2.03.07	Hyperthermic Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies		
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Section:	2.0 Medicine	**Page:**	Page 1 of 36

Policy Statement

I. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of surgery may be considered **medically necessary** for the treatment of **either** of the following:
   A. Pseudomyxoma peritonei
   B. Diffuse malignant peritoneal mesothelioma

II. The use of HIPEC may be considered **medically necessary** in newly diagnosed epithelial ovarian or fallopian tube cancer at the time of interval cytoreductive surgery when **all** of the following criteria are met:
   A. The individual has stage III disease (see Policy Guidelines)
   B. The individual is not eligible for primary cytoreductive surgery or surgery had been performed but was incomplete and will receive neoadjuvant chemotherapy and subsequent interval debulking surgery (see Policy Guidelines)
   C. It is expected that complete or optimal cytoreduction can be achieved at time of the interval debulking surgery (see Policy Guidelines)

III. The use of HIPEC in all other settings to treat ovarian cancer, including but not limited to stage IIIC or IV ovarian cancer, is considered **investigational**.

IV. Cytoreductive surgery plus HIPEC is considered **investigational** for:
   A. Peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer
   B. All other indications, including goblet cell tumors of the appendix

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Ovarian cancer staging is as follows:

- Stage I: The cancer is confined to the ovary or fallopian tube.
- Stage II: The cancer involves 1 or both ovaries with pelvic extension.
- Stage III: The cancer has spread within the abdomen.
- Stage IV: The cancer is widely spread throughout the body.

Eligibility for neoadjuvant chemotherapy and interval debulking surgery is based on a high perioperative risk profile (i.e., the individual is a poor candidate to withstand an aggressive initial cytoreductive procedure) or a low likelihood of achieving cytoreduction to less than 1 cm (i.e., the individual has extensive disease that precludes upfront optimal cytoreduction) or surgery has been performed but was incomplete (i.e., after surgery, 1 or more residual tumors measuring less than 1 cm in diameter were present).

Complete cytoreduction is defined as no visible disease and optimal cytoreduction as 1 or more residual tumors measuring 10 mm or less in diameter remaining.

Coding

The coding for this overall procedure would likely involve codes for the surgery, Intraperitoneal Chemotherapy and Hyperthermia.

Cytoreduction
There is no specific CPT code for the surgical component of this complex procedure. It is likely that a series of CPT codes would be used to describe exploratory laparotomies of various components of the abdominal cavity, in addition to specific codes for resection of visceral organs, depending on the extent of the carcinomatosis.

Intraperitoneal Chemotherapy
CPT code 96446 identifies "chemotherapy administration into the peritoneal cavity via implanted port or catheter." When performed using a temporary catheter or performed intraoperatively, the unlisted code 96549 (unlisted chemotherapy procedure) would be reported.

Hyperthermia
This procedure does not refer to the external application of heat as described by CPT code 77605. There are no codes for the heating of the chemotherapy.

Description

Cytoreductive surgery (CRS) includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination. Cytoreductive surgery may be followed by infusion of intraperitoneal chemotherapy with or without heating, which is intended to improve the tissue penetration of the chemotherapy. When heated, this is referred to as hyperthermic intraperitoneal chemotherapy (HIPEC). Cytoreductive surgery and HIPEC have been proposed for a number of intra-abdominal and pelvic malignancies such as pseudomyxoma peritonei and peritoneal carcinomatosis from colorectal, gastric, or endometrial cancer.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Mitomycin, oxaliplatin, carboplatin, and other drugs used for HIPEC have not been approved by the U.S. Food and Drug Administration (FDA) for this indication.

Several peritoneal lavage systems (FDA product code: LGZ) have been cleared for marketing by the FDA through the 510(k) process to provide "warmed, physiologically compatible sterile solution" (e.g., Performer® HT perfusion system; RanD). None have received marketing approval or clearance to administer chemotherapy. The FDA has issued warnings to manufacturers of devices that are FDA-

cleared for peritoneal lavage using sterile saline solutions when these devices are marketed for off-label use in HIPEC.

Table 1. Hyperthermic Intraperitoneal Lavage Devices Cleared by the U.S. Food and Drug Administration

Device	Manufacturer	Date Cleared	510(k) No.	Indication
FluidSmart	THERMEDX LLC	9/5/2017	K172048	For irrigation, distention, fluid warming, and fluid volume/deficit measurements in endoscopic procedures within gynecology, urology, and orthopedic disciplines.
Hang&Go PAC	RanD S.r.l.	12/28/2016	K161613	To recirculate, filtrate and perfuse physiologically compatible sterile solution (i.e. saline solution) in the thoracic or abdominal cavity
The Belmont Hyperthermia Pump	BELMONT INSTRUMENT CORPORATION	9/2/2015	K152208	To raise the temperature of the thoracic or peritoneal cavity to the desired target temperature by continuously lavaging the cavity with circulating warmed sterile solution

Rationale

Background

Pseudomyxoma Peritonei

Pseudomyxoma peritonei is a clinicopathologic disease characterized by the production of mucinous ascites and mostly originates from epithelial neoplasms of the appendix. Appendix cancer is diagnosed in fewer than 1000 Americans each year; less than half are epithelial neoplasms.[1,]The incidence of pseudomyxoma peritonei is estimated at 2 cases per 1 million individuals.[2,] As mucin-producing cells of the tumor proliferate, the narrow lumen of the appendix becomes obstructed and subsequently leads to appendiceal perforation. Neoplastic cells progressively colonize the peritoneal cavity and produce copious mucin, which collects in the peritoneal cavity. Pseudomyxoma peritonei ranges from benign (disseminated peritoneal adenomucinosis) to malignant (peritoneal mucinous carcinomatosis), with some intermediate pathologic grades. Clinically, this syndrome ranges from early pseudomyxoma peritonei, usually discovered during imaging or laparotomy performed for another reason, to advanced cases with a distended abdomen, bowel obstruction, and starvation.

Treatment

The conventional treatment of pseudomyxoma peritonei is surgical debulking, repeated as necessary to alleviate pressure effects. However, repeated debulking surgeries become more difficult due to progressively thickened intra-abdominal adhesions, and this treatment is palliative, leaving visible or occult disease in the peritoneal cavity.[3,]

Peritoneal Carcinomatosis of Colorectal Origin

Peritoneal dissemination develops in 10% to 15% of patients with colon cancer.

Treatment

Despite the use of increasingly effective regimens of chemotherapy and biologic agents to treat advanced disease, peritoneal metastases are associated with a median survival of 6 to 7 months.

