Intraoperative Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

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Instructions for Use

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Application

UnitedHealthcare Commercial

This Medical Policy applies to all UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Colorado.

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:

- Ovarian cancer following neoadjuvant chemotherapy
- 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:
  - Adenocarcinoma of the appendix or goblet cell carcinoma
  - Colon
  - Rectum

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, except as noted above

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): Cytoreductive Surgery is surgery with the goal of 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). Optimal Cytoreductive Surgery is done with a curative intent to leave no macroscopic disease (Tangiitgamol, et al 2014).

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 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

Description of Services

Hyperthermic Intraperitoneal chemotherapy (HIPEC) is a treatment used immediately following CRS 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.

Clinical Evidence

A systematic review by Auer et al. (2020) evaluated two RCTs with 184 and 245 patients with newly diagnosed, primary stage III epithelial ovarian, fallopian tube or primary peritoneal carcinoma. The authors concluded that HIPEC should be considered for

those with partial or complete response following neoadjuvant chemotherapy and complete or optimal interval CRS; however, there is insufficient evidence to recommend the addition of HIPEC with primary CRS when performed outside of a clinical trial. For patients with recurrent ovarian cancer, colorectal or gastric peritoneal carcinomatosis, mesothelioma or disseminated mucinous neoplasms, there is insufficient evidence to recommend CRS with HIPEC outside of a clinical trial or research protocol. There are currently many ongoing RCTs evaluating the role of HIPEC with CRS in ovarian, colorectal, and gastric cancers with peritoneal dissemination; centers involved in treating patients with PM and disseminated mucinous neoplasms are encouraged to publish treatment data.

Glehen et al. (2010a) conducted a retrospective, multicenter single-arm study to evaluate toxicity and prognostic factors after CRS and HIPEC and/or early postoperative intraperitoneal chemotherapy (EPIC) for peritoneal carcinomatosis from non-gynecologic 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. The findings are limited by lack of a contemporary comparison group undergoing a different treatment.

Peritoneal Mesothelioma (PM)

Due to the rare nature of peritoneal mesothelioma (PM), 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.

Hayes reviewed six retrospective cohort studies and eight retrospective uncontrolled studies examining the efficacy and safety of CRS plus HIPEC in patients with PM. Although the quality of evidence was low, it did suggest that HIPEC in addition to CRS may confer some benefits with respect to overall survival (OS) in select patients. While current evidence suggests that the rate of major complications is high (up to 39%), the most common major complications attributable to HIPEC were reported in ≤ 20% of patients. Given the high likelihood of disease-related mortality in this patient population, the potential benefit of this treatment should be considered relative to the risk of harm. A lack of comparative studies and substantial variation across patient populations and treatment protocols underscore the need for additional studies to fill persisting evidence gaps and establish definitive patient selection criteria (Hayes, 2019a; updated 2023).

Verma et al. (2018) performed a cohort study of 1514 patients to evaluate management patterns, outcomes, and prognostic factors of malignant PM in the USA. 379 (25%) underwent observation, 370 (24%) received chemotherapy only, 197 (13%) CRS alone, 352 (23%) CRS/chemo, and 216 (14%) CRS/HIPEC. No major temporal trends in management were noted. Factors predictive of CRS administration included younger age, female gender, insurance status, residence in educated areas, living farther from treating institutions, and treatment at academic centers ($p < 0.05$ for all). Compared with epithelioid histology, those with sarcomatoid and biphasic histology were less and more likely to undergo CRS, respectively ($p < 0.05$ for both). In all CRS patients, 30- and 90-day mortality rates were 0.8 and 1.2%, respectively. At median follow-up of 50 months, median OS in the respective groups was 6, 17, 21, 52, and 61 months ($p < 0.001$). Poor prognostic factors included advanced age, male gender, uninsured/Medicaid insurance, and sarcomatoid/biphasic histology ($p < 0.05$ for all). While this study demonstrated significant differences in survival between those receiving CRS plus HIPEC and CRS alone, chemotherapy alone and observation, no significant differences were found when compared with those who received CRS with chemotherapy. There are no randomized trials currently ongoing in this patient population for the use of HIPEC. The authors acknowledged the challenges that exist in trying to obtain level 1 evidence for the use of HIPEC for this indication; however, standardized treatment approaches at high-volume centers engaged in multi-institutional collaborations will provide survival benchmarks and feasibility data for future comparative studies.

Helm et al. (2015) performed a systematic review and meta-analysis of the literature evaluating CRS and HIPEC for treating malignant PM. 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. The authors concluded that HIPEC is a viable additional treatment option and may extend life in selected groups;

it warrants further study in randomized controlled trials (RCTs). (Publications by Yan 2009, Blackham 2010, and Chua 2011, which were previously cited in this policy, are included in this systematic review).

