randomization, prior to the fourth cycle of chemotherapy, one week after completion of chemotherapy, and during follow-up at three, six, nine, 12, 15, 18, 21, and 24 months. In the intention-to-treat analysis, 110/123 patients (89%) in the surgery group and 99/122 patients (81%) in the surgery plus- HIPEC group had a clinically significant disease recurrence or death (p=0.003). The median recurrence-free survival was 3.5 months longer in the group that underwent cytoreduction surgery with HIPEC than in the group that underwent surgery alone (14.2 months vs. 10.7 months). The probability of recurrence free survival at three years was 8% in the surgery group and 17% in the surgery plus- HIPEC group. A total of 76/123 patients (62%) in the surgery group and 61/122 (50%) patients in the surgery-plus-HIPEC group died (p=0.02). The probability of overall survival at three years was 48% in the surgery group and 62% in the surgery-plus-HIPEC group. There were no significant differences between the two groups in regards to adverse events of any grade, postoperative complications, and health-related quality-of-life outcomes. The authors indicated the estimated rate of recurrence would have been lower and median recurrence free survival might have been greater if the primary end point had been based on clinical symptoms rather than on measurement of the CA-125 level. Also, due to the severity of illness of the trial

participants in this study, the survival in the control group was shorter when compared to previous studies. Additional trials are needed to validate the outcomes of this study.

In 2019, Koole et al. published the results of a secondary outcome that was measured during the randomized phase III trial (OVHIPEC) that was previously published by van Driel, et al. in 2018. Koole et al. evaluated the effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on patient's health-related quality of life (HRQoL). HRQoL questionnaires were administered at baseline, after surgery, after end of treatment, and every three months thereafter.Of the 245 patients that were randomized, 197 patients (80%) completed at least one questionnaire. No significant difference over time in the HRQoL summary scores was observed between the two groups ($p>0.133$). Additionally, the pattern over time for fatigue, neuropathy and gastro-intestinal symptoms did not significantly differ between treatment arms. The authors concluded that the addition of HIPEC to interval CRS does not negatively impact HRQoL in patients with stage III ovarian cancer who are treated with interval CRS due to the extent of disease.

Mendivil et al. (2017) reported results of a cohort study that compared survival rates of advanced stage ovarian cancer patients who were treated with primary induction therapy alone (n=69) or in conjunction with consolidation HIPEC (n=69). Subjects in group A underwent CRS with intravenous chemotherapy and HIPEC while those who comprised the historical control, group B, were treated with CRS and intravenous chemotherapy alone. Patients were selected for HIPEC administration who had adequate bone marrow, renal and hepatic function, and blood coagulation parameters within normal limits. Candidates also had to have attained an Eastern Cooperative Oncology Group performance status 0–2. Exclusion criteria were low grade or non-invasive disease, a non-ovarian malignancy or evidence of another cancer within the past three years, active systemic infection, history of acute coronary syndromes within the last six months, uncontrolled hypertension, history of cerebral artery disease and prior stroke, or a life expectancy of < 12 weeks. Outcomes included progression-free and overall survival rates. The median follow-up was 36 months (range 7–49) for the group A patients and 44 months (range 6–78) for the group B subjects. The mean progression-free survival for group A patients was 25.1 months, compared to 20.0 months in group B subjects ($p=0.024$). Additional statistical analysis incorporating maintenance therapy, disease stage and histology, surgery, and the inclusion of HIPEC treatment revealed a significantly decreased risk for disease progression in the patients treated with HIPEC ($p=0.0027$). For overall survival, 82.6% of patients in Group A and 75.3% in Group B ($p=0.29$) were alive at the conclusion of the study. The mean overall survival for the subjects in group A was 33.8 months, and 33.6 months in group B ($p=0.947$), a difference that was not statistically significant. In terms of adverse effects, a total of 20 patients developed grade ≤ 2 nausea on postoperative day. In addition, there were 22 patients in Group A who had grade ≤ 2 anemia and 24 subjects who experienced grade ≤ 2 thrombocytopenia and neutropenia. Overall toxicity for HIPEC patients was reported to be relatively mild and easily managed. Acknowledged study limitations include the retrospective evaluation and selection bias that may have impacted outcomes. It was concluded that although these results suggest that the inclusion of consolidation HIPEC in the advanced ovarian cancer treatment regimen may be associated with a decreased risk of disease progression, additional investigation is needed to further define the role of consolidation HIPEC in the management of ovarian cancer.