Peritoneal Carcinomatosis of Gastric Origin

Peritoneal carcinomatosis is detected in more than 30% of patients with advanced gastric cancer and is a poor prognostic indicator. The median survival is 3 months, and 5-year survival is less than 1%.[4,] Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis.[5,]

Treatment

Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for a cure.[6,]

Peritoneal Mesothelioma

Malignant mesothelioma is a relatively uncommon malignancy that may arise from the mesothelial cells lining the pleura, peritoneum, pericardium, and tunica vaginalis testis. In the United States, 200 to 400 new cases of diffuse malignant peritoneal mesothelioma are registered every year, accounting for 10% to 30% of all-type mesothelioma.[7,] Diffuse malignant peritoneal mesothelioma has traditionally been considered a rapidly lethal malignancy with limited and ineffective therapeutic options. The disease is usually diagnosed at an advanced stage and is characterized by multiple variably sized nodules throughout the abdominal cavity. As the disease progresses, the nodules become confluent to form plaques, masses, or uniformly cover peritoneal surfaces. In most patients, death eventually results from locoregional progression within the abdominal cavity. In historical case series, treatment by palliative surgery, systemic or intraperitoneal chemotherapy, and abdominal irradiation has resulted in median survival of 12 months.

Treatment

Surgical cytoreduction (resection of visible disease) in conjunction with hyperthermic intraperitoneal chemotherapy (HIPEC) is designed to remove visible tumor deposits and residual microscopic disease. By delivering chemotherapy intraperitoneally, drug exposure to the peritoneal surface is increased some 20-fold compared with systemic exposure. In addition, previous animal and in vitro studies have suggested that the cytotoxicity of mitomycin C is enhanced at temperatures greater than 39°C (102.2°F).

Ovarian Cancer

Several different types of malignancies can arise in the ovaries; epithelial carcinoma is the most common, accounting for 90% of malignant ovarian tumors. Epithelial ovarian cancer is the fifth most common cause of cancer death in women in the United States. Most ovarian cancer patients (>70%) present with widespread disease, and annual mortality is 65% of the incidence rate. In addition, African American women reportedly have a higher prevalence of presenting with more advanced tumors, being undertreated or untreated, and having shorter disease-free survival compared to other racial groups.[8,]

Treatment

Current management of advanced epithelial ovarian cancer is cytoreductive surgery (CRS) followed by combination chemotherapy. Tumor recurrences are common, and the prognosis for recurrent disease is poor.

Cytoreductive surgery plus HIPEC in combination with systemic chemotherapy is being studied for primary and recurrent disease. Because HIPEC is administered at the time of surgery, treatment-related morbidity may be reduced compared with intraperitoneal chemotherapy administered postoperatively.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life (QOL), and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome

measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Pseudomyxoma Peritonei

Clinical Context and Therapy Purpose

The purpose of cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) in individuals with pseudomyxoma peritonei is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with pseudomyxoma peritonei.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9,] It may be followed by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C or a platinum agent. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

Comparators

The following therapies are currently being used to treat pseudomyxoma peritonei: CRS alone and systemic chemotherapy.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival (e.g., progression-free survival [PFS]), QOL, treatment-related mortality, and treatment-related morbidity.

Morbidity and mortality from the procedure are measured in the early postoperative period. Survival outcomes (PFS and OS) should be measured out to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Discussion for this indication is divided into primary treatment and treatment for recurrence. Table 2 summarizes relevant studies on CRS plus HIPEC in pseudomyxoma peritonei.

Primary Treatment

Studies describing CRS plus HIPEC as primary treatment in pseudomyxoma peritonei are summarized in Table 2; studies that included at least 60 patients are discussed further in the text below.

Jimenez et al (2014) retrospectively reviewed a prospective database of patients with peritoneal carcinomatosis maintained by a U.S. medical center.[10,] Two hundred two patients with peritoneal carcinomatosis from appendiceal cancer who underwent CRS plus HIPEC were included; 125 (62%) patients had high-grade tumors (peritoneal mucinous carcinomatosis), and 77 (38%) patients had low-grade tumors (disseminated peritoneal adenomucinosis). Results for the entire cohort and for subgroups defined by tumor histology are shown in Table 2. In the high-grade peritoneal mucinous carcinomatosis group, Peritoneal Cancer Index (PCI) score (scale range, 0 to 39), completeness of cytoreduction, and lymph node status were significantly associated with survival; in the low-grade disseminated peritoneal adenomucinosis group, completeness of cytoreduction was significantly associated with survival.

Glehen et al (2010) published a retrospective, multicenter cohort study that evaluated toxicity and prognostic factors after CRS plus HIPEC and/or unheated intraperitoneal chemotherapy for 5 days postoperatively.[11,] Patients had diffuse peritoneal disease from malignancies of multiple different histologic origins. Exclusion criteria were perioperative chemotherapy performed more than 7 days after surgery and the presence of extra-abdominal metastases. The study included 1290 patients from 25 institutions who underwent 1344 procedures between 1989 and 2007. In 1154 procedures, HIPEC was performed. Postoperative mortality was 4.1%. The principal origin of peritoneal carcinomatosis was pseudomyxoma peritonei in 301 patients. Median OS for patients with pseudomyxoma peritonei was not reached (the median OS for all patients was 34 months).

Additional information about the subgroup of patients with pseudomyxoma peritonei was provided by Elias et al (2010).[12,] Cytoreductive surgery was conducted in 219 (73%) patients, and HIPEC was performed in 255 (85%). The primary tumor site was the appendix in 91% of patients, the ovary in 7%, and unknown in 2%. Tumor histology was disseminated peritoneal adenomucinosis in 51%, peritoneal carcinomatosis with intermediate features in 27%, and peritoneal mucinous carcinomatosis in 22%. The postoperative mortality was 4% and the morbidity rate was 40%. Mean follow-up was 88 months. One-, 3-, and 5-year OS rates were 89.4%, 84.8%, and 72.6%, respectively. The 10-year OS rate was 54.8%. Median OS had not yet been reached but would exceed 100 months. Disease-free

survival (DFS) was 56% at 5 years (the median duration of DFS was 78 months). A multivariate analysis identified 5 prognostic factors: extent of peritoneal seeding (p=.004), institution (p<.001), pathologic grade (p=.03), sex (p=.02), and use of HIPEC (p=.04). When only the 206 patients with complete CRS were considered, the extent of peritoneal seeding was the only significant prognostic factor (p=.004).