From a prospective database, Baratti et al. (2013) selected 108 patients with diffuse malignant PM 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 diffuse malignant PM is primarily dependent on pathologic and biologic features. Patients with diffuse malignant PM surviving ≥ 7 years appeared to be cured. Cure rate was 43.6%.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for malignant pleural mesothelioma have limited information on PM. 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, 2023).

Peritoneal Surface Oncology Group International (PSOGI)

PSOGI/EURACAN clinical practice guidelines on peritoneal mesothelioma state that CRS plus HIPEC is recommended in patients with diffuse malignant PM rather than palliative systemic chemotherapy, provided that the patient has a sufficient clinical condition for a major operation, has resectable disease, and that the treatment is done in a specialized center. Level of evidence: B (moderate). Strength of recommendation: I (strong positive) (Kusamura et al. 2021a).

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 observational studies suggest that HIPEC, in combination with CRS, is safe and effective for PMP when compared to standard treatment options.

Kusamura et al. (2021b) analyzed data from the PSOGI registry to evaluate outcomes after CRS and HIPEC (n = 1548) compared with CRS alone (n = 376) in patients with PMP. The data included 1924 patients with histologically confirmed PMP due to an appendiceal mucinous neoplasm. Subset analyses included optimal cytoreduction, suboptimal cytoreduction, high- and low-grade histologic findings and different HIPEC drug regimens. HIPEC including oxaliplatin plus combined fluorouracil-leucovorin, cisplatin plus mitomycin, mitomycin, and other oxaliplatin-based regimens were used. Primary outcomes were OS, severe morbidity, return to operating room, and 30- and 90-day mortality. Patients with CRS alone were older, had less lymph node involvement, received more preoperative systemic chemotherapy and had higher proportions of high-grade disease and incomplete cytoreductions. HIPEC was not associated with a higher risk of worse surgical outcomes except with mitomycin, with higher odds of morbidity. HIPEC was associated with a significantly better OS in all subsets. The weighted 5-year OS was 57.8% versus 46.2% for CRS-HIPEC and CRS alone, respectively. Compared with the CRS alone group, the CRS-HIPEC group also had better 5-year OS in all subsets. Treatment with CRS-HIPEC was superior to CRS alone when the drug schedules were oxaliplatin plus fluorouracil-leucovorin or cisplatin plus mitomycin. No prognostic advantage was observed in subgroups receiving mitomycin and other oxaliplatin-based HIPEC. Within the entire series, incidence of 90-day mortality was 4.2%; 30-day mortality, 2.1%; return to the operating room, 9.3%; and severe morbidity, 32.0%.

Di Leo et al. (2020) conducted a single institution single-arm study following CRS and HIPEC in patients with PMP. This review prospectively collected data from 32 patients (11 men and 21 women) affected by PMP of appendiceal origin who underwent CRS and HIPEC from 2008 to 2016 in one institution. The median age of the patients was 53 years (range 25-77 years). After CRS, all patients underwent HIPEC (mytomicin C 3.3 mg/m2/L and cisplatin 25 mg/m2/L at 41° C for 60 min) with a closed abdomen technique. The median follow-up time for surviving patients was 43 (18-119) months. The median peritoneal cancer index (PCI) was 17. Complete CRS (CC0) was achieved in in 22 patients (69%). The majority of patients (88%) had grade I-II complications, three (9%) had grade III complications, and one (3%) patient had a grade IV complication. There were no perioperative mortalities. One year and 5-year OS were 90% and 58%, respectively. Regardless of histotype, disease-free survival was 95% at 1 year and 46% at 5 years. The authors concluded that CRS in combination with HIPEC is a feasible

treatment strategy and can achieve a satisfactory outcome in patients with PMP of appendiceal origin. The findings are limited by lack of contemporary comparison group.

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 OS 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 OS.

A systematic review and meta-analysis by McBride et al. (2013) reported 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 little difference in mortality and morbidity between the different centers. 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 PFS 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 PFS. Older age, major postoperative complications, debulking surgery (CCR 2 or 3), prior chemotherapy treatment and pathological subtype PMCA were independent predictors of a poorer OS. The authors noted that minimizing nondefinitive operative and systemic chemotherapy treatments before cytoreduction may improve outcomes. Optimal cytoreduction achieves the best outcomes.

Peritoneal Carcinomatosis Resulting from Colorectal Cancer, Small Bowel, and Adenocarcinoma of the Appendix

Accumulating data from several observational studies has shown 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.

Based on a clinical evidence assessment by ECRI (2022), the evidence for HIPEC and CRS for colorectal peritoneal metastases is inconclusive. Assessment of the evidence includes 12 systematic reviews which contain a large body of evidence that show that CRS with HIPEC works better than chemotherapy or CRS but carries a substantial risk of patient injury. There is a 3-year survival rate of 50% and a 5-year survival rate of 30% with serious complications reported in 30% of patients. There is also great variability in HIPEC protocols so outcomes may differ. Large RCTs are needed to compare and validate HIPEC treatments in specific patient groups as well as determine adjuvant chemotherapy's utility in CRS with HIPEC.