Huo et al. (2015) performed a systematic review and meta-analysis (n=37 studies) to evaluate the safety and efficacy of HIPEC with CRS for epithelial ovarian carcinoma (EOC). The review included comparative studies (n=9) which consisted of a single RCT, and cohort studies (n=28) that examined HIPEC plus 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 EOC. 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 benefit of HIPEC with CRS was reported to continue through eight year survival. Pooled analysis of all studies showed the following:

- primary EOC: median, one-, three-, and five-year OS rates were 46.1 months, 88.2%, 62.7% and 51%, respectively
- recurrent EOC: median, one-, three-, and five-year- OS rates were 34.9 months, 88.6%, 64.8% and 46.3%, respectively
- pooled median 30-day post-HIPEC mortality rate for primary and recurrent EOC was 1.8% (range: 0.7.1%) and 1.8% (range: 0–13.6%), respectively

- pooled rate of major morbidities for primary and recurrent EOC was 31.3% (range: 1.8–55.6%) and 26.2% (1.8-55.6%), respectively

In addition to limitations which include a lack of RCTs and small patient populations in available studies, the authors note limitations of varying eligibility criteria and minimal reporting of DFS in studies. It was concluded that although data suggest the addition of HIPEC to CRS and chemotherapy improves OS rates for EOC, ongoing RCTs will further clarify the role of HIPEC for patients with EOC.

Chiva et al. (2015) performed a systematic review of the evidence on CRS/HIPEC for treatment of primary advanced (n=11 studies/248 patients) and recurrent ovarian cancer (n=8 studies/499 patients) with a focus on survival outcomes. Studies were included in which patients who were treated with neoadjuvant chemotherapy. Excluded studies were those without information about either the disease-free interval (DFI) or the overall survival. Average follow-up was 32 months for the advanced group and 30 months for the recurrent group. Complete cytoreduction or minimal residual disease was achieved in primary and recurrent groups, 88% and 93% respectively. The severity of the disease measured with the PCI index was higher in the primary than in the recurrent group (14.5 versus 9.8). The weighted median overall survival for primary ovarian cancer patients treated with CRS and HIPEC was 37.3 months (range 27–78), the median disease-free survival was 14.4 months (range 12–30) and the five-year survival rate was 40% (range 28–72). Severe morbidity was higher in the recurrent group (19 versus 25%), with similar mortality rates. For the recurrent group, the overall survival after HIPEC was 36.5 months (range 23–62), and the median disease-free survival was 20.2 months (range 11–24). The authors describe these survival results for primary ovarian cancer as modest compared to studies that have evaluated standard treatment approaches. Acknowledged limitations of the reviewed evidence include the retrospective design of studies and the overall heterogeneity in terms of patient selection criteria, chemotherapeutic regimens, and time of administration. According to the authors, “this review has failed to show a clear survival benefit that justifies the use this technique as a standard daily practice”.

Spiliotis et al. (2015) published results of an RCT (n=120) of women with advanced recurrent EOC after initial treatment with CRS or debulking surgery and systemic chemotherapy. Exclusion criteria included pleural disease or lung metastasis; more than three sites of bowel obstruction; and evidence of bulking disease in retroperitoneal area or on the mesentery. The inclusion criteria were women between ages 18 and 70 years; Gynecologic Oncology Group performance status one or two; no evidence of disease beyond the abdomen; and no visceral metastasis. Patients were randomized to receive CRS followed by HIPEC and subsequent systemic chemotherapy (n=60) or CRS followed by systemic chemotherapy (n=60). The primary outcome was mean overall survival depending on factors such as disease stage, completeness of cytoreduction, and peritoneal cancer index (PCI). The mean overall survival in the HIPEC group was 26.7 versus 13.4 months in the non-HIPEC group, a difference that was statistically significant (p=0.006). Completeness of cytoreduction and PCI score (≤ 15) were found to be associated with survival. Treatment-related morbidity and mortality were not reported.

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 EOC. 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 CRS 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.

Similar overall survival rates have been reported in a number of prospective and retrospective studies and comparative studies with patient populations ranging from 47–511 and a follow-up range of 24–65 months (Ceresoli, et al., 2018; Di Giorgio, et al., 2017; Di Giorgio, et al., 2008; Bae, et al., 2007; Cotte, et al., 2007). Several clinical trials are currently underway evaluating HIPEC for different stages of ovarian cancer.

Peritoneal Cancer

Literature Review: 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 CRS 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., 2009; Ceelen, et al., 2008; Elias, et al., 2007; Gusani, et al., 2008; 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 for 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

American Society of Colon and Rectal Surgeons (ASCRS): The ASCRS published clinical practice guidelines for the treatment of colon cancer (Vogel et al., 2017). The treatment of patients with a diagnosis of colon cancer is guided by the stage at presentation with surgery being the primary form of treatment with chemotherapy in the adjuvant setting. Peritoneal carcinomatosis is most often one of multiple sites of metastatic cancer from colorectal cancer. 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.