Chua et al (2009) reported on the long-term survival of 106 patients with pseudomyxoma peritonei treated between 1997 and 2008 with CRS plus HIPEC and/or unheated intraperitoneal chemotherapy for 5 days postoperatively.[13,] Sixty-nine percent of patients had complete cytoreduction. Eighty-three (78%) patients had HIPEC intraoperatively, 81 (76%) patients had unheated postoperative intraperitoneal chemotherapy, and 67 (63%) patients had both. Seventy-three patients had disseminated peritoneal adenomucinosis, 11 had peritoneal mucinous carcinomatosis, and 22 had mixed tumors. The mortality rate was 3%, and the severe morbidity rate was 49%. The median follow-up was 23 months (range, 0 to 140 months). The median OS was 104 months with a 5-year OS rate of 75%. Median PFS was 40 months with 1-, 3-, and 5-year PFS rates of 71%, 51%, and 38%, respectively. Factors influencing OS included the histopathologic type of tumor (p=.002), with the best survival in patients with disseminated peritoneal adenomucinosis and worst survival in patients with peritoneal mucinous carcinomatosis. Other factors influencing survival were the use of both HIPEC and unheated postoperative intraperitoneal chemotherapy, completeness of cytoreduction, and severe morbidity.

Vaira et al (2009) reported on a single institution's experience managing pseudomyxoma peritonei with CRS and HIPEC in 60 patients, 53 of whom had final follow-up data.[14,] The postoperative morbidity rate was 45%; no postoperative deaths were observed. The primary tumor was appendiceal adenocarcinoma in 72% of patients and appendiceal adenoma in 28%. Approximately half of the patients with adenocarcinoma had received previous systemic chemotherapy. Five- and 10-year OS rates were 94% and 85%, respectively; 5- and 10-year DFS rates were 80% and 70%, respectively. Significant differences in improved OS were observed in patients who had complete CRS (p<.003) and in those with histologic type disseminated peritoneal adenomucinosis compared with those with peritoneal mucinous carcinomatosis (p<.014).

Elias et al (2008) reported on the results of 105 consecutive patients with pseudomyxoma peritonei treated between 1994 and 2006 with CRS plus HIPEC.[3,] The primary tumor was the appendix in 93 patients, ovary in 3, urachus in 1, pancreas in 1, and indeterminate in 7. Tumor histology was disseminated peritoneal adenomucinosis in 48% of patients, intermediate in 35%, and peritoneal mucinous carcinomatosis in 17%. At the end of the surgery, 72% of patients had no visible residual peritoneal lesions. The postoperative mortality rate was 7.6% and the morbidity rate was 67.6%. The median follow-up was 48 months, and 5-year OS and PFS rates were 80% (95% confidence interval [CI], 68% to 88%) and 68% (95% CI, 55% to 79%), respectively. On multivariate analysis, 2 factors had a negative influence on DFS: serum carbohydrate antigen 19-9 level (a marker of biliopancreatic malignancy) greater than 300 units/mL and nondisseminated peritoneal adenomucinosis tumor histology.

Table 2. Primary and Recurrence Study Results for CRS Plus HIPEC in Pseudomyxoma Peritonei

Study	N	Postoperative Mortality/Morbidity, %	Median OS, mo	5-Year OS, %	Median PFS, mo	5-Year PFS, %
Primary treatment						
Jimenez et al (2014)[10,]	202	0/16	90	56	40	44
High-grade tumor (peritoneal	125	NR	47	41	26	34

Study	N	Postoperative Mortality/Morbidity, %	Median OS, mo	5-Year OS, %	Median PFS, mo	5-Year PFS, %
mucinous carcinomatosis)						
Low-grade tumor (disseminated peritoneal adenomucinosis)	77	NR	Not reached[a]	83	NR	58
Marcotte et al (2014)[15,]	58	2/40	NR	77	NR	50[b]
Glehen et al (2010)[11,]	301	4/40	34	73	78	56
Chua et al (2009)[13,]	106	3/49	104	75	40	38
Vaira et al (2009) [14,]	60	0/45	NR	94	NR	80
Elias et al (2008)[3,]	105	8/68	>100	80	NR	68
Yan et al (2007)[16,] (SR)	NR	NR	51 to 156	52 to 96	NR	NR
Recurrence						
Lord et al (2015)[17,,c]	35	NR	129.5[e]	79	NR	NR
Sardi et al (2013)[18,,d]	26	0/42	NR	34	NR	NR

CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; NR: not reported; OS: overall survival; PFS: progression-free survival; SR: systematic review.
[a] Median OS not reached with mean follow-up of 36 months.
[b] Five-year disease-free survival.
[c] Data from Lord et al (2015) represents 35 patients who had recurrence and redo CRS plus HIPEC out of 512 patients in the total study cohort.
[d] Results after second procedure shown.
[e] Mean OS.

Recurrence

From the same U.S. medical center database studied by Jimenez et al (2014; previously described), Sardi et al (2013) identified 26 patients who underwent repeat CRS plus HIPEC for peritoneal carcinomatosis recurrence.[18,] Sixteen (62%) patients had high-grade peritoneal mucinous carcinomatosis and 10 (38%) patients had low-grade disseminated peritoneal adenomucinosis. Patients eligible for repeat CRS plus HIPEC had Eastern Cooperative Oncology Group Performance Status scores of 0 or 1. The proportion of patients who had a preoperative PCI score of less than 20 was 35% before the second procedure and 75% before the third procedure (1/4 patients). There were no 30-day postoperative deaths; postoperative morbidity was 42% after the second procedure and 50% after the third procedure. After the second procedure, 1-, 3-, and 5-year OS rates were 91%, 53%, and 34%, respectively. After the third procedure, the 1-year OS rate was 75%.

Lord et al (2015) reported on a retrospective cohort study of 512 patients with perforated appendiceal tumors and pseudomyxoma peritonei who received CRS plus HIPEC at a single center in the U.K. and achieved complete cytoreduction.[17,] Thirty-five (26%) of 137 patients who experienced recurrence underwent repeat CRS plus HIPEC; median time to recurrence was 26 months. Complete cytoreduction was achieved (again) in 20 (57%) patients. The mean OS in patients without recurrence (n=375), patients who recurred and had repeat CRS plus HIPEC (n=35), and patients who recurred but did not have repeat CRS plus HIPEC (n=102) was 171 months (95% CI, 164 to 178 months), 130 months (95% CI, 105 to 153 months), and 101 months (95% CI, 84 to 119 months) across the 3 groups,

respectively (p=.001). Five-year survival rates were 91%, 79%, and 65%, respectively. The incidence of complications was similar between primary and repeat procedures.

