Intraoperative Hyperthermic Intraperitoneal Chemotherapy (HIPEC) (for North Carolina Only)

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Instructions for Use

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Related Policy

- Clinical Trials (for North Carolina Only)

Application

This Medical Policy only applies to the state of North Carolina.

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 federal, state, or contractual requirements 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.

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.

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 1,290 patients from 25 institutions who underwent 1,344 procedures. HIPEC was performed in 1,154 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, nine 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.

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.

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, 2021).

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 2021)

Verma et al. (2018) performed a cohort study of 1,514 patients to evaluate management patterns, outcomes, and prognostic factors of malignant PM in the USA. Three hundred seventy-nine (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 one-, three- and five-year survival of 84, 59, and 42%, respectively. Patients receiving EPIC and those receiving cisplatin intraperitoneal chemotherapy alone or in combination had an improved five-year survival. The authors concluded that HIPEC is a viable additional treatment option for patients with invasive

epithelial ovarian cancer (EOC) and may extend life in selected groups; it warrants further study in randomized controlled trials (RCTs).

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 seven years, representing 19 survivors of 39 patients (43.6%) with potential follow-up ≥ seven 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 ≥ seven years appeared to be cured. Cure rate was 43.6%.

Using a multicenter data registry, Chua et al. (2011b) identified 26 patients with multicystic PM treated by CRS and HIPEC. The primary endpoint was OS. 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 PM. OS was 56% and 17% at three and five years, respectively. Patients receiving cisplatin were more likely to be alive at one, two, and three 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.

A multicenter registry evaluated CRS combined with HIPEC for diffuse malignant PM. 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 three- and five-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 PM (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 PM. Seven prospective observational studies, involving 240 patients, were included. The median survival ranged from 34-92 months. The one-, three- and five-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 OS when compared to historical controls.

Clinical Practice Guidelines

Peritoneal Surface Oncology Group International (PSOGI)/EURACAN clinical practice guidelines on peritoneal mesothelioma state that CRS plus HIPEC is recommended in diffuse malignant PM patients 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 case series 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 = 1,548) compared with CRS alone (n = 376) in patients with PMP. The data included 1,924 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 five-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 five-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-institute outcomes 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 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 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 five-year OS were 90% and 58%, respectively. Regardless of histotype, disease-free survival was 95% at one year and 46% at five 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.

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 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 five-year mortality and morbidity. Observed to expected (OE) ratios were calculated for both mortality and morbidity. Mean and median three-year, five-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 OS. 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 five-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 three 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 five-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).

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

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.

In the multicenter PRODIGE 7 study, Quenet et al. (2021) randomized 265 patients with colorectal peritoneal metastases to CRS plus oxaliplatin-based HIPEC (n = 133) or CRS alone (n = 132). Patients had undergone complete macroscopic resection or surgical resection with less than 1 mm residual tumor tissue. The primary endpoint was OS. After median follow-up of 63.8 months, median OS was 41.7 months in the CRS plus HIPEC group and 41.2 months in the CRS alone group. At 30 days, two (2%) treatment-related deaths had occurred in each group. At 30 days, grade 3 or worse adverse events were similar in frequency between groups; however, at 60 days, grade 3 or worse adverse events were more common in the CRS plus HIPEC group.

A National Institute for Health and Care Excellence (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).

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, 2021).

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, 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).

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.

Hall et al. (2017) noted that although historically, patients with peritoneal carcinomatosis secondary to colorectal cancer have a poor overall prognosis, recent data supports the use of CRS and heated intraperitoneal chemotherapy (CRS + HIPEC) to specifically address the peritoneal disease. Retrospective studies on CRS + HIPEC have been promising, showing significant improvements in OS compared with systemic chemotherapy alone. However, CRS + HIPEC carries morbidity similar to other advance oncology procedures such as liver resection and pancreatoduonectomy. It is hoped that ongoing clinical trials will clarify its role in the treatment of patients with peritoneal metastatic colorectal cancer

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. (2015a) reported a median survival of 31 months in sixteen patients following CRS and HIPEC.

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.

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 two-year and five-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 = 1,084) or palliative surgery and/or systemic chemotherapy (n = 1,408). 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 five-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 five-year survival ranged between 13% and 22% (median 13%). 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 two- and five-year OS 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 OS 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.

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).

A 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 ten 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 five-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 five-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., 2014; de Cuba et al., 2013).

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.

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 five regions versus greater than five 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 eight-year follow-up to the previous study. In the standard arm, four patients were still alive, two with and two without disease. In the HIPEC arm, five patients were still alive, two with and three 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 five-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.