Chen et al. (2022) conducted a systematic review to assess the effectiveness of CRS with HIPEC for small bowel adenocarcinoma (SBA) with peritoneal metastasis (PM). Twelve studies that included 164 cases (accounting for the overlapping patients between single center and multicenter studies) were included. The majority of the patients had complete cytoreduction prior to HIPEC, and most used an open technique using mitomycin C or oxaliplatin. HIPEC duration ranged from 30-120 minutes, with the median being 60 minutes. Temperatures ranged between 40°-43°C (104°-109° F). Early postoperative intraperitoneal chemotherapy (EPIC) was added as a supplement to microscopic tumor treatment in 12 patients in the included studies. The primary outcomes were PFS and OS. Secondary outcomes included overall and type of morbidity, treatment related deaths, mean length of stay and quality of life (QOL). The results showed, of the 164 patients, OS was 9-32 months with

a 5-year OS rate between 25%-38%. Three treatment related deaths were reported. Between 20% and 50% of patients experienced a Clavien-Dindo grade III/IV complication. These included intraperitoneal abscess, septicemia, and intestinal fistula. None of the studies included QOL outcomes. Better outcomes were seen in well differentiated tumors, no lymph node involvement, lower PCI scores, complete cytoreduction, under the age of 70 and undergoing treatment within 6 months of diagnosis. The authors concluded that CRS-HIPEC may result in increased survival for select patients. Furthermore, while CRS-HIPEC has the potential to improve survival, treatment failure is common and may not be better than chemotherapy alone, and the risks need to be evaluated with the potential OS. This study is limited by a small number of participants and heterogeneity of the included studies and retrospective data analysis; however, these limitations are due to the rare nature of this condition. (Publications by Liu 2016 and van Oudheusden 2015a, which were previously cited in this policy, are included in this systematic review).

Li et al. (2022, included in the ERCI report above) evaluated the impact of CRS with HIPEC on OS and provided reference for the treatment of patients with colorectal cancer and peritoneal metastasis. There were 10 studies included in the review with a total of 3200 patients. There were 788 patients in the CRS and HIPEC groups and 2412 patients in the control groups. Three of the studies were RCTs and 7 were cohort studies which were considered high quality by the authors. The OS of patients in the CRS with HIPEC group was higher than that of the control group noting large heterogeneity of the studies. Additionally, the authors noted a higher OS in patients who had OPEN HIPEC as compared to control group as well as patients who received HIPEC in the 60–100-minute timeframe when compared to control group. Limitations of the review include a higher number of cohort studies (7) as opposed to RCTs (3), subgroup analysis was limited to 3 studies comparing CRS which limits the evidence and conclusions drawn, and the hazard rate (HR) values of two of the RCTs included were 0.98 and 0.99 which did not show satisfactory for HR values. The authors noted that while the quality of evidence was high, further studies are needed to verify findings. (Publications by Quenet 2021, Franco 2010, Elias 2009, and Verwaal 2008, which were previously cited in this policy, are included in this systematic review).

The value of cytoreduction and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) for patients with peritoneally metastasized goblet cell carcinoids (GCCs) and mixed adeno-neuroendocrine carcinomas (MANECs) is currently unclear. Sluiter et al., (2020) compared outcomes of CRS-HIPEC to surgery alone for peritoneally metastasized GCCs and MANECs by evaluating two cohort studies for patients with peritoneally metastasized GCCs and MANECs treated with (1) CRS-HIPEC in Dutch and Belgian centers (n = 45) and (2) surgery alone, from the Netherlands Cancer Registry (n = 569). Primary outcome was OS and secondary outcomes were morbidity and hospital mortality. Following propensity score matching, OS was compared in univariate and multivariate analysis. The authors concluded that treatment with CRS-HIPEC for patients with PM of GCCs and MANECs in specialized HIPEC centers seems associated with substantially better outcome/survival rates compared to surgery without HIPEC at the expense of acceptable morbidity and mortality. These data support that care of patients with PM of GCCs and MANECs should be offered in expert centers that have the option for CRS-HIPEC.

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.

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 OS 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 OS ranged between 5 and 24 (median 12.5) months, and 5-year survival ranged between 13% and 22% (median 13%). Median survival was 23.9 months in the standard group versus 62.7 months in the HIPEC group.

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 versus recurrence), site (appendix versus colon versus rectum), number of regions involved (less than 5 regions versus 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.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

The 2022 ASCO guideline for metastatic colorectal cancer (Morris et al., 2022) states that oxaliplatin-based HIPEC is not recommended as an addition to cytoreductive surgery for treating patients with colorectal cancer (Evidence quality: Moderate; Strength of Recommendation: Strong).