Section Summary: Pseudomyxoma Peritonei

Retrospective cohort studies and systematic reviews have reported median survival ranging from 47 to 156 months and 5-year OS ranging from 41% to 96% for patients with primary treatment for pseudomyxoma peritonei treated with CRS plus HIPEC. Two retrospective studies reported results of CRS plus HIPEC for recurrence with 5-year OS rates of 34% and 79%. Although no direct comparisons between CRS plus HIPEC and other interventions have been published, traditional surgical debulking is not curative, and complete CRS alone (without HIPEC) has been associated with a 5-year OS of approximately 50%, along with high recurrence rates (91%, with a median DFS of 24 months).[3,] Median PFS with CRS plus HIPEC as primary treatment has been reported as 40 to 78 months, with 5-year PFS rates of 38% to 80%. Procedure-related morbidity and mortality have generally decreased over time. Because the prevalence of pseudomyxoma peritonei is very low, conducting comparative trials is difficult.

Peritoneal Carcinomatosis of Colorectal Origin

Clinical Context and Therapy Purpose

The purpose of CRS plus HIPEC in individuals with peritoneal carcinomatosis of colorectal origin is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with peritoneal carcinomatosis of colorectal origin.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9,] It may be followed by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C or a platinum agent. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

Comparators

The following therapies are currently being used to treat peritoneal carcinomatosis of colorectal origin: CRS alone and systemic chemotherapy.

Outcomes

The general outcomes of interest are OS, disease-specific survival (e.g., PFS), QOL, treatment-related mortality, and treatment-related morbidity.

Morbidity and mortality from the procedure are measured in the early postoperative period. Survival outcomes (PFS and OS) should be measured out to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Li et al (2022) published a systematic review and meta-analysis of studies evaluating CRS with HIPEC.[19,] A total of 10 trials (3 RCTs) with 3200 patients were included. Cytoreductive surgery plus HIPEC improved OS compared with control (hazard ratio [HR], 0.53; 95% CI, 0.38 to 0.73; p<.00001; I^2=82.9%). A notable limitation of the analysis is the large number of observational trials and high heterogeneity among trials.

Huang et al (2017) published a systematic review and meta-analysis of studies assessing CRS plus HIPEC in patients with peritoneal carcinomatosis from colorectal cancer.[20,] Reviewers included 76 studies published between 1993 and 2016. Fifteen studies were controlled, 1 of which was an RCT, and 61 were uncontrolled studies. In a meta-analysis of the controlled studies, there was a significantly higher survival rate in patients who received CRS plus HIPEC compared with standard therapy (e.g., palliative surgery alone or with systemic chemotherapy) (pooled HR , 2.67; 95% CI, 2.21 to 3.23; I^2=0%, p<.001). In sensitivity analyses, date of publication, geographic location of study conduct, and chemotherapy regimen used in the HIPEC procedure did not have a significant impact. In the controlled studies, the mean mortality rate was 4.3% in the CRS plus HIPEC group compared with 6.2% in the traditional treatment group (p=.423). The mean morbidity rate was 19.8% in the CRS plus HIPEC group and 20.5% in the traditional treatment group (p=.815). In all 76 studies, the mean mortality rate was 2.8% and mean morbidity rate was 33%.

Two systematic reviews published in 2014 examined QOL outcomes in patients with peritoneal carcinomatosis who underwent CRS plus HIPEC.[21,22,] Both reviews included studies that used structured QOL scales; Shan et al (2014) included 15 studies (N=1583),[21,] 14 of which appeared in the review of 20 studies (N=1181 patients) by Seretis et al (2014).[22,] No RCTs were identified. Studies were heterogeneous in terms of sample sizes (median, 60 patients; range, 5 to 216 patients), response rates (most <85%), primary cancers (e.g., gastrointestinal, ovarian, endometrial, mesothelioma), QOL scales, and timing of QOL evaluations. Nonetheless, both reviews reported a decline in health-related QOL compared with baseline values up to 4 months posttreatment. At 1 year, QOL scores improved to baseline values or above. In a random-effects meta-analysis of 8 studies (n=499), overall health (I^2=38%) and emotional health (I^2=41%) showed statistically significant improvements compared with baseline, but physical (I^2=60%), social (I^2=0%), and functional (I^2=74%) health did not.[21,] Improvements were small to medium (standardized mean difference, <0.4 for all outcomes). Although this evidence would suggest improvements from baseline in some QOL domains, the absence of parallel control groups limits interpretation of the results.

Randomized Controlled Trials

Two RCTs have compared CRS plus HIPEC to CRS alone in patients with peritoneal colorectal metastases. Trials not previously included in the meta-analyses above are summarized in Tables 3 through 6 below.

Quenet et al (2021) reported results from a randomized, open label RCT comparing CRS plus oxaliplatin-based HIPEC to CRS alone in patients with colorectal cancer and peritoneal metastases (Tables 3 through 6).[23,] Most patients in the trial achieved complete cytoreduction, and all patients had <1 mm of residual disease after cytoreduction. After a median follow-up of 63.8 months, the primary endpoint of median OS was not significantly different between groups. Other survival

outcomes were also similar between groups. Subgroup analyses did not identify any differences in OS between treatments in any subgroup. Grade 3 or 4 adverse events were similar between groups in the first 30 days post-treatment, but CRS plus HIPEC was associated with higher adverse event rates 31 to 60 days posttreatment. Limitations of this trial include a short duration of HIPEC administration (30 minutes vs. 90 to 120 minutes) and the extensive use of systemic oxaliplatin-based chemotherapy prior to surgery.

Table 3. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Quenet et al (2021)[23,]	France	17	2008-2014	265 patients aged 18 to 70 years with colorectal cancer with peritoneal metastases, WHO performance status of 0 or 1, and PCI ≤25; all patients had complete macroscopic resection or surgical resection with less than 1 mm residual tumor tissue	133 patients received CRS plus HIPEC	132 patients received CRS alone

CRS: cytoreductive surgery; HIPEC; hyperthermic intraperitoneal chemotherapy; PCI: Peritoneal Cancer Index; RCT: randomized controlled trial; WHO: World Health Organization.