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. HIPEC is being applied to ovarian cancers, with considerable variation in patient selection, drugs administered, and time at target temperatures. According to the NCI, while exploratory trials are ongoing in the setting of recurrent ovarian cancer, such modalities should not be used as a substitute for intraperitoneal cisplatin-based regimens following initial therapy. The role of HIPEC remains experimental in the treatment of patients with high-grade serous ovarian cancers (NCI, 2019).

The NCI stated that a number of clinical trials have studied hyperthermia in combination with radiation therapy and/or chemotherapy. These studies have focused on the treatment of many types of cancer (e.g., rectum, liver, appendix, cervix, peritoneal lining [mesothelioma]). NCI further stated that many of these studies, but not all, have shown a significant reduction in tumor size when hyperthermia is combined with other treatments.

However, not all studies have shown increased survival in patients receiving the combined treatments (NCI, 2011).

National Comprehensive Cancer Network (NCCN): According to the NCCN practice guidelines for colon cancer, complete CRS and/or HIPEC can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved (NCCN, 2019a). The NCCN expressed a need for RCTs to address the risks and benefits associated with these modalities.

The NCCN practice guidelines for ovarian cancer stated for that for stage III disease, HIPEC with cisplatin (100mg/m^2) can be considered at the time of interval debulking surgery (IDS) (NCCN, 2019d).

Peritoneal Surface Malignancy Group (PSMG): The PSMG issued a consensus statement on the use of CRS 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).

Centers for Medicare & Medicaid Services (CMS):

- National Coverage Determinations (NCDs): Hyperthermia for Treatment of Cancer (110.1). Effective date 12/31/1984. The Coverage Policy is broader in scope than the NCD. Refer to the CMS NCD table of contents link in the reference section.
- Local Coverage Determinations (LCDs): No Local Coverage Determinations found.

Use Outside of the US

A guideline on the management of epithelial cancer of the ovary, fallopian tube, and primary peritoneum issued by the French research group for oncologic gynecologic surgery (FRANCOGYN), the French national college of gynecologists and obstetricians (CNGOF), the French society of gynecologic oncology (SFOG), the national investigators' group for studies in ovarian and breast cancer (GINECO-ARCAGY), and endorsed by national cancer institute (INCa) stated that hyperthermic intraperitoneal chemotherapy (HIPEC) can be offered following three cycles of intravenous (IV) chemotherapy and after complete interval surgery for stage III disease and (Lavoue, et al., 2019).

Alberta Health Services published a clinical practice guideline in 2018 for metastatic colorectal cancer. The guideline stated that cytoreductive surgery and heated intra-peritoneal chemotherapy can be considered for limited intra-peritoneal metastases. Treatment would require involvement of a multidisciplinary team that should include a hepatobiliary surgeon, thoracic surgeon, and a surgical oncologist (Alberta Health Services, 2018).

An expert consensus on CRS plus HIPEC was published by Li et al. (2016) under the framework of the China Anti-Cancer Association. The consensus report systematically evaluated the CRS plus HIPEC procedures to lay the foundation for formulating PC treatment guidelines specific to the national conditions of China. HIPEC is recommended as the treatment of choice for PC originating from abdominopelvic tumors, such as gastric cancer, colorectal cancer, appendiceal cancer, ovarian cancer, primary peritoneal cancer and peritoneal mesothelioma, for patients who meet the following criteria:

- primary tumor can be radically resected or optimal CRS can be achieved
- absence of widespread systemic metastases
- age 20–75 years

- Karnofsky performance status scale > 70
- positive free cancer cells in ascites or abdominal lavage solution
- peritoneal metastasis with peritoneal cancer index (PCI) < 20
- patients with high risk of peritoneal dissemination (e.g., tumor perforation, complete bowl obstruction, tumor invading the serosa layer or adjacent organs)

According to the report, contraindications to undergoing CRS plus HIPEC include any lung, liver, brain or bone metastasis, or prominent retroperitoneal lymph node metastasis during preoperative assessment and moderate/severe contraction of mesentery (Li, et al., 2016).

A 2010 guidance issued by the National Institute for Clinical Excellence (NICE) states that the "current evidence on the efficacy of CRS 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, 2010).

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) as outlined in the Coverage Policy section:

CPT®* Codes	Description
77605	Hyperthermia, externally generated; deep (ie, heating to depths greater than 4 cm)
96446	Chemotherapy administration into the peritoneal cavity via indwelling port or catheter
96549	Unlisted chemotherapy procedure

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