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 CRS with intraperitoneal chemotherapy. Grade of recommendation: 1B – strong recommendation based on moderate-quality evidence. ASCRS practice guidelines for the management of rectal cancer do not address HIPEC (You et al., 2020).

American Society of Peritoneal Surface Malignancies (ASPSM)

ASPSM consensus guidelines on standardizing the delivery of HIPEC in colorectal cancer patients support that the majority of the surgical oncologists favored the closed method of delivery with a standardized dual dose of mitomycin for a 90-min chemoperfusion for patients undergoing CRS for peritoneal carcinomatosis of colorectal origin (Turaga et al., 2014).

National Institute for Health and Care Excellence (NICE)

A NICE guideline states that evidence on the safety of CRS with HIPEC for peritoneal carcinomatosis shows frequent and serious but well-recognized complications. Evidence on its efficacy is limited in quality. Patient selection should be done by an experienced multidisciplinary team, and the procedure should only be done in highly specialized centers by clinicians with specialist expertise and specific training in these procedures (NICE, 2021).

NICE guidelines on colorectal cancer recommends that people with metastatic colorectal cancer in the peritoneum be offered systemic anti-cancer therapy and after discussion with a multidisciplinary team, be referred to a surgery center specializing in CRS. Although the evidence on the effectiveness of CRS and HIPEC was mixed, the guidelines state these procedures should be considered (NICE, 2020).

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for colon cancer state that complete CRS 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). The guidelines also note that the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach controversial (NCCN, 2023).

NCCN clinical practice guidelines for small bowel adenocarcinoma state that HIPEC cannot be recommended as a treatment option until more robust data becomes available. Data supporting the use of HIPEC in small bowel adenocarcinoma patients with peritoneal carcinomatosis is extremely limited, consisting entirely of small, retrospective studies. In addition, the recent phase III PRODIGE 7 study showed no benefit of oxaliplatin-based HIPEC in colorectal cancer patients compared to cytoreduction alone. Significant morbidity and mortality are associated with the procedure and recurrences are common (NCCN, 2023).

Peritoneal Surface Oncology Group International (PSOGI)

A consensus document from 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

Gastric Cancer

There is limited but conflicting evidence suggesting improved survival in gastric cancer patients with limited peritoneal carcinomatosis and complete cytoreduction with HIPEC. However, the role of HIPEC is still evolving and currently it cannot be recommended outside of a clinical trial protocol. Additional studies are needed to validate these results in various 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.

Deng et al. (2022) evaluated the short- and long-term survival of HIPEC in the patients with advanced gastric cancer (AGC). A search of RCTs was conducted using Pub Med, Cochrane Library, Embase and other databases. A total of 13 trials with 1091 patients was found; 556 patients were randomized to the HIPEC group while 535 patients were randomized to the control group. The quality assessment of the articles was based on the Cochrane bias risk standard and independently assessed by two reviewers. The main end point was OS and safety endpoints such as nausea, vomiting and intestinal leakage were evaluated as well. Upon completion of the study analysis, the authors' concluded no significant differences between the AGC group and the control group were noted in either the survival rate or safety risks. Limitations included omission of several baseline characteristics which may have led to mixed bias, RCTs did not describe blinding method used, the five-year data obtained was prior to 2001, studies were geographically limited, and heterogeneity was high. Future studies to further evaluate the efficacy of HIPEC should include large RCTs with long-term outcomes. (Publications by Yang 2011 and Rudloff 2014 which were previously cited in this policy are included in this systematic review).

In another systematic review, Martins et al. (2022) also evaluated OS comparison in GCPC patients. A literature search returned forty-three articles for eligibility, but only nine fit the criteria; five studies were included in the qualitative synthesis and four studies in the quantitative synthesis. Studies used included individuals over the age of 18 years old with GCPC which compared CRS+HIPEC to CRS alone. Generally, the results revealed the OS rate after one year to be 3.65 times higher for CRS+HIPEC than for the CRS group only (RR = 3.65, 95% CI = 1.01–13.26, p = 0.050), however, severe heterogeneity was observed. After reviewing each of the studies individually, the authors found if the last study was removed from the analysis, the OS rate increased to 6.42 times higher for CRS+HIPEC than for CRS alone. At 3 years, the authors did not find anything statistically significant, but the OS rate after 5 years was three times higher for the CRS+HIPEC group than for CRS alone. Complications appeared to be similar amongst the two groups and recurrence rates appeared to be lower for the CRS + HIPEC group. The authors concluded treatment of CRS+HIPEC for patients with GCPC appears to be more beneficial than when compared to CRS alone. Limitations included lack of RCTs, small sample sizes within studies for evaluation and lack of studies. Furthermore, the wide confidence interval and heterogeneity in findings decrease the confidence in the results. Due to the lack of available studies, additional robust studies should be conducted on OS and the efficacy of HIPEC in the treatment of GCPC.