Table 4. Summary of Key RCT Results

Study	Median OS, mo	Median RFS, mo	5-year OS, %	5-year RFS, %	Grade 3 or 4 AEs, %
Quenet et al (2021)[23,]					*Days 1 through 30; Days 31 through 60*
N			265	265	
CRS alone	41.2	11.1	36.7	13.1	32; 15
CRS plus HIPEC	41.7	13.1	39.4	14.8	42; 26
HR (95% CI)	1.00 (0.63 to 1.58)	0.91 (0.71 to 1.15)			
p	.99	.43	NR	NR	.083;.035

AE: adverse event; CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; NR: not reported; OS: overall survival; RCT: randomized controlled trial; RFS: relapse-free survival.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Quenet et al (2021)[23,]	3. Approximately 90% of patients achieved complete cytoreduction, which may have limited the benefit achieved with the addition of HIPEC; patients deemed not amenable to complete resection were excluded from the trial			6. No clinical significant difference found between treatment groups	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
HIPEC: hyperthermic intraperitoneal chemotherapy.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as

intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Quenet et al (2021)[23,]	2. Open-label	1-3. Not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

A trial by Verwaal et al (2003), included in Huang et al (2017), randomized 105 patients with peritoneal carcinomatosis to standard treatment with systemic chemotherapy (fluorouracil and leucovorin) and palliative surgery, if necessary (i.e., treatment of bowel obstruction), or to CRS plus HIPEC followed by standard systemic chemotherapy.[24,] Patients with other sites of metastases (i.e., lung or liver) were excluded. The primary endpoint was OS, measured from the time of randomization to death from any cause. After a median follow-up of 21.6 months, 20 (39%) of 51 patients in the standard therapy group were still alive compared with 30 (55%) of 54 patients in the cytoreduction group (HR for death, 0.55; 95% CI, 0.32 to 0.95; p =.032). The median OS in the control group was 12.6 months compared with 22.4 months in the cytoreduction group. Subgroup analysis revealed that OS was particularly poor among patients with a residual tumor measuring greater than 2.5 mm and in patients with tumor involvement in 6 or more regions in the abdomen. In these groups, median survival was approximately 5 months compared with 29 months in patients with no residual tumor. In the cytoreduction group, 4 (8%) patients died from treatment. The most important complications were small bowel leakage and abdominal sepsis; the most common grade 3 and 4 adverse events were leukopenia (7 [15%] patients) and gastrointestinal fistula (7 [15%] patients), respectively.

Verwaal et al (2008) reported on the 8-year follow-up to the RCT and evaluated all patients alive until 2007.[25,] Minimum follow-up was 6 years (median, 7.8 years; range, 6 to 9.6 years). During follow-up, 1 patient crossed over from the standard arm to the CRS plus HIPEC arm after recurrent disease 30 months post-randomization. The median disease-specific survival was 12.6 months in the standard arm and 22.2 months in the CRS plus HIPEC arm (p=.028). Median PFS was 7.7 months in the standard arm and 12.6 months in the CRS plus HIPEC arm (p=.02).

Section Summary: Peritoneal Carcinomatosis of Colorectal Origin

Two RCTs, a number of observational studies, and systematic reviews of these studies have been published. A 2017 systematic review included 76 studies, of which 15 were controlled and 1 was an RCT. In a meta-analysis of the controlled studies, there was a significantly higher survival rate in patients who received CRS plus HIPEC compared with standard therapy (e.g., palliative surgery alone or with

systemic chemotherapy). Also, in the controlled studies, CRS plus HIPEC was not associated with a significantly higher rate of treatment-related morbidity. One RCT, in which patients were followed for at least 6 years, demonstrated improved survival in patients with peritoneal carcinomatosis due to colorectal cancer who received CRS plus HIPEC and systemic chemotherapy compared with patients who received systemic chemotherapy alone. At the 8-year follow-up, disease-specific survival was 22.2 months in the CRS plus HIPEC arm and 12.6 months in the control arm. However, procedure-related morbidity and mortality were relatively high; 4 (8%) patients in the CRS plus HIPEC group died from treatment. A more recent RCT found no survival benefit with CRS plus HIPEC over CRS alone, and a higher rate of adverse events 31 to 60 days post-procedure in the CRS plus HIPEC group. The lack of benefit seen with HIPEC in this trial may have been due to several factors, including the short duration of HIPEC treatment, the extensive use of preprocedural systemic chemotherapy, and the high rates of complete cytoreduction achieved in both groups.

Peritoneal Carcinomatosis of Gastric Origin

Clinical Context and Therapy Purpose

The purpose of CRS plus HIPEC in individuals with peritoneal carcinomatosis of gastric origin is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with peritoneal carcinomatosis of gastric origin.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9,] It may be followed by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C or a platinum agent. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

Comparators

The following therapies are currently being used to treat peritoneal carcinomatosis of gastric origin: CRS alone and systemic chemotherapy.

Outcomes

The general outcomes of interest are OS, disease-specific survival (e.g., PFS), QOL, treatment-related mortality, and treatment-related morbidity.

Morbidity and mortality from the procedure are measured in the early postoperative period. Survival outcomes (PFS and OS) should be measured out to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Granieri et al (2022) published a meta-analysis of 12 RCTs that evaluated patients (N=1376) with gastric cancer who underwent CRS plus HIPEC compared to usual standard care in both prophylactic and curative settings. [26,] The included RCTs were all unblinded. Median follow-up duration (reported in 5 studies) was 35.4 months for patients in the treatment group. In the analysis of all studies, the 1,2,3, and 5-year OS rate for patients was 86.9%, 70.5%, 63.7%, and 55.7%, respectively. A survival benefit was noted for CRS plus HIPEC at all timepoints, however, a significant difference was only found in 1 (relative risk [RR], 0.6; 95% CI, 0.47 to 0.75; p<.0001), 2 (RR, 0.7; 95% CI, 0.57 to 0.87; p=.0009) and 3 (RR, 0.68; 95% CI, 0.57 to 0.81; p<.0001) year follow-up.

Desiderio et al (2017) published a meta-analysis of controlled studies comparing CRS plus HIPEC with standard surgical management in the treatment of advanced gastric cancer.[27,] A separate analysis was conducted of studies focused on patients with and without peritoneal carcinomatosis. For the treatment of patients with peritoneal carcinomatosis of gastric origin, reviewers identified 2 small RCTs (discussed below) and 12 controlled nonrandomized studies. In a meta-analysis of survival at 1 year, there was a significantly higher survival rate in the group receiving HIPEC than the group receiving control treatment (RR, 0.67; 95% CI, 0.52 to 0.86; p=.002). However, there was no significant difference between HIPEC and control groups in 2-year survival (RR, 0.87; 95% CI, 0.73 to 1.04; p=.12) or 3-year survival (RR, 0.99; 95% CI, 0.93 to 1.06; p=.85).

Randomized Controlled Trials

Rudloff et al (2014) reported on results of a preliminary, open-label RCT in 17 patients from several U.S. centers who had gastric cancer metastatic to the liver and lung and peritoneal carcinomatosis.[28,] Eligible patients could, in the opinion of the principal investigator, be resected to "no evidence of disease" based on imaging studies or staging laparoscopy. Patients were assigned using a computerized randomization algorithm to systemic chemotherapy (n=8) or to systemic chemotherapy plus gastrectomy and CRS plus HIPEC (n=9). Median and 1-year OS were 4.3 months and 0%, respectively, in the control group, and 11.3 months and 78%, respectively, in the CRS plus HIPEC group (statistical testing not reported). Factors associated with survival more than 1 year in the CRS plus HIPEC group were complete cytoreduction and initial PCI score of 15 or less. Enrollment to complete a larger planned trial was discontinued due to slow accrual.