Clinical Practice Guidelines

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).

Gastric Cancer

There is some evidence demonstrating improved survival in gastric cancer patients with limited peritoneal carcinomatosis and complete cytoreduction. However, its role is still evolving and currently it cannot be recommended outside of a clinical trial protocol. 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.

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, 2021).

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 five-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 tended to demonstrate 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 (2,520 patients) were included. For patients without the presence of peritoneal carcinomatosis, the OS rates between the HIPEC and control groups at three or five years resulted in favor of the HIPEC group. No difference in the three-year OS but a prolonged median survival of four 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. 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.

Seshadri and Glehen (2016) stated that peritoneal metastasis, either synchronous or metachronous, is commonly seen in gastric cancer. It is associated with a poor prognosis, with a median survival of less than one year. The outcomes are not significantly improved by the use of systemic chemotherapy. These investigators reviewed evidence from randomized trials, predominantly from Asian countries, on the role of HIPEC in gastric cancer. CRS and HIPEC has been used in three situations in gastric cancer. Besides its role as a definitive treatment in patients with established peritoneal metastasis (PM), it has been used as a prophylaxis against peritoneal recurrence after curative surgery and also as a palliative treatment in advanced peritoneal metastasis with intractable ascites. While prophylactic HIPEC has been shown to reduce peritoneal recurrence and improve survival in many randomized trials, palliative HIPEC can reduce the need for frequent paracentesis in selected patients. The authors concluded that although CRS with HIPEC has shown promise in increasing the survival of selected patients with established PM from gastric cancer, larger studies are needed before this can be accepted as a standard of care.

Its role is still evolving and currently it cannot be recommended outside of a clinical trial protocol. Selection of patients is critical to achieve good results in the clinical setting due to the associated risks for morbidity and mortality.

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 OS 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 OS 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, two patients close to two years at last follow-up and one patient more than four years. No patient in the SA arm lived beyond 11 months. The authors concluded that maximal CRS 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 = 1,906) 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 one, two, three, give, and nine years. Compared with surgery alone, combination therapy was associated with a significant reduction in recurrence rate at two, three, and five 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 1,062 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 OS 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 one-, three- and five-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 one-, three- and five-year survival rate of 61, 30 and 23%, respectively.

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, 2021).

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, 2021).

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.

Bouchard-Fortier et al. (2020) performed a systematic review and meta-analysis to assess outcomes and perioperative morbidity following HIPEC in patients (n = 2,252) with primary EOC. Thirty-five studies were included. The timing, temperature and chemotherapeutic agents used for HIPEC differed across studies. Reported OS was highly variable (three-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.

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 three-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 three-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 three-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 three-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 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 one 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 2020).

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.

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.

van Driel et al. (2018) investigated whether the addition of HIPEC to interval CRS would improve outcomes among patients who were receiving neoadjuvant chemotherapy for stage III EOC. 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 CRS 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 OS, 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 CRS without HIPEC (surgery group) and in 99 of the 122 patients (81%) who underwent CRS 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 OS 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% versus 43%). The authors concluded that among women with advanced ovarian cancer, HIPEC plus complete or optimal interval CRS resulted in longer survival than CRS 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 CRS.

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 OS 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 OS 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.

Spiliotis et al. (2015) evaluated the use of HIPEC for treating recurrent EOC. In an eight-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 versus 26.8 months). In the non-HIPEC group, there was a statistically significant difference between platinum-sensitive versus platinum-resistant disease (15.2 versus 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.

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.

In a prospective phase II study, Ansaloni et al. (2012) analyzed the results of CRS and HIPEC in 39 patients with advanced 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 one patient (3%), and doxorubicin alone for one patient (3%). Microscopically complete cytoreduction was achieved for 35 patients (90%), macroscopic cytoreduction was achieved for three patients (7%) and a gross tumor debulking was performed for one patient (3%). Postoperative complications occurred in seven patients (18%) and reoperations in three 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 OS 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 OS 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 OS 30.3 months with 2-, 5- and 10-year OS 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 two 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 five-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 OS 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.

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)

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 June 14, 2021)

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Policy History/Revision Information

Date	Summary of Changes
01/01/2022	**Coverage Rationale** • Removed language indicating intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), when performed in conjunction with Cytoreductive Surgery (CRS), is proven and medically necessary for treating peritoneal Carcinomatosis resulting from small bowel cancer, provided there are no extra-abdominal metastases **Supporting Information** • Updated *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CSNCT0573.01

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