Zhang et al. (2022) assessed the effectiveness and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) combined with surgery for different stages of advanced gastric cancer (AGC). A search was conducted using the Web of Science (WOS), Medline, PubMed, Embase, Cochrane Library, and China National Knowledge Infrastructure (CNKI) websites. Based on the inclusion criteria, the authors were able to utilize 23 of the 40 articles found; ten of which were RCTs. The RCTs were assessed using the Cochrane Risk of Bias Tool and non-RCTs used the MINORs score. The studies were divided into two groups: AGC without carcinomatosis group and gastric cancer with peritoneal carcinomatosis (GCPC). The meta-analysis involved 1892 patients: 1201 patients in the AGC group and 691 patients in the GCPC. Treatment consisted of HIPEC + radical surgery, radical surgery alone, HIPEC + cytoreductive surgery, and cytoreductive surgery or systemic chemotherapy alone. In the ACG group, the RCT and non-RCT analyses were reviewed separately. The authors found in the RCT studies, the HIPEC technique

was favored, and the 5-year survival rate of this group was substantially higher than that of the control group. In the GCPC group, again the RCT and non-RCT analysis were reviewed separately, but the RCT analyses showed no significant difference between the two groups in the 1-, 2- and 3-year survival rate. For the AGC group, the authors found the OS rate was increased and recurrence rates were decreased. In the GCPC group, the authors found the results indicated that HIPEC with surgery is the most favorable treatment method. The authors concluded standard surgical management when combined with preventive HIPEC can prolong an individual's survival and reduce the recurrence rate. Limitations included low number of RCTs, particularly for the GCPC group and the inability to generalize the results to Western populations; future RCTs are warranted.

Brenkman et al. (2019) noted that survival after potentially curative treatment of GC remains low, mostly due to peritoneal recurrence. This systematic review gave an overview of available comparative studies concerning prophylactic HIPEC for patients with GC with neither clinically evident metastases nor positive peritoneal cytology who undergo potentially curative gastrectomy. After a thorough review of the literature, a total of 11 studies were included comparing surgery plus prophylactic HIPEC versus surgery alone: three RCTs and eight nonrandomized comparative studies, involving 1,145 patients. Risk of bias was high in most of the studies. Morbidity after prophylactic HIPEC was 17 to 60 % compared to 25 to 43 % after surgery alone; OS was 32 to 35 months after prophylactic HIPEC and 22 to 28 months after SA. The 5-year survival rates were 39 to 87 % after prophylactic HIPEC and 17 to 61 % after SA, which was statistically significant in three studies. Peritoneal recurrence occurred in 7 to 27 % in the HIPEC group, compared to 14 to 45 % after surgery alone. This review suggested that prophylactic HIPEC for GC could be performed safely, may prevent peritoneal recurrence and may prolong survival. However, studies were heterogeneous and outdated, which emphasized the need for well-designed trials conducted according to current standards.

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 OS 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 OS 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 OS 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 CRS is a critical prognostic factor for survival. The authors 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.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for gastric cancer state that HIPEC or laparoscopic HIPEC may be a therapeutic alternative for carefully selected stage IV patients in the setting of ongoing clinical trials and is under further clinical investigation (NCCN, 2023).

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. Postoperative intraperitoneal chemotherapy has been demonstrated to improve OS and is recommended based on high-level evidence (NCCN, 2023).

Filis et al. (2022) conducted a systematic review and meta-analysis to assess the available level I evidence for use versus non-use of HIPEC in advanced primary and recurrent ovarian cancer. The primary outcome being measured was OS with a secondary outcome of disease-free survival (DFS) for primary ovarian cancer and PFS for recurrent ovarian cancer. The review included six RCT's four of which evaluated primary ovarian cancer (519 patients) and two which evaluated recurrent ovarian cancer (218 patients). For primary ovarian cancer, the combination of HIPEC with interval CRS and neoadjuvant chemotherapy significantly improved the 5-year OS and DFS when compared to standard treatment alone. In the absence of neoadjuvant chemotherapy, the use of HIPEC combined with CRS showed no advantage to survival. For recurrent ovarian cancer, the use of HIPEC was not associated with any survival advantage. Limitations of the review include lack of information for survival and PFS directly reported in the studies examined, potential bias with neoadjuvant chemotherapy given to selected patients, and

designs were not homogenous as different chemotherapy drugs were administered. (Publications by van Driel 2018 and Spiliotis 2015, which were previously cited in this policy, are included in this systematic review).