Yang et al (2011) randomized 68 patients (1:1) to CRS plus HIPEC or to CRS alone.[29,] Median OS was 11.0 months (95% CI, 10.0 to 11.9 months) in the CRS plus HIPEC group and 6.5 months (95% CI, 4.8 to 8.2 months) in the CRS-only group (p=.046). One-, 2-, and 3-year OS rates in the CRS plus HIPEC and CRS-only groups were 41.2% and 29.4%, 14.7% and 5.9%, and 5.9% and 0%, respectively. The incidence of serious adverse events was similar between groups (15% in the CRS plus HIPEC group vs. 12% in the CRS-only group).

Section Summary: Peritoneal Carcinomatosis of Gastric Origin

A 2022 meta-analysis identified 12 RCTs evaluating CRS plus HIPEC in both prophylactic and curative settings. A survival benefit was noted in the CRS plus HIPEC groups at 1, 2, and 3 years. A 2017 meta-analysis identified 2 RCTs and 12 controlled nonrandomized studies comparing CRS plus HIPEC with standard surgical management in patients with peritoneal carcinomatosis due to gastric cancer. The meta-analysis found significantly increased rates of survival in the CRS plus HIPEC group at 1 year but there was no difference in survival rates at 2 or 3 years. One small (N=17) preliminary RCT showed improved survival in patients with peritoneal carcinomatosis due to gastric cancer who received CRS plus HIPEC compared with patients who received chemotherapy alone. Another (N=68) RCT showed

improved survival in patients who received CRS plus HIPEC compared with CRS alone. Additional study in a larger sample is needed.

Peritoneal Carcinomatosis of Endometrial Origin

Clinical Context and Therapy Purpose

The purpose of CRS plus HIPEC in individuals with peritoneal carcinomatosis of endometrial origin is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with peritoneal carcinomatosis of endometrial origin.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9,] It may be followed by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C or a platinum agent. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

Comparators

The following therapies are currently being used to treat peritoneal carcinomatosis of endometrial origin: CRS alone and systemic chemotherapy.

Outcomes

The general outcomes of interest are OS, disease-specific survival (e.g., PFS), QOL, treatment-related mortality, and treatment-related morbidity.

Morbidity and mortality from the procedure are measured in the early postoperative period. Survival outcomes (PFS and OS) should be measured out to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Cohort Studies

No RCTs or nonrandomized comparative studies were identified. Two noncomparative, non-U.S. retrospective cohort studies have reported outcomes for CRS plus HIPEC in primary or recurrent endometrial cancer with peritoneal metastasis; these studies are summarized in Tables 7 and

8.[30,31,] These studies are limited by their retrospective observational designs and lack of control groups.

Navarro-Barrios et al (2020) reported on a cohort of 43 patients with primary (n=15) or recurrent (n=28) peritoneal dissemination of endometrial cancer undergoing CRS plus HIPEC.[30,] Histopathologic subtype of cancer was endometroid carcinoma in 35% of patients and non-endometroid carcinoma in 65%. Median PCI at the time of surgery was 12 (interquartile range, 7 to 19). Complete cytoreduction was achieved in 41 (95%) patients. Postoperative complications were observed in 14 patients (33%). Five-year relapse-free survival (RFS) and OS were 23% and 34%, respectively. Factors associated with decreased RFS were preoperative chemotherapy (p=.027), resection of more than 3 peritoneal areas (p=.010), cytoreduction of the supramesocolic compartment (p=.023), HIPEC treatment with paclitaxel (p=.013), and the presence of metastatic lymph nodes in histological analysis (p=.029). Of note, 21 patients (61%) underwent adjuvant therapies after CRS plus HIPEC, further limiting the study's ability to specifically demonstrate benefit for CRS plus HIPEC.

Cornali et al (2018) reported on a cohort of 33 patients undergoing primary (n=5) or secondary (n=28) CRS plus HIPEC for peritoneal metastatic spread from advanced or recurrent endometrial cancer.[31,] Median PCI was 15 (range, 3 to 35). Complete cytoreduction was achieved in 22 patients (66.6%). Major postoperative morbidity (Clavien-Dindo grade 3 or 4) occurred in 21%, and the postoperative mortality rate was 3% (1 patient experienced intraoperative massive pulmonary embolism). Adjuvant chemotherapy was given to 30 patients post-surgery. Rates of 5-year OS and PFS were 30% and 15.5%, respectively. Median OS and PFS were 33.1 months and 18 months, respectively. Complete cytoreduction was associated with increased OS (p<.016).

Table 7. Summary of Key Cohort Study Characteristics for CRS Plus HIPEC in Peritoneal Carcinomatosis of Endometrial Origin

Study	Country	Dates	Participants	Follow-Up
Navarro-Barrios et al (2020)[30,]	Spain (8 centers)	2012-2018	Patients with endometrial cancer and primary or recurrent peritoneal dissemination undergoing CRS plus HIPEC; ECOG performance status 0 to 2	Median, 25 months (IQR, 10 to 37 months)
Cornali et al (2018)[31,]	Italy and Greece (2 centers)	2002-2016	Patients with peritoneal metastatic spread from advanced or recurrent endometrial cancer; age <75 years; ECOG performance status 0 to 2	Median, 73 months (range, 8 to 141 months)

CRS: cytoreductive surgery; ECOG: Eastern Cooperative Oncology Group; HIPEC: hyperthermic intraperitoneal chemotherapy; IQR: interquartile range.

Table 8. Summary of Key Cohort Study Results for CRS Plus HIPEC in Peritoneal Carcinomatosis of Endometrial Origin

Study	N	Postoperative complications, %	Postoperative morbidity/mortality, %	5-year OS, %	Median OS, mo	5-year RFS, %	5-year PFS, %	Median PFS, mo
Navarro-Barrios et al (2020)[30,]	43	33	NR	34	NR	23	NR	NR
Cornali et al (2018)[31,]	33	NR	21/3	30	33.1	NR	15.5	18

CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; NR: not reported; OS: overall survival; PFS: progression-free survival; RFS: relapse-free survival.

Section Summary: Peritoneal Carcinomatosis From Endometrial Cancer

Two uncontrolled retrospective cohort studies in patients with primary or recurrent endometrial cancer and peritoneal carcinomatosis have suggested that survival with CRS plus HIPEC may be better than systemic chemotherapy (median OS, 33.1 months vs. <12 months in published reports). However, 1 study reported a complication rate of 33%, and major postoperative morbidity was

reported in 21% of patients in another study. Further, there were absent parallel control groups, and potential bias was introduced by confounding factors, such as disease history, cancer subtype, preoperative PCI score, and treatment. Randomized trials comparing CRS plus HIPEC with standard treatment (surgery [including CRS], systemic chemotherapy, brachytherapy, radiotherapy, and/or hormone therapy) in larger numbers of patients are needed.

Peritoneal Mesothelioma

Clinical Context and Therapy Purpose

The purpose of CRS plus HIPEC in individuals with peritoneal mesothelioma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with peritoneal mesothelioma.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9,] It may be followed by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C or a platinum agent. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

Comparators

The following therapies are currently being used to treat peritoneal mesothelioma: CRS alone, systemic chemotherapy, and radiotherapy.

Outcomes

The general outcomes of interest are OS, disease-specific survival (e.g., PFS), QOL, treatment-related mortality, and treatment-related morbidity.

Morbidity and mortality from the procedure are measured in the early postoperative period. Survival outcomes (PFS and OS) should be measured out to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

For a systematic review, Baratti et al (2011) searched the PubMed database for studies on the clinical management of diffuse malignant peritoneal mesothelioma.[7,] They included 14 studies with a total of 427 patients, 289 of whom underwent CRS plus HIPEC with 106 receiving both HIPEC and early postoperative intraperitoneal chemotherapy. Studies that included patients with well-differentiated or low-grade types of mesothelioma were excluded. All selected studies were prospective, uncontrolled case series. The mean patient age ranged from 49 to 56 years. All institutions used peritonectomy and multivisceral resection to remove the visible disease. Protocols for HIPEC varied widely across institutions in terms of techniques, drugs, carriers, timing, and temperatures. Operative mortality and morbidity were reported in 11 single-institution case series. Operative mortality rates ranged from 0% to 10.5%. Overall, death occurred in 11 (3.1%) of 373 assessable patients. In a multi-institutional series, mortality was 2.2%. Morbidity (severe and life-threatening complications) varied from 20% to 41%. For patients who underwent CRS plus HIPEC, median OS ranged from 29.5 to 92 months. The median OS was not reached in 3 series but exceeded 100 months in 1 of them. One-, 2-, 3-, and 5-year OS rates varied from 43% to 88%, 43% to 77%, 43% to 70%, and 33% to 68%, respectively. In 4 studies, median PFS ranged from 7.2 to 40 months.

Results of a systematic review by Helm et al (2015), which included 7 studies published after the Baratti et al (2011) review, aligned with Baratti's findings: pooled 1-, 3-, and 5-year survival estimates were 84%, 59%, and 42%, respectively.[32,]

Observational Studies

Table 9 summarizes relevant observational studies on peritoneal mesothelioma; the largest studies (N>50 patients) are discussed further below.

Table 9. Study Results for CRS Plus HIPEC in Peritoneal Mesothelioma

Study	N	Postoperative, %		Median OS, mo	5-Year OS, %	Median PFS, mo
		Mortality	Morbidity			
Robella et al (2014)[33,]	42	7	36	65	44	NR
Alexander et al (2013)[34,]	211	2	30	38	41	NR
Glehen et al (2010)[11,]	88	NR	NR	41	NR	NR
Yan et al (2009)[35,]	401	NR	NR	53	47	NR

CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; NR: not reported; OS: overall survival; PFS: progression-free survival.

The largest observational study (which was included in both systematic reviews) was an international registry study by Yan et al (2009), for which 401 (99%) patients had a complete follow-up.[35,] Of these patients, 92% received HIPEC. Median and 1-, 3-, and 5-year survival rates were 53 months, 81%, 60%, and 47%, respectively.

Alexander et al (2013) reported on 211 patients from 3 U.S. tertiary care centers who had malignant peritoneal mesothelioma and had undergone CRS plus HIPEC.[34,] On multivariate analysis, factors statistically associated with favorable outcome were age younger than 60 years, complete or almost complete cytoreduction, low histologic grade, and HIPEC with cisplatin (rather than mitomycin C).

In the retrospective, multicenter cohort study by Glehen et al (2010), discussed in the Pseudomyxoma Peritonei section, the principal origin of the tumor was peritoneal mesothelioma in 88 patients.[11,] The median survival for this group of patients was 41 months. Independent prognostic indicators in multivariate analysis were: institution, the origin of peritoneal carcinomatosis, completeness of CRS, the extent of carcinomatosis, and lymph node involvement.

Section Summary: Peritoneal Mesothelioma

Retrospective cohort studies have shown median and 5-year OS ranging from 30 to 92 months and from 33% to 68%, respectively, for patients with peritoneal mesothelioma treated with CRS plus

HIPEC. Although no RCTs or comparative studies have been published, historical case series have reported a median survival of 12 months with treatment by palliative surgery, systemic or intraperitoneal chemotherapy, and abdominal irradiation. Procedure-related morbidity and mortality rates with CRS plus HIPEC have remained relatively steady over time, at approximately 35% and 5%, respectively. Because the prevalence of peritoneal mesothelioma is very low, conducting comparative trials is difficult.

Newly Diagnosed Stage III Ovarian Cancer

Clinical Context and Therapy Purpose

The purpose of CRS plus HIPEC in individuals with newly diagnosed stage III ovarian cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with newly diagnosed stage III ovarian cancer.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9,] It may be followed by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C or a platinum agent. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

Comparators

The following therapies are currently being used to treat newly diagnosed stage III ovarian cancer: CRS alone and systemic chemotherapy.

Outcomes

The general outcomes of interest are OS, disease-specific survival (e.g., PFS), QOL, treatment-related mortality, and treatment-related morbidity.

Morbidity and mortality from the procedure are measured in the early postoperative period. Survival outcomes (PFS and OS) should be measured out to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Kim et al (2022) published a systematic review and meta-analysis evaluating HIPEC on patients with ovarian cancer.[36,] Fifteen studies (N=1806) of patients with advanced (stage IC to IV) ovarian cancer were included. Patients were stratified according to recent (<6 months) and non-recent (≥6 months) chemotherapy. Progression-free survival and OS were improved with HIPEC in patients who had recent chemotherapy exposure (HR, 0.585; 95% CI, 0.422 to 0.811 and HR, 0.519; 95% CI, 0.346 to 0.777, respectively). However, in patients without recent chemotherapy, HIPEC did not improve PFS (HR, 1.037; 95% CI, 0.84 to 1.571) or OS (HR, 0.932; 95% CI, 0.607 to 1.430). In the full population both PFS (HR, 0.733; 95% CI, 0.538 to 0.999) and OS (HR, 0.715; 95% CI, 0.545 to 0.937) were improved with HIDEC.

Zhang et al (2019) published a systematic review and meta-analysis assessing the impact of HIPEC on patients with ovarian cancer.[37,] Thirteen studies (N ranging from 12 to 122) with patients with advanced (stage IC to IV) primary ovarian cancer were included. Groups treated with HIPEC had a better OS (HR, 0.59; 95% CI, 0.46 to 0.72) and PFS (HR, 0.41; 95% CI, 0.32 to 0.54) than those who did not receive HIPEC. The review was limited by the inclusion of only English language studies, the small number of RCTs (n=2) identified for inclusion, and only 1 of the included studies reporting information about adverse events.

Wang et al (2019) published a systematic review analyzing the effects of HIPEC and CRS for ovarian cancer patients.[38,] Thirteen studies, all but 3 of which were also used in Zhang et al (2019), were included in the review. In a subgroup analysis of patients with primary ovarian cancer, OS (HR, 0.57; 95% CI, 0.40 to 0.83; p=.04) and DFS (HR, 0.61; 95% CI, 0.47 to 0.80; p<.01) were significantly improved for the HIPEC group. The study was limited by the level of heterogeneity among the study populations and by some of the included studies not reporting morbidity for the control group.

Randomized Controlled Trials

Antonio et al (2022) conducted a single-center, parallel-group, phase 3, RCT in patients with ovarian cancer (stage IIIB/IIIC).[39,] Tables 10 and 11 summarize trial characteristics and results. All 71 patients were originally treated with neoadjuvant systemic chemotherapy then randomized to CRS alone or CRS with cisplatin-based HIPEC. Patients treated with HIPEC had improved DFS and OS.

Van Driel et al (2018) reported that CRS plus HIPEC reduced mortality for patients with newly diagnosed stage III epithelial ovarian cancer (see Tables 10 and 11).[40,] Disease recurrence or death occurred in 81% of patients treated with CRS plus HIPEC compared with 89% treated with CRS alone. At 5-year follow-up, 50% of patients treated with CRS plus HIPEC had died compared with 62% treated with CRS alone (p=.02). Median OS was 45.7 months in the HIPEC group and 33.9 months in the control group. The incidence of grade 3 or 4 adverse events was similar in both groups (25% for surgery alone vs. 27% for CRS plus HIPEC; p=.76).

Table 10. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Antonio et al (2022)[39,]	Spain	1	2012-2018	71 women with stage IIIB/IIIC primary epithelial ovarian cancer, tubal carcinoma, or primary peritoneal carcinoma who received 3 cycles of adjuvant chemotherapy	35 patients received CRS plus HIPEC	36 patients received CRS
Van Driel et al (2018)[40,]	EU	8	2007-2017	245 women with newly diagnosed stage III epithelial ovarian cancer after 3 cycles of carboplatin and paclitaxel and complete or optimal cytoreduction	122 patients received CRS plus HIPEC	123 patients received CRS alone

CRS: cytoreductive surgery; EU: European Union; HIPEC; hyperthermic intraperitoneal chemotherapy; RCT: randomized controlled trial.

Table 11. Summary of Key RCT Results

Study	Disease Recurrence or Death, n (%)	Median RFS, mo	Mortality , n (%)	Median OS, mo	Grade 3 or 4 AEs, %
Antonio et al (2022)[39],					
N	71				
CRS alone		12		45	27.8
CRS plus HIPEC		18		52	28.6
HR (95% CI)	0.12 (0.02 to 0.89)				
p	.038			.19	
Van Driel et al (2018)[40],					
N	245				
CRS alone	110 (89)	10.7	76 (62)	33.9	25
CRS plus HIPEC	99 (81)	14.2	61 (50)	45.7	27
HR (95% CI)	0.66 (0.50 to 0.87)		0.67 (0.48 to 0.94)		
p	.003		.02		.76

AE: adverse event; CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; OS: overall survival; RCT: randomized controlled trial; RFS: relapse-free survival (disease recurrence or progression or death).

The limitations tables (see Tables 12 and 13) below display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement. The major limitation of the van Driel et al (2018) trial was the lack of blinding, which might be expected to have a minor effect on the objective measure of mortality.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Antonio et al (2022)[39],	4. Single-center study conducted in Spain				
Van Driel et al (2018)[40],	3. There were very selective inclusion criteria, so the effect of the intervention on a broader patient population (e.g., recurrent disease) is unknown				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Antonio et al (2022)[39],		4. Blinding not reported				

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Van Driel et al (2018)[40,]		1-3. Not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Newly Diagnosed Stage III Ovarian Cancer

Evidence for HIPEC includes systematic reviews and RCTs in patients with newly diagnosed stage III epithelial ovarian cancer who were treated with neoadjuvant chemotherapy and had complete or optimal cytoreduction. In the largest RCT , HIPEC increased the time to disease recurrence and reduced mortality. It did not increase serious adverse events compared with surgery alone. The major limitation in the trial was the lack of blinding, which might be expected to have a minor effect on the objective measure of mortality.

Recurrent Stage IIIC or IV Ovarian Cancer

Clinical Context and Therapy Purpose

The purpose of CRS plus HIPEC in individuals with recurrent stage IIIC or IV ovarian cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with recurrent stage IIIC or IV ovarian cancer.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9,] It may be followed by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C or a platinum agent. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

Comparators

The following therapies are currently being used to treat recurrent stage IIIC or IV ovarian cancer: CRS alone and systemic chemotherapy.

Outcomes
The general outcomes of interest are OS, disease-specific survival (e.g., PFS), QOL, treatment-related mortality, and treatment-related morbidity.

Morbidity and mortality from the procedure are measured in the early postoperative period. Survival outcomes (PFS and OS) should be measured out to 5 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
A systematic review and meta-analysis of studies assessing CRS plus HIPEC for treating ovarian cancer was published by Huo et al (2015).[41,] Reviewers selected studies that included more than 10 patients with primary or recurrent ovarian cancer who were treated with CRS plus HIPEC. Thirty-seven studies were identified, 9 comparative studies and 28 uncontrolled studies. Only 1 RCT (Spiliotis et al [2015][42,]), described below, was identified in the literature search. A pooled analysis of 8 studies comparing CRS plus HIPEC with CRS plus non-HIPEC chemotherapy found significantly higher 1-year survival in the CRS plus HIPEC group (odds ratio [OR], 4.24; 95% CI, 2.17 to 8.30). There were similar findings on 3-year survival (pooled OR , 4.31; 95% CI, 2.11 to 8.11). Most of the comparative studies were not randomized and thus subject to potential selection and observational biases.

Kim et al (2022; see previous indication) also included a subgroup analