

INTRAOPERATIVE HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

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[Instructions for Use](#) ⓘ

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COVERAGE RATIONALE

See [Benefit Considerations](#) ⓘ

Note: This Medical Policy does not apply to normothermic (no hyperthermia is used) postoperative intraperitoneal chemotherapy, delivered via an indwelling port or catheter, used to treat ovarian cancer.

When performed in conjunction with Cytoreductive Surgery (CRS), intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is proven and medically necessary for treating the following conditions:

- Peritoneal mesothelioma
- Pseudomyxoma Peritonei (PMP) resulting from a mucus-producing tumor
- Peritoneal Carcinomatosis resulting from the following cancers, provided there are no extra-abdominal metastases:
 - Colon
 - Rectum
 - Small bowel
 - Adenocarcinoma of the appendix

Due to insufficient evidence of efficacy, intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is unproven and not medically necessary for all other indications, including, but not limited to, peritoneal Carcinomatosis resulting from the following cancers:

- Gastric
- Ovarian

DEFINITIONS

Carcinomatosis: A condition in which multiple tumors develop simultaneously, usually after dissemination from a primary source (Merriam-Webster). Peritoneal Carcinomatosis occurs on the surface of the peritoneum.

Cytoreductive Surgery (CRS)/Debulking: Surgery to remove as much tumor as possible. Optimal cytoreduction is generally considered the removal of all tumors greater than 1 cm for ovarian cancer (Whitney and Spirtos, 2009) and greater than 2.5 mm for other forms of malignancy (Jacquet and Sugarbaker, 1996).

HIPEC: Hyperthermic intraperitoneal chemotherapy.

Intraperitoneal: Within the Peritoneum.

Peritoneum: Tissue that lines the abdomen and organs in the abdomen.

Pseudomyxoma Peritonei (PMP): A rare disease characterized by slowly progressive tumors that spread throughout the peritoneal cavity producing large amounts of mucus (mucinous ascites). The tumors result from the rupture of a mucus-producing neoplasm (adenoma or adenocarcinoma) that typically arises from the appendix or bowel.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

Coding Clarification: CPT codes 49418 and 96446 do not apply to intraoperative hyperthermic intraperitoneal chemotherapy. These codes represent procedures typically done postoperatively via an indwelling port or catheter.

CPT Code	Description
96549	Unlisted chemotherapy procedure

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DESCRIPTION OF SERVICES

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a treatment used immediately following cytoreductive surgery for treating some cancers that have spread into the peritoneal cavity. Following surgery to remove as much of the tumor as possible, a solution of heated chemotherapy drugs is pumped into the abdomen to target any cancer cells that remain. Because the drugs are confined to the peritoneal cavity, a much higher concentration of chemotherapy can be used, minimizing adverse effects. Heating the drugs prior to administration is thought to enhance the therapeutic effect of the drugs. This method is often referred to as the Sugarbaker technique, named after the developer and advocate of this procedure.

BENEFIT CONSIDERATIONS

Some benefit documents allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for these services.

Depending on the member specific benefit plan document, coverage for some procedures may be available through participation in an eligible clinical trial.

CLINICAL EVIDENCE

Glehen et al. (2010a) conducted a retrospective, multicenter cohort study to evaluate toxicity and prognostic factors after CRS and HIPEC and/or early postoperative intraperitoneal chemotherapy (EPIC) for peritoneal carcinomatosis from nongynecologic malignancies. The study included 1290 patients from 25 institutions who underwent 1344 procedures. HIPEC was performed in 1154 procedures. The principal origins of peritoneal carcinomatosis were colorectal adenocarcinoma (n=523), PMP (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 cancer, not reached for patients with PMP, 9 months for patients with gastric cancer, 41 months for patients with peritoneal mesothelioma and 77 months for patients with appendiceal adenocarcinoma. Patient age, extent of disease and institutional experience had a significant influence on toxicity. Prognostic indicators were institutional experience, origin of peritoneal carcinomatosis, completeness of CRS, extent of disease and lymph node involvement.

A National Institute for Health and Care Excellence (NICE) guideline concludes that current evidence on the efficacy of CRS followed by HIPEC for peritoneal carcinomatosis 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 which need to be balanced against the perceived benefit for each patient. This procedure should only be used with special arrangements for clinical governance, consent and audit or research. NICE encourages further research in the form of randomized controlled trials with clear descriptions of patient selection

criteria and the types of cancer being treated. The chemotherapy regimens used should be well defined and outcome measures should include survival and quality of life (NICE, 2010).

Peritoneal Mesothelioma

Due to the rare nature of peritoneal mesothelioma, no randomized controlled trials comparing HIPEC to standard treatment protocols were identified in the clinical literature. However, results from observational studies suggest that HIPEC, in combination with CRS, improves survival when compared to standard treatment options.

Helm et al. (2015) performed a systematic review and meta-analysis of the literature evaluating CRS and HIPEC for treating malignant peritoneal mesothelioma. Twenty studies reporting on 1,047 patients were included in the analysis. Complete cytoreduction was performed in 67% of patients. Pooled estimates of survival yielded a 1-, 3- and 5-year survival of 84, 59 and 42%, respectively. Patients receiving EPIC and those receiving cisplatin intraperitoneal chemotherapy alone or in combination had an improved 5-year survival.

From a prospective database, Baratti et al. (2013) selected 108 patients with diffuse malignant peritoneal mesothelioma (DMPM) undergoing complete cytoreduction and closed-abdomen HIPEC. Operative mortality was 1.9% and major morbidity 38.9%. Median follow-up was 48.8 months. Median overall (OS) and progression-free (PFS) survival were 63.2 months and 25.1 months, respectively. The survival curve reached a plateau after 7 years, representing 19 survivors of 39 patients (43.6%) with potential follow-up ≥ 7 years. Prognostic markers were mostly positive. Epithelial histological subtype, negative lymph-nodes and low Ki-67 markers correlated with both increased OS and PFS. The authors concluded that after complete cytoreduction and HIPEC, prognosis of DMPM is primarily dependent on pathologic and biologic features. Patients with DMPM surviving ≥ 7 years appeared to be cured. Cure rate was 43.6%.