Bouchard-Fortier et al. (2020) performed a systematic review and meta-analysis to assess outcomes and perioperative morbidity following HIPEC in patients (n = 2252) with primary epithelial ovarian cancer (EOC). Thirty-five studies were included. The timing, temperature and chemotherapeutic agents used for HIPEC differed across studies. Reported OS was highly variable (3-year OS range: 46-77%). Three comparative cohort studies and one randomized trial reported statistically significant survival benefits for HIPEC over surgery alone, while two comparative cohort studies did not. The pooled proportions for grade III-IV morbidity and postoperative death at 30 days were 34% and 0% respectively. One RCT suggested that HIPEC at the time of interval CRS should be considered in patients with primary EOC. However, there is significant heterogeneity in the literature regarding an appropriate HIPEC regimen and short- and long-term outcomes. High-quality prospective RCTs are needed to clarify the role of HIPEC in the first-line treatment of primary EOC. (Publications by Deraco 2011, Helm 2010 and van Driel 2018, which were previously cited in this policy, are included in this systematic review).

Lei et al. (2020) conducted a cohort study (n = 584) at five high-volume centers in China to compare survival outcomes between CRS with HIPEC (n = 425) versus CRS alone (n = 159) for patients with stage III EOC. The median follow-up period was 42 months. Primary outcomes were median survival time and 3-year OS. The median survival time was 49.8 months for patients undergoing CRS plus HIPEC and 34 months for patients undergoing CRS alone. The 3-year OS rate was 60.3% for patients undergoing CRS plus HIPEC and 49.5% for patients undergoing CRS alone. Participants were further stratified into complete and incomplete surgery subgroups. In the complete surgery subgroup, the median OS was 53.9 months for the CRS plus HIPEC group and 42.3 months for the CRS alone group. The 3-year OS rate was 65.9% in the CRS plus HIPEC group and 55.4% in the CRS alone group. In the incomplete surgery subgroup, the median OS was 29.2 months for the CRS plus HIPEC group and 19.9 months with CRS alone. The 3-year OS rate was 44.3% in the CRS plus HIPEC group and 36.7% in the CRS alone group, but the difference was not statistically significant. These results are limited by the retrospective and observational study design. Due to this and other limitations, the authors have launched a prospective, multicenter, large-scale RCT to compare CRS followed by HIPEC with CRS alone for stage III EOC.

A Hayes report analyzed two randomized controlled trial (RCT), one prospective cohort study, and eight retrospective cohort studies examining the efficacy and safety of CRS plus HIPEC compared with CRS alone for PC due to ovarian cancer in patients with PM. Although the quality of evidence was low, it did suggest that HIPEC in addition to CRS may be more effective than CRS alone in improving OS in some patients. 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 HIPEC per se. The most common complications attributable to HIPEC include hematological toxicity and renal insufficiency/failure, occurring in < 20% of patients (Hayes, 2019b; updated 2022).

In a meta-analysis, Kim et al. (2019) identified patients with ovarian cancer who could obtain survival benefit from HIPEC. A total of 13 case-control studies and two RCTs were included in this meta-analysis. These investigators examined the effect of HIPEC on disease-free survival (DFS) and OS, and performed subgroup analyses based on the study design, adjustment of confounding variables, and quality of the study. HIPEC improved both DFS (HR, 0.603; 95 % CI: 0.513 to 0.709) and OS (HR, 0.640; 95 % CI: 0.519 to 0.789). In cases of primary disease, HIPEC improved DFS (HR, 0.580; 95 % CI: 0.476 to 0.706) and OS (HR, 0.611; 95 % CI: 0.376 to 0.992). Sub-group analyses revealed that HIPEC did not improve OS but improved DFS of patients with residual tumors of less than or equal to 1 cm or no visible tumors. In cases of recurrent disease, HIPEC was associated with better OS (HR, 0.566; 95 % CI: 0.379 to 0.844) but not with DFS. Sub-group analyses also revealed similar tendencies. However, HIPEC improved DFS of patients with residual tumors of less than or equal to 1 cm or no visible tumors, while it improved OS of only those with residual tumors of less than or equal to 1 cm. The authors concluded that HIPEC may improve DFS of patients with ovarian cancer when residual tumors were less than or equal to 1 cm or not visible. It may also improve OS of only patients with recurrent disease whose residual tumors were less than or equal to 1 cm. The researchers noted that additional relevant clinical trials are needed to select the appropriate patients and to demonstrate the effect of HIPEC on their prognosis in the near future. (Publications by Cascales-Campos 2014, Spiliotis 2015, and van Driel 2018, which were previously cited in this policy, are included in this systematic review).

Wang et al. (2019) conducted a systematic review and meta-analysis to investigate whether CRS plus HIPEC in ovarian cancer patients improved OS, disease free survival and adverse effects when compared to CRS alone. Thirteen studies were included in the analysis: two randomized controlled trials and 11 observational studies. Studies included participants with a mix of primary and recurrent cancer. For primary ovarian cancer patients, HIPEC significantly improved OS and disease-free survival

compared with the CRS group. For recurrent ovarian cancer patients, HIPEC significantly improved OS but not disease-free survival. In a subgroup analysis, improved OS and disease-free survival were observed in patients who received HIPEC based on the following factors: studies published before 2015, studies with ≥ 100 patients, a single drug protocol, 90-minute HIPEC duration and a regimen of CRS plus HIPEC followed by chemotherapy. Tolerable toxicity, morbidity, mortality, and quality of life outcomes were reported. The authors noted that further studies based on individual data or multicenter RCTs are needed to confirm and update these findings.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for ovarian cancer state that HIPEC with cisplatin (100 mg/m^2) can be considered at the time of interval debulking surgery (IDS) following neoadjuvant chemotherapy for stage III ovarian disease (NCCN, 2023).

Other Cancers

NCCN clinical practice guidelines on cervical cancer (2021), uterine neoplasms (2021), hepatobiliary cancers (2021), neuroendocrine and adrenal tumors (2021) and soft tissue sarcoma (2021) do not mention HIPEC as a management tool.

Hayes analyzed one retrospective cohort study, three prospective uncontrolled studies, and five retrospective uncontrolled studies examining the efficacy and safety of CRS plus HIPEC in patients with sarcomas and peritoneal involvement. The overall quality of the body of evidence was rated as very low for CRS plus HIPEC for the treatment of sarcomas with peritoneal involvement. A lack of comparative studies and substantial variation across patient populations and treatment protocols underscore the need for additional studies to fill persisting evidence gaps and establish definitive patient selection criteria (Hayes, 2019c; updated 2023).

Frassini et al. (2022) conducted a systematic review and meta-analysis to provide an overview of the effectiveness and safety of intraperitoneal treatments in the management of pancreatic cancer. Eleven studies (212 patients) were included in the analysis. The patients were placed into three groups, HIPEC (64 patients), pressurized intraperitoneal aerosol chemotherapy (PIPAC) (55 patients), and normothermic intraperitoneal chemotherapy (NIPEC) (93 patients). The primary outcome measured was survival rate. For patients in the HIPEC group who had surgical treatment along with HIPEC, the survival rate at three years was 24% compared to 5.3% in PIPAC and 7.9% in NIPEC. The authors conducted further subgroup analysis on patients who underwent HIPEC along with surgical resection following neoadjuvant chemotherapy without evidence of peritoneal disease location and noted the 3-year SR was 25.5%. Limitations of the review include lack of any RCTs on this topic, small sample sizes with included studies, and unclear staging within the included studies. Additionally, because of the non-randomized design of the included studies, there was moderate to serious risk of bias in all domains that were measured. The authors note that RCTs with a strict selection of patients are necessary to support this treatment.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

CRS plus HIPEC is a procedure and, therefore, not subject to FDA regulation. However, there are many surgical instruments approved for use in pelvic and abdominal surgery. Refer to 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 April 12, 2023)

References

Auer RC, Siajohanathan D, Biagi J, et al. Indications for hyperthermic intraperitoneal chemotherapy with cytoreductive surgery: a systematic review. Eur J Cancer. 2020 Mar;127:76-95.

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, 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.

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.

Bouchard-Fortier G, Cusimano MC, Fazelzad R, et al. Oncologic outcomes and morbidity following heated intraperitoneal chemotherapy at cytoreductive surgery for primary epithelial ovarian cancer: a systematic review and meta-analysis. Gynecol Oncol. 2020 Jul;158(1):218-228.

Brenkman HJF, Paeva M, van Hillegersberg R, et al. Prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) for gastric cancer - A systematic review. J Clin Med. 2019 Oct 15;8(10):1685.

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.

Chen V, Jones M, Cohen L, et al. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in small bowel adenocarcinoma with peritoneal metastasis: a systematic review. Pleura Peritoneum. 2022 Nov 18;7(4):159-167.

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.

Deng H, Li B, Qin X. The short- and long-term survival of hyperthermic intraperitoneal chemotherapy (HIPEC) in the advanced gastric cancer with/without peritoneal carcinomatosis: a systematic review and meta-analysis of randomized controlled trials. Updates Surg. 2022 Dec;74(6):1805-1816.

Deraco M, Kusamura S, Virzì 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.

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.

Di Leo A, Corasce A, Weindelmayer J, et al. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in pseudomyxoma peritonei of appendiceal origin: result of a single centre study. Updates Surg. 2020 Dec;72(4):1207-1212.

ECRI. Hyperthermic intraperitoneal chemotherapy and cytoreductive surgery for colorectal peritoneal metastases. Clinical Evidence Assessment. 2022 Sept.

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. 2010 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.

Filis P, Mauri D, Markozannes G, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC) for the management of primary advanced and recurrent ovarian cancer: a systematic review and meta-analysis of randomized trials. ESMO Open. 2022 Oct;7(5):100586.

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.

Frassini S, Calabretto F, Granieri S, et al. Intraperitoneal chemotherapy in the management of pancreatic adenocarcinoma: A systematic review and meta-analysis. Eur J Surg Oncol. 2022 Sep;48(9):1911-1921.

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. 2010 Dec 15;116(24):5608-18.

Hayes, Inc. Health Technology Assessment. Hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis resulting from peritoneal mesothelioma. Lansdale, PA: Hayes, Inc.; November 2019a. Updated January 2023.

Hayes, Inc. Health Technology Assessment. Hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis resulting from ovarian cancer. Lansdale, PA: Hayes, Inc.; August 2019b. Updated September 2022.

Hayes, Inc. Health Technology Assessment. Hyperthermic intraperitoneal chemotherapy for sarcoma with peritoneal involvement. Lansdale, PA: Hayes, Inc.; December 2019c. Updated March 2023.

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.

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

Kim SI, Cho J, Lee EJ, et al. Selection of patients with ovarian cancer who may show survival benefit from hyperthermic intraperitoneal chemotherapy: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(50):e18355.

Kusamura S, Kepenekian V, Villeneuve L, et al.; PSOGI. Peritoneal mesothelioma: PSOGI/EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol. 2021a Jan;47(1):36-59.

Kusamura S, Barretta F, Yonemura Y, et al.; Peritoneal Surface Oncology Group International (PSOGI) and the French National Registry of Rare Peritoneal Surface Malignancies (RENAPE). The role of hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei after cytoreductive surgery. JAMA Surg. 2021b Mar 1;156(3):e206363.

Lei Z, Wang Y, Wang J, et al.; Chinese Peritoneal Oncology Study Group (Gynecologic Oncology Study Group). Evaluation of cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for stage III epithelial ovarian cancer. JAMA Netw Open. 2020 Aug 3;3(8):e2013940.

Li J, Wang AR, Chen XD, et al. Effect of hyperthermic intraperitoneal chemotherapy in combination with cytoreductive surgery on the prognosis of patients with colorectal cancer peritoneal metastasis: a systematic review and meta-analysis. World J Surg Oncol. 2022 Jun 14;20(1):200.

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.

Martins M, Santos-Sousa H, Araújo F, et al. Impact of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer with peritoneal carcinomatosis: a systematic review and meta-analysis. Ann Surg Oncol. 2022 Nov;29(12):7528-7537.

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 12, 2023.

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. 2014 Oct 14;111(8):1500-8.

Morris VK, Kennedy EB, Baxter NN, et al. Treatment of metastatic colorectal cancer: ASCO Guideline. J Clin Oncol. 2023 Jan 20;41(3):678-700.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Cervical cancer. v1.2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colon cancer. v1.2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Gastric cancer. v1.2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hepatobiliary cancers. v3.2021.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Mesothelioma: Pleural. V1.2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Neuroendocrine and adrenal tumors. v2.2022.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. v1.2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Small bowel adenocarcinoma. v1.2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Soft tissue sarcoma. v1.2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Uterine neoplasms. v1.2023.

National Institute for Health and Care Excellence (NICE). Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. IPG688. March 2021.

National Institute for Health and Care Excellence (NICE). Colorectal cancer. NG151. January 2020.

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.

Quénet F, Elias D, Roca L, et al.; UNICANCER-GI Group and BIG Renape Group. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Feb;22(2):256-266.

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.

Sluitor N, van der Bilt J, Croll D, et al. Cytoreduction and HIPEC versus surgery without HIPEC for goblet cell carcinoids and mixed adeno-neuroendocrine carcinomas: a propensity score matched analysis of centers in the Netherlands and Belgium. Clin Colorectal Cancer. 2020 Sep;19(3):e87-e99.

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.

Tangiitgamol S, Manuirivithaya S, Laopaioon M, et al. Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Dataase Syst R. 2013:4:CD006014.

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.

Verma V, Sleightholm RL, Rusthoven CG, et al. Malignant peritoneal mesothelioma: national practice patterns, outcomes, and predictors of survival. Ann Surg Oncol. 2018 Jul;25(7):2018-2026.

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.

Wang Y, Ren F, Chen P, et al. Effects of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) versus cytoreductive surgery for ovarian cancer patients: a systematic review and meta-analysis. Eur J Surg Oncol. 2019 Mar;45(3):301-309.

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

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.

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.

You YN, Hardiman KM, Bafford A, et al.; On Behalf of the Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of rectal cancer. Dis Colon Rectum. 2020 Sep;63(9):1191-1222.

Zhang JF, Lv L, Zhao S, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC) combined with surgery: a 12-year meta-analysis of this promising treatment strategy for advanced gastric cancer at different stages. Ann Surg Oncol. 2022 May;29(5):3170-3186.

Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Application** ***Individual Exchange Plans*** • Removed language indicating this Medical Policy does not apply to Individual Exchange benefit plans in the states of Massachusetts, Nevada, and New York **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Removed *Benefit Considerations* section • Archived previous policy version 2023T0573K

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.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, 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.