Using a multicenter data registry, Chua et al. (2011b) identified 26 patients with multicystic peritoneal mesothelioma treated by CRS and HIPEC. The primary endpoint was overall survival. A secondary endpoint was the incidence of treatment-related complications. There was no perioperative mortality. Six patients developed grade III or IV complications. After a median follow-up of 54 (range 5-129) months, all 26 patients were still alive.

Blackham et al. (2010) compared outcomes of HIPEC using mitomycin (n=19) versus cisplatin (n=15) following CRS in 34 patients with malignant peritoneal mesothelioma (MPM). Overall survival was 56% and 17% at 3 and 5 years, respectively. Patients receiving cisplatin were more likely to be alive at 1, 2 and 3 years. Median survival for mitomycin and cisplatin was 10.8 and 40.8 months, respectively. Median disease-free survival and progression-free survival were 10.3 and 9.1 months, respectively.

Baratti et al. (2010) performed a retrospective analysis of 12 patients with multicystic peritoneal mesothelioma (MCPM) who underwent CRS and HIPEC. Nine patients had recurrent disease after previous debulking surgery. Median follow-up was 64 months (range 5-148). Optimal cytoreduction was performed in all the procedures. One grade IV postoperative complication and no operative deaths occurred. Five- and ten-year progression-free survival was 90% and 72%.

A multicenter registry evaluated CRS combined with HIPEC for diffuse, malignant, peritoneal mesothelioma. Among 401 patients, 187 (46%) had complete or near-complete cytoreduction, and 372 (92%) received HIPEC. The median follow-up period was 33 months. One hundred twenty-seven patients (31%) had grades 3 to 4 complications. Nine patients (2%) died perioperatively. The mean length of hospital stay was 22 days. The overall median survival was 53 months, and 3- and 5-year survival rates were 60% and 47%, respectively. Four prognostic factors were independently associated with improved survival in the multivariate analysis: epithelial subtype, absence of lymph node metastasis, completeness of cytoreduction scores of CC-0 or CC-1 and receipt of HIPEC. The authors reported that these results suggest that CRS combined with HIPEC achieved prolonged survival in selected patients with diffuse malignant peritoneal mesothelioma (Yan et al., 2009).

Yan et al. (2007a) conducted a systematic review to assess the efficacy of CRS combined with perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma (DMPM). Seven prospective observational studies, involving 240 patients, were included. The median survival ranged from 34-92 months. The 1-, 3- and 5-year survival varied from 60% to 88%, 43% to 65% and 29% to 59%, respectively. The perioperative morbidity varied from 25% to 40% and mortality ranged from 0% to 8%. The authors reported improved overall survival when compared to historical controls.

NCCN clinical practice guidelines for malignant pleural mesothelioma have limited information on peritoneal mesothelioma. However, the guidelines do state that although intraoperative adjuvant therapy, such as heated chemotherapy, is still under investigation, it may be considered as part of a reasonable multidisciplinary approach to locally aggressive disease (NCCN, 2018).

Pseudomyxoma Peritonei (PMP)

Due to the rare nature of PMP, no randomized controlled trials comparing HIPEC to standard treatment protocols were identified in the clinical literature. Although the evidence is limited in quality, results from retrospective case series suggest that HIPEC, in combination with CRS, is safe and effective for PMP when compared to standard treatment options.

Shaib et al. (2015) evaluated the impact of HIPEC after CRS on survival in patients with appendiceal mucinous neoplasms (AMN). Patient data were collected from three tertiary care centers: Emory University, Ohio State University and Wayne State University. One of the three centers did not use HIPEC. Between 1990 and 2010, 163 AMN patients were identified. Histology showed 60 patients had diffuse peritoneal adenomucinosis, 88 had peritoneal mucinous carcinomatosis (PMCA) and 15 had PMCA with indeterminate or discordant features. Complete surgical resection was achieved in 76 patients. HIPEC was used in 79 patients. The median overall survival was 77 months for patients who received HIPEC compared with 25 months for patients who did not. Histopathologic subtype, complete surgical resection and HIPEC were independent predictors for improved overall survival.

A systematic review and meta-analysis by McBride et al. (2013) reported improved survival in patients with PMP of appendiceal origin receiving intraperitoneal chemotherapy with CRS. Twenty-nine studies were identified, with 15 studies from different treatment centers that were specifically analyzed for differences in 5-year mortality and morbidity. Observed to expected (OE) ratios were calculated for both mortality and morbidity. Mean and median 3-year, 5-year and 10-year survival rates were 77.18%/77.85%, 76.63%/79.5% and 57.3%/55.9%, respectively. Data analyses indicated that, despite differences in treatment regimens (use of HIPEC, duration of therapy, type of chemotherapy agent, size of the studies and experience of the centers, etc.), there was not much of a difference in mortality and morbidity between the different centers. Survival was improved regardless of treatment modality. Although this treatment strategy is associated with an increased risk of morbidity, the increase in survival may be acceptable in proposing an alternative to debulking procedures alone. Additional research into chemotherapy regimens and patient selection could help demonstrate further ways to improve survival and reduce morbidity for this disease.

Chua et al. (2012) evaluated outcome and long-term survival after CRS and HIPEC in patients with PMP of appendiceal origin. The international, multicenter registry study included 2,298 patients from 16 specialized units. Treatment-related mortality was 2% and major operative complications occurred in 24% of patients. The median survival rate was 196 months (16.3 years) and the median progression-free survival rate was 98 months (8.2 years), with 10- and 15-year survival rates of 63% and 59%, respectively. Multivariate analysis identified prior chemotherapy treatment, pathological subtype peritoneal mucinous carcinomatosis (PMCA), major postoperative complications, high peritoneal cancer index, debulking surgery (completeness of cytoreduction, 2 or 3) and not using HIPEC as independent predictors for a poorer progression-free survival. Older age, major postoperative complications, debulking surgery (CCR 2 or 3), prior chemotherapy treatment and pathological subtype PMCA were independent predictors of a poorer overall survival. The authors noted that minimizing nondefinitive operative and systemic chemotherapy treatments before cytoreduction may improve outcomes. Optimal cytoreduction achieves the best outcomes.

A systematic review by Yan et al. (2007b) assessed the efficacy of CRS combined with HIPEC for patients with PMP. Ten studies showed 5-year survival ranging from 52-96%. The overall morbidity rate varied from 33 to 56%. The overall mortality rates ranged from 0 to 18%. Five studies were relatively large series (n≥100). Two studies had relatively long-term follow-up (48 and 52 months). The median follow-up in the remaining studies was shorter than 3 years. The authors concluded that the observational studies available for evaluation demonstrated promising long-term results. Due to the rarity of the disease, further well-designed prospective multicenter studies would be beneficial.

In a 10-year prospective single center study, Murphy et al. (2007) evaluated 123 consecutive patients who underwent CRS for PMP. Complete cytoreduction was achieved in 67% of patients who went on to receive HIPEC. Of the patients who had complete tumor removal, the 5-year disease free survival was 75%. Postoperative mortality was 5%.

Several retrospective studies reported improved survival and noted surgeon experience, extent of disease and complete cytoreduction as significant prognostic factors (Elias et al., 2010b; Baratti et al., 2008; Smeenk et al., 2007).

A NICE guideline concludes that current evidence on the safety and efficacy of complete cytoreduction for PMP does not appear adequate for this procedure. The procedure has considerable risk of serious side effects and efficacy has not been clearly established. NICE considers complete cytoreduction for peritoneal carcinomatosis in a separate report (NICE, 2004).

Peritoneal Carcinomatosis Resulting from Colorectal Cancer

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

Mirnezami et al. (2014a) conducted a meta-analysis comparing outcomes following CRS and HIPEC to systemic chemotherapy alone in patients with colorectal peritoneal metastases. Four studies provided comparative survival data for patients undergoing CRS and HIPEC (n=187) versus systemic chemotherapy (n=155). Pooled analysis demonstrated superior 2-year and 5-year survival with CRS and HIPEC compared with systemic chemotherapy.

Two earlier meta-analyses reported improved survival in colorectal cancer patients treated with CRS combined with HIPEC (Cao et al., 2009; Shen et al., 2009).

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

A 2006 systematic review by Yan et al. (2006) evaluated the efficacy of CRS combined with HIPEC for patients with peritoneal carcinomatosis from colorectal carcinoma. Two randomized controlled trials, one comparative study, one multicenter registry study and 10 case-series studies were evaluated. The level of evidence was low in 13 of the 14 eligible studies. The median survival varied from 13 to 29 months, and 5-year survival rates ranged from 11% to 19%. Patients who received complete cytoreduction benefited most, with median survival varying from 28 to 60 months and 5-year survival ranging from 22% to 49%. The overall morbidity rate varied from 23% to 44%, and the mortality rate ranged from 0% to 12%. The authors reported that CRS combined with HIPEC is associated with improved survival, compared with systemic chemotherapy, for peritoneal carcinomatosis from colorectal carcinoma.

Additional systematic reviews of the same studies have been performed (Huang et al., 2017; Waite et al., 2017; van Oudheusden et al., 2015; Mirnezami et al., 2014b; Williams et al., 2013; de Cuba et al., 2013).

Verwaal et al. (2003) performed a randomized controlled trial to confirm findings from earlier uncontrolled studies that aggressive cytoreduction in combination with HIPEC is superior to standard treatment in patients with peritoneal carcinomatosis of colorectal cancer origin. A total of 105 patients were randomly assigned to receive either standard therapy of systemic chemotherapy with or without palliative surgery (n=51), or experimental therapy of aggressive cytoreduction with HIPEC and the same systemic chemotherapy regime (n=51). After a median follow-up period of 21.6 months, the median survival was 12.6 months in the standard therapy arm and 22.3 months in the experimental therapy arm. Treatment-related morbidity was high, and the mortality in the HIPEC group was 8%, mostly related to bowel leakage. Subgroup analysis of the HIPEC group showed that both the extent of disease prior to cytoreduction and the completeness of cytoreduction were predictive of long-term survival. To improve patient selection in the future, additional exploratory analyses were performed to identify potential prognostic factors. Presentation (primary vs. recurrence), site (appendix vs. colon vs. rectum), number of regions involved (less than 5 regions vs. greater than 5 regions) and completeness of cytoreduction were analyzed. The analysis of prognostic factors in the HIPEC arm showed that patients with cancer deposits in six or seven regions of the abdomen do poorly, both in respect to direct postoperative complications and long-term survival. Complete or nearly complete resection seems to be a prerequisite for a favorable outcome.

In 2008, Verwaal et al. published an 8-year follow-up to the previous study. In the standard arm, 4 patients were still alive, 2 with and 2 without disease. In the HIPEC arm, 5 patients were still alive, 2 with and 3 without disease. The median progression-free survival was 7.7 months in the control arm and 12.6 months in the HIPEC arm. The median disease-specific survival was 12.6 months in the control arm and 22.2 months in the HIPEC arm. The 5-year survival was 45% for those patients in whom complete cytoreduction was achieved. The authors concluded that HIPEC does significantly add to survival in patients with peritoneal carcinomatosis from colorectal cancer, with the possibility of long-term survival in selected patients.

Several case-control studies have shown improved survival following CRS and HIPEC for treating peritoneal carcinomatosis resulting from colorectal cancer. Chua et al. (2011a) concluded that modern systemic therapies were associated with improved outcomes in patients with colorectal peritoneal carcinomatosis treated systemically alone or with CRS combined with perioperative intraperitoneal chemotherapy. Franko et al. (2010) reported median survival of 34.7 months in the CRS and HIPEC group (n=67) versus 16.8 months in the control group (n=38). Elias et al. (2009)

reported 2- and 5-year overall survival rates of 81% and 51% for the HIPEC group (n=48), respectively, and 65% and 13% for the standard group (n=48), respectively. Median survival was 23.9 months in the standard group versus 62.7 months in the HIPEC group.

In 2010a, Elias et al. published a retrospective multicenter study of 523 patients with peritoneal carcinomatosis of colorectal origin treated with CRS and perioperative intraperitoneal chemotherapy (HIPEC or EPIC). The median follow-up was 45 months. Mortality and grades 3 to 4 morbidity at 30 days were 3% and 31%, respectively. Overall median survival was 30.1 months. Five-year overall survival was 27%, and five-year disease-free survival was 10%. Complete CRS was performed in 84% of the patients, and median survival was 33 months. Positive independent prognostic factors were complete CRS, limited extent of disease, no lymph node involvement and the use of adjuvant chemotherapy. Neither the grade of disease nor the presence of liver metastases had a significant prognostic impact.

In 2004, Glehen et al. published a retrospective multicenter study of 506 patients with peritoneal carcinomatosis of colorectal origin treated with CRS and perioperative intraperitoneal chemotherapy (HIPEC and/or EPIC). The median follow-up was 53 months. The morbidity and mortality rates were 22.9% and 4%, respectively. The overall median survival was 19.2 months. In those patients who underwent complete cytoreduction, median survival was 32.4 months compared with 8.4 months for patients in who did not have complete cytoreduction. Positive independent prognostic indicators were complete cytoreduction, treatment by a second procedure, limited extent of disease, age less than 65 years and use of adjuvant chemotherapy. Complete CRS was the most important prognostic indicator. The use of neoadjuvant chemotherapy, lymph node involvement, presence of liver metastasis and poor histologic differentiation were negative independent prognostic indicators.

Two small studies evaluated CRS and HIPEC for treating peritoneal metastases from small bowel cancer. In 31 patients with peritoneal carcinomatosis, the median survival after CRS and HIPEC was 36 months, and the median survival after diagnosis was 50 months (Liu et al., 2016). van Oudheusden et al. (2015) reported a median survival of 31 months in sixteen patients following CRS and HIPEC.

A consensus document from the Peritoneal Surface Oncology Group International (PSOGI) makes the following recommendations (O'Dwyer et al., 2015):

- CRS, defined as removal of macroscopic peritoneal disease, combined with HIPEC, is the treatment that is indicated for selected patients with moderate- to small-volume peritoneal metastases secondary to colorectal cancer
- CRS and HIPEC should be avoided in patients who are unlikely to undergo a complete or near-complete resection, or who are unlikely to achieve a full recovery because of comorbidities
- CRS and HIPEC should not be offered at institutions where there is insufficient knowledge or insufficient skill to achieve a complete cytoreduction and to manage the safe administration of perioperative chemotherapy so that morbidity and mortality are acceptable
- Developing centers should seek support from established teams to assist in their development while gaining experience in these techniques
- Integration of this treatment strategy into the total care of the patient with colorectal cancer has become a necessary matter of discussion for multidisciplinary teams.

NCCN clinical practice guidelines for colon and rectal cancers state that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for select patients with limited peritoneal metastases for whom complete removal of all known tumor can be achieved (R0). NCCN recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities (NCCN, 2018; NCCN, 2018).

Professional Societies

American Society of Colon and Rectal Surgeons (ASCRS)

ASCRS practice guidelines (Vogel et al., 2017) for the treatment of colon cancer state that the treatment of patients with isolated peritoneal carcinomatosis should be multidisciplinary and individualized, and may include cytoreductive surgery with intraperitoneal chemotherapy. Grade of recommendation: 1B – strong recommendation based on moderate-quality evidence.

Society of Surgical Oncology

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

Gastric Cancer

There is some evidence demonstrating improved survival in gastric cancer patients with limited peritoneal carcinomatosis and complete cytoreduction. Many of the studies included patients who were almost exclusively of

Asian descent. Additional studies are needed to validate these results in Western populations. Further randomized clinical trials comparing CRS and HIPEC to standard treatment protocols are needed. GASTRICHIP ([NCT01882933](#)) and GASTRIPEC ([NCT02158988](#)) are two randomized, multicenter phase III studies in progress to validate results in European and Caucasian patients.

Desiderio et al. (2017) performed a meta-analysis of studies comparing HIPEC and standard oncological management for the treatment of advanced stage gastric cancer with and without peritoneal carcinomatosis. The primary outcomes were overall survival and disease recurrence. Secondary outcomes were overall complications, type of complications and sites of recurrence. A total of 11 randomized controlled trials and 21 non-randomized control trials (2520 patients) were included. For patients without the presence of peritoneal carcinomatosis, the overall survival rates between the HIPEC and control groups at 3 or 5 years resulted in favor of the HIPEC group. No difference in the 3-year overall survival but a prolonged median survival of 4 months in favor of the HIPEC group was seen in patients with peritoneal carcinomatosis. HIPEC was associated with significantly higher risk of complications (drug toxicity) for both patients with and without peritoneal carcinomatosis. The results demonstrate a survival advantage of HIPEC as a prophylactic strategy and suggest that 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. Author noted limitations reiterated the difficulty in applying results in Asia to Western populations and identifying the role and timing of adjuvant chemotherapy and its impact. Future randomized controlled trials should better define patient selection criteria.

Rudloff et al. (2014) conducted a small prospective randomized trial to compare the impact of systemic chemotherapy versus multi-modality therapy (complete CRS, HIPEC and systemic chemotherapy) on overall survival in patients with gastric carcinomatosis. Patients with measurable metastatic gastric adenocarcinoma involving the peritoneum, and resectable to "no evidence of disease," were randomized to gastrectomy, metastasectomy, HIPEC and systemic FOLFOXIRI (GYMS arm) or FOLFOXIRI alone (SA arm). Seventeen patients were enrolled (16 evaluable). Median overall survival was 11.3 months in the GYMS arm and 4.3 months in the SA arm. Four patients in the GYMS arm survived >12 months, 2 patients close to 2 years at last follow-up and 1 patient more than 4 years. No patient in the SA arm lived beyond 11 months. The authors concluded that maximal cytoreductive surgery combined with regional HIPEC and systemic chemotherapy in selected patients with gastric carcinomatosis and limited disease burden can achieve prolonged survival. However, the small number of patients did not allow for statistical comparison. Larger studies are needed to confirm these results in Western populations.

Mi et al. (2013) performed a meta-analysis of 16 randomized controlled trials (n=1906) to assess the effectiveness and safety of adjuvant intraoperative 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 1, 2, 3, 5 and 9 years. Compared with surgery alone, combination therapy was associated with a significant reduction in recurrence rate at 2, 3 and 5 years. The authors concluded that surgery combined with HIPEC may improve survival rate and reduce the recurrence rate, with acceptable safety, compared to surgery alone.

Sun et al. (2012) performed a meta-analysis of 10 randomized controlled trials to evaluate the effectiveness and safety of HIPEC for patients with advanced gastric cancer. A total of 1062 patients were divided into the HIPEC group (n=518) and control group (n=544). A significant improvement in survival was observed in the HIPEC group compared to the control group. Findings indicated that there was a lower peritoneal recurrence rate in the HIPEC group compared to the control group. Results of the analysis suggest that HIPEC may improve the overall survival rate for patients who receive resection for advanced gastric cancer and help to prevent peritoneal local recurrence among patients with serosal invasion in gastric cancer.

Gill et al. (2011) performed a systematic review of the literature regarding the efficacy of CRS and HIPEC in patients with gastric cancer with peritoneal carcinomatosis. Overall median survival was 7.9 months and improved to 15 months for patients with completeness of cytoreduction scores of 0 or 1. The 30-day mortality rate was 4.8%.

In a prospective, randomized phase III clinical trial, Yang et al. (2011) evaluated the efficacy and safety of CRS plus HIPEC for the treatment of peritoneal carcinomatosis from gastric cancer. Sixty-eight patients were randomized to receive CRS alone (n=34) or CRS plus HIPEC (n=34). Median survival was 11 months in the CRS plus HIPEC group compared to 6.5 months in the group receiving CRS alone. After complete macroscopic cytoreduction (CC 0/1), median survival increased to 13.5 months in the CRS plus HIPEC group.

A multicenter retrospective nonrandomized study by Glehen et al. (2010b) evaluated outcomes in 159 patients with peritoneal carcinomatosis from gastric cancer who underwent CRS followed by HIPEC (n=150) and/or EPIC (n=12). The median follow-up was 20.4 months. Postoperative mortality and grade 3-4 morbidity rates were 6.5 and 27.8%, respectively. The overall median survival was 9.2 months and 1-, 3- and 5-year survival rates were 43, 18 and 13%, respectively. The only independent prognostic indicator was the completeness of CRS. For patients treated by

complete CRS, the median survival was 15 months with a 1-, 3- and 5-year survival rate of 61, 30 and 23%, respectively.

A systematic review and meta-analysis by Yan et al. (2007c) evaluated the effectiveness and safety of adjuvant intraperitoneal chemotherapy for patients with locally advanced resectable gastric cancer. Thirteen studies, including 1648 patients, were included. Patients were randomly assigned to receive surgery combined with intraperitoneal chemotherapy (n=873) versus surgery without intraperitoneal chemotherapy (n=775). The studies used various intraperitoneal chemotherapy regimens. Based on the 4 studies investigating the efficacy of HIPEC, a significant improvement in survival was associated with HIPEC alone or HIPEC combined with EPIC.

NCCN clinical practice guidelines for gastric cancer do not address intraoperative HIPEC (NCCN, 2018).

Ovarian Cancer

Note: This Medical Policy does not apply to normothermic (no hyperthermia is used) postoperative intraperitoneal chemotherapy, delivered via an indwelling port or catheter, used to treat ovarian cancer.

There is a growing body of literature evaluating *intraoperative* HIPEC as a treatment option for ovarian cancer. Most studies are observational and involve heterogeneous patient populations at various time points of the disease. Defined standards are needed for many parameters such as timing of the procedure, temperature of chemotherapy solution, duration of perfusion and which chemotherapeutic agents to use. Several prospective, randomized trials are ongoing.

A systematic review and meta-analysis by Huo et al. (2015) assessed the safety and efficacy of HIPEC with CRS for epithelial ovarian carcinoma. Nine comparative studies and 28 studies examining HIPEC plus CRS for primary and/or recurrent ovarian cancer were included. Only one study was a randomized controlled trial. Pooled data showed that the addition of HIPEC to CRS and chemotherapy improved overall survival rates for both primary and recurrent EOC. The authors reported that there is an emerging body of evidence supporting the use of HIPEC with CRS and systemic chemotherapy for primary (stage III) and recurrent epithelial ovarian carcinoma compared to CRS and chemotherapy alone. Maximal cytoreduction remains essential for overall survival rates, even when HIPEC is used. Eligibility criteria varied across studies, the total number of patients in each study was small and disease-free survival was often poorly reported. Ongoing randomized controlled trials will further clarify the role of HIPEC for patients with advanced and recurrent ovarian cancer.

van Driel et al. (2018) investigated whether the addition of HIPEC to interval cytoreductive surgery would improve outcomes among patients who were receiving neoadjuvant chemotherapy for stage III epithelial ovarian cancer. In a multicenter, open-label, phase III trial, 245 patients, who had stable disease after three cycles of carboplatin and paclitaxel, were randomized to undergo interval cytoreductive surgery either with or without HIPEC with cisplatin. These patients were not eligible for primary cytoreduction due to extensive abdominal disease. Randomization was performed at the time of surgery for patients with complete cytoreduction (no visible disease) or after surgery in patients with one or more residual tumors measuring 10 mm or less in diameter (optimal cytoreduction). Three additional cycles of carboplatin and paclitaxel were administered after surgery. The primary end point was recurrence-free survival. Secondary end points included overall survival, side-effects and health-related quality of life. In the intention-to-treat analysis, events of disease recurrence or death occurred in 110 of the 123 patients (89%) who underwent cytoreductive surgery without HIPEC (surgery group) and in 99 of the 122 patients (81%) who underwent cytoreductive surgery with HIPEC (surgery-plus-HIPEC group). The median recurrence-free survival was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group. At a median follow-up of 4.7 years, 76 patients (62%) in the surgery group and 61 patients (50%) in the surgery-plus-HIPEC group had died. The median overall survival was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group. The percentage of patients who had adverse events of grade 3 or 4 was similar in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group). The overall percentage of bowel resections performed was similar in the two groups, but the percentage of patients who underwent a colostomy or an ileostomy after surgery was significantly higher in the surgery-plus-HIPEC group than in the surgery group (72% vs. 43%). The authors concluded that among women with advanced ovarian cancer, HIPEC plus complete or optimal interval cytoreductive surgery resulted in longer survival than cytoreductive surgery alone. Additional trials are needed to determine the ways in which HIPEC differs from postoperative intravenous or intraperitoneal chemotherapy and whether HIPEC is also effective after primary cytoreductive surgery.

Spiliotis et al. (2015) evaluated the use of HIPEC for treating recurrent epithelial ovarian cancer. In an 8-year period (2006-2013), 120 women with advanced ovarian cancer who experienced disease recurrence after initial treatment with conservative or debulking surgery and systemic chemotherapy were randomized into two groups. Group A was comprised of 60 patients treated with CRS followed by HIPEC and then systemic chemotherapy. Group B was comprised of 60 patients treated with CRS only and systemic chemotherapy. The mean survival for group A was 26.7 versus 13.4 months in group B. Three-year survival was 75% for group A versus 18% for group B. In the HIPEC group, the mean survival was not different between patients with platinum-resistant disease versus platinum-sensitive

disease (26.6 vs. 26.8 months). In the non-HIPEC group, there was a statistically significant difference between platinum-sensitive versus platinum-resistant disease (15.2 vs. 10.2 months). The authors concluded that the use of HIPEC, extent of disease and extent of cytoreduction play an important role in the survival of patients with recurrence in an initially advanced ovarian cancer. While these results are promising, additional randomized controlled trials are needed to conclude that HIPEC + CRS + chemotherapy is superior to CRS + chemotherapy alone for ovarian cancer.

In a prospective phase II study, Ansaloni et al. (2012) analyzed the results of CRS and HIPEC in 39 patients with advanced epithelial ovarian cancer (EOC). Thirty patients (77%) had recurrent EOC and 9 (23%) had primary EOC. For HIPEC, cisplatin and paclitaxel were used for 11 patients (28%), cisplatin and doxorubicin for 26 patients (66%), paclitaxel and doxorubicin for 1 patient (3%) and doxorubicin alone for 1 patient (3%). Microscopically complete cytoreduction was achieved for 35 patients (90%), macroscopic cytoreduction was achieved for 3 patients (7%) and a gross tumor debulking was performed for 1 patient (3%). Postoperative complications occurred in 7 patients (18%) and reoperations in 3 patients (8%). There was one postoperative death. Recurrence was seen in 23 patients (59%) with a mean recurrence time of 14.4 months (range, 1-49 months). The authors concluded that HIPEC after extensive CRS for advanced EOC is feasible with acceptable morbidity and mortality. Additional follow-up and further studies are needed to determine the effects of HIPEC on survival.

Deraco et al. (2011) conducted a multicenter phase II trial to assess overall survival after CRS and HIPEC in treatment-naïve EOC with advanced peritoneal involvement. Twenty-six women with stage III-IV EOC underwent CRS and closed-abdomen HIPEC with cisplatin and doxorubicin followed by systemic chemotherapy with carboplatin and paclitaxel. Macroscopically complete cytoreduction was achieved in 15 patients and minimal residual disease (≤ 2.5 mm) remained in 11. Major complications occurred in four patients and postoperative death in one. After a median follow-up of 25 months, 5-year overall survival was 60.7% and 5-year progression-free survival 15.2% (median 30 months). The authors reported that in select patients with advanced stage EOC, upfront CRS and HIPEC provided promising results in terms of outcome. Morbidity was comparable to aggressive cytoreduction without HIPEC. Postoperative recovery delayed the initiation of adjuvant systemic chemotherapy but not sufficiently to impact negatively on survival. These data warrant further evaluation in a randomized clinical trial.

Helm et al. (2010) published initial data from a U.S. registry (HYPER-O) collecting data on surgical and gynecologic oncologists' experience with HIPEC for invasive EOC. Borderline and nonepithelial cancers were excluded. A total of 141 women were eligible for analysis treated at the following time points: frontline (n = 26), interval debulking (n = 19), consolidation (n = 12) and recurrence (n = 83). Treatment was with a platinum agent (n = 72), mitomycin (n = 53) or a combination (n = 14). Median follow-up was 18 months (range, 0.3-140.5 months) and median overall survival 30.3 months with 2-, 5- and 10-year overall survival probabilities of 49.1%, 25.4%, and 14.3%, respectively. Of the 141 patients, 110 (78%) experienced recurrence of ovarian cancer and 87 died, 3 (0.5%) dying within 30 days of surgery. In the multivariable analysis, the factors significant for increased survival were sensitivity to platinum response, completeness of cytoreduction scores of 1 or 0, carboplatin alone or a combination of 2 or more chemotherapy agents used and duration of hospital stays of 10 days or less. These results warrant further study in randomized controlled trials.

Chua et al. (2009) performed a systematic review of 19 studies reporting the efficacy of CRS and HIPEC for ovarian cancer peritoneal carcinomatosis. Patients with both advanced and recurrent ovarian cancer were included. All studies were uncontrolled, observational case series. The overall rate of severe perioperative morbidity ranged from 0 to 40% and mortality rate varied from 0 to 10%. The overall median survival following treatment with HIPEC ranged from 22 to 64 months with a median disease-free survival ranging from 10 to 57 months. In patients with optimal cytoreduction, a 5-year survival rate ranging from 12 to 66% could be achieved. The authors acknowledge that the HIPEC protocol varied in each study, but note that the evidence suggests that complete CRS and HIPEC may have benefits that are comparable to the current standard of care. A randomized trial is required to establish the role of HIPEC in ovarian cancer.

Bijelic et al. (2007) performed a systematic review of 14 studies to evaluate CRS combined with HIPEC in the treatment of ovarian cancer. A wide variety of drug doses, methods of intraperitoneal chemotherapy administration and volume of chemotherapy solution were used. Seven studies showed that patients with complete cytoreduction had the greatest benefit. 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%. The median mortality was 3% (range 0%-10%). The authors concluded that CRS combined with HIPEC is a treatment option for patients with ovarian cancer that is worthy of further investigation.

Several retrospective studies have reported similar results (Cascales Campos et al., 2014; Robella et al., 2014; Bakrin et al., 2013; Bakrin et al., 2012; Deraco et al., 2012; Parson et al., 2011). Completeness of cytoreduction was the most statistically significant factor related to ovarian cancer survival.

NCCN clinical practice guidelines for ovarian cancer do not address *intraoperative* HIPEC (NCCN, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

There are many surgical instruments approved for use in pelvic and abdominal surgery. See the following website to search for specific products. Devices used for performing hyperthermic therapy have been identified under the product codes LOC and MLW. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed March 28, 2018)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC). Local Coverage Determinations (LCDs) do not exist at this time. (Accessed April 12, 2018)

REFERENCES

- Ansaloni L, Agnoletti V, Amadori A, et al. Evaluation of extensive cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with advanced epithelial ovarian cancer. *Int J Gynecol Cancer*. 2012 Jun;22(5):778-85.
- Bakrin N, Bereder JM, Decullier E, et al; FROGHI (FRench Oncologic and Gynecologic HIPEC) Group. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. *Eur J Surg Oncol*. 2013 Dec;39(12):1435-43.
- Bakrin N, Cotte E, Golfier F, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. *Ann Surg Oncol*. 2012 Dec;19(13):4052-8.
- Baratti D, Kusamura S, Cabras AD, et al. Diffuse malignant peritoneal mesothelioma: long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Cancer*. 2013 Oct;49(15):3140-8.
- Baratti D, Vaira M, Kusamura S, et al. Multicystic peritoneal mesothelioma: outcomes and patho-biological features in a multi-institutional series treated by cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). *Eur J Surg Oncol*. 2010 Nov;36(11):1047-53.
- Baratti D, Kusamura S, Nonaka D, et al. Pseudomyxoma peritonei: clinical pathological and biological prognostic factors in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Ann Surg Oncol*. 2008 Feb;15(2):526-34.
- Bijelic L, Jonson A, Sugarbaker PH. Systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer. *Ann Oncol*. 2007 Dec;18(12):1943-50.
- Blackham AU, Shen P, Stewart JH, et al. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for malignant peritoneal mesothelioma: mitomycin versus cisplatin. *Ann Surg Oncol*. 2010 Oct;17(10):2720-7.
- Cao C, Yan TD, Black D, Morris DL. A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol*. 2009 Aug;16(8):2152-65.
- Cascales Campos P, Gil J, Parrilla P. Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with primary and recurrent advanced ovarian cancer. *Eur J Surg Oncol*. 2014 Aug;40(8):970-5.
- Chua TC, Esquivel J, Pelz JO, Morris DL. Summary of current therapeutic options for peritoneal metastases from colorectal cancer. *J Surg Oncol*. 2013 May;107(6):566-73.
- Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol*. 2012 Jul 10;30(20):2449-56.
- Chua TC, Morris DL, Saxena A, et al. Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: a multicenter study. *Ann Surg Oncol*. 2011a Jun;18(6):1560-7.
- Chua TC, Yan TD, Deraco M, et al.; Peritoneal Surface Oncology Group. Multi-institutional experience of diffuse intra-abdominal multicystic peritoneal mesothelioma. *Br J Surg*. 2011b Jan;98(1):60-4.

Chua TC, Robertson G, Liauw W, et al. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery in ovarian cancer peritoneal carcinomatosis: systematic review of current results. *J Cancer Res Clin Oncol*. 2009 Dec;135(12):1637-45.

de Cuba EM, Kwakman R, Knol DL, et al. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases: Systematic review of all literature and meta-analysis of observational studies. *Cancer Treat Rev*. 2013 Jun;39(4):321-7.

Deraco M, Kusamura S, Virzi S, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: multi-institutional phase-II trial. *Gynecol Oncol*. 2011 Aug;122(2):215-20.

Deraco M, Virzi S, Iusco DR, et al. Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study. *BJOG*. 2012 Jun;119(7):800-9.

Desiderio J, Chao J, Melstrom L, et al. The 30-year experience - a meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. *Eur J Cancer*. 2017 Jul;79:1-14.

ECRI Institute. Hotline Response. Hyperthermia with chemotherapy for treating rectal and colorectal cancers. September 2016. Archived report.

Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol*. 2010a Jan 1;28(1):63-8.

Elias D, Gilly F, Quenet F, et al.; Association Française de Chirurgie. Pseudomyxoma peritonei: a French multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy. *Eur J Surg Oncol*. 2010b May;36(5):456-62.

Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol*. 2009 Feb 10;27(5):681-5.

Esquivel J, Sticca R, Sugarbaker P, et al.; Society of Surgical Oncology. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. *Ann Surg Oncol*. 2007 Jan;14(1):128-33.

Franko J, Ibrahim Z, Gusani NJ, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. *Cancer*. 2010 Aug 15;116(16):3756-62.

Gill RS, Al-Adra DP, Nagendran J, et al. Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. *J Surg Oncol*. 2011 Nov 1;104(6):692-8.

Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer*. 2010a Dec 15;116(24):5608-18.

Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Surg Oncol*. 2010b Sep;17(9):2370-7.

Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol*. 2004 Aug 15;22(16):3284-92.

Helm JH, Miura JT, Glenn JA, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. *Ann Surg Oncol*. 2015 May;22(5):1686-93.

Helm CW, Richard SD, Pan J, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer: first report of the HYPER-O registry. *Int J Gynecol Cancer*. 2010 Jan;20(1):61-9.

Huang CQ, Min Y, Wang SY, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival for peritoneal carcinomatosis from colorectal cancer: a systematic review and meta-analysis of current evidence. *Oncotarget*. 2017 Apr 27;8(33):55657-55683.

Huo YR, Richards A, Liauw W, Morris DL. Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer: A systematic review and meta-analysis. *Eur J Surg Oncol*. 2015 Dec;41(12):1578-89.

Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res*. 1996;82:359-74.

Liu Y, Ishibashi H, Takeshita K, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal dissemination from small bowel malignancy: results from a single specialized center. *Ann Surg Oncol*. 2016 May;23(5):1625-31.

Loggie BW, Thomas P. Gastrointestinal cancers with peritoneal carcinomatosis: surgery and hyperthermic intraperitoneal chemotherapy. *Oncology (Williston Park)*. 2015 Jul;29(7):515-21.

McBride K, McFadden D, Osler T. Improved survival of patients with pseudomyxoma peritonei receiving intraperitoneal chemotherapy with cytoreductive surgery: a systematic review and meta-analysis. *J Surg Res*. 2013 Jul;183(1):246-52.

Merriam-Webster online dictionary. <https://www.merriam-webster.com>. Accessed April 5, 2018.

Mi DH, Li Z, Yang KH, et al. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: a systematic review and meta-analysis of randomised controlled trials. *Int J Hyperthermia*. 2013;29(2):156-67.

Mirnezami R, Mehta AM, Chandrakumaran K, et al. Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. *Br J Cancer*. 2014a Oct 14;111(8):1500-8.

Mirnezami R, Moran BJ, Harvey K, et al. Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal metastases. *World J Gastroenterol*. 2014b Oct 14;20(38):14018-32.

Murphy EM, Sexton R, Moran BJ. Early results of surgery in 123 patients with pseudomyxoma peritonei from a perforated appendiceal neoplasm. *Dis Colon Rectum*. 2007 Jan;50(1):37-42.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colon cancer. v2.2018.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Gastric cancer. v1.2018.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Malignant pleural mesothelioma. v2.2018.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. v2.2018.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Rectal cancer. v1.2018.

National Institute for Health and Care Excellence (NICE). Complete cytoreduction for pseudomyxoma peritonei (Sugarbaker technique). IPG56. April 2004.

National Institute for Health and Care Excellence (NICE). Cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. IPG 331. February 2010.

O'Dwyer S, Verwaal VJ, Sugarbaker PH. Evolution of treatments for peritoneal metastases from colorectal cancer. *J Clin Oncol*. 2015 Jun 20;33(18):2122-3.

Parson EN, Lentz S, Russell G, et al. Outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface dissemination from ovarian neoplasms. *Am J Surg*. 2011 Oct;202(4):481-6.

Robella M, Vaira M, Marsanic P, et al. Treatment of peritoneal carcinomatosis from ovarian cancer by surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). *Minerva Chir*. 2014 Feb;69(1):27-35.

Rubino MS, Abdel-Misih RZ, Bennett JJ, et al. Peritoneal surface malignancies and regional treatment: a review of the literature. *Surg Oncol*. 2012 Jun;21(2):87-94.

Rudloff U, Langan RC, Mullinax JE, et al. Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: results of the GYMSSA trial. *J Surg Oncol*. 2014 Sep;110(3):275-84.

Shaib WL, Martin LK, Choi M, et al. Hyperthermic intraperitoneal chemotherapy following cytoreductive surgery improves outcome in patients with primary appendiceal mucinous adenocarcinoma: a pooled analysis from three tertiary care centers. *Oncologist*. 2015 Aug;20(8):907-14.

Shen P, Stewart JH 4th, Levine EA. The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for metastatic colorectal cancer with peritoneal surface disease. *Curr Probl Cancer*. 2009 May-Jun;33(3):154-67.

Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FA. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg*. 2007 Jan;245(1):104-9.

Spiliotis J, Halkia E, Lianos E, et al. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. *Ann Surg Oncol*. 2015 May;22(5):1570-5.

Sun J, Song Y, Wang Z, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. *BMC Cancer*. 2012 Nov 16;12:526.

Turaga K, Levine E, Barone R, et al. Consensus guidelines from The American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. *Ann Surg Oncol*. 2014 May;21(5):1501-5.

van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med*. 2018 Jan 18;378(3):230-240.

van Oudheusden TR, Lemmens VE, Braam HJ, et al. Peritoneal metastases from small bowel cancer: Results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in The Netherlands. *Surgery*. 2015 Jun;157(6):1023-7.

van Oudheusden TR, Nienhuijs SW, Luyer MD, et al. Incidence and treatment of recurrent disease after cytoreductive surgery and intraperitoneal chemotherapy for peritoneally metastasized colorectal cancer: A systematic review. *Eur J Surg Oncol*. 2015 Oct;41(10):1269-77.

Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol*. 2003 Oct 15;21(20):3737-43.

Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol*. 2008 Sep;15(9):2426-32.

Vogel JD, Eskicioglu C, Weiser MR, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the treatment of colon cancer. *Dis Colon Rectum*. 2017 Oct;60(10):999-1017.

Waite K, Youssef H. The role of neoadjuvant and adjuvant systemic chemotherapy with cytoreductive surgery and heated intraperitoneal chemotherapy for colorectal peritoneal metastases: a systematic review. *Ann Surg Oncol*. 2017 Mar;24(3):705-720.

Whitney CW, Spirto N. *Gynecologic Oncology Group Surgical Procedures Manual*. Philadelphia: Gynecologic Oncology Group; 2009.

Williams BH, Alzahrani NA, Chan DL, et al. Repeat cytoreductive surgery (CRS) for recurrent colorectal peritoneal metastases: yes or no? *Eur J Surg Oncol*. 2014 Aug;40(8):943-9.

Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol*. 2009 Dec 20;27(36):6237-42.

Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. *Ann Oncol*. 2007a May;18(5):827-34.

Yan TD, Black D, Savady R, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. *Ann Surg Oncol*. 2007b Feb;14(2):484-92.

Yan TD, Black D, Sugarbaker PH, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. *Ann Surg Oncol*. 2007c Oct;14(10):2702-13.

Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. *J Clin Oncol*. 2006 Aug 20;24(24):4011-9.

Yang XJ, Huang CQ, Suo T, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol*. 2011 Jun;18(6):1575-81.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	<ul style="list-style-type: none"> Reorganized policy template; simplified and relocated <i>Instructions for Use</i> and <i>Benefit Considerations</i> section Simplified coverage rationale (no change to guidelines) Archived previous policy version 2018T0573E

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state

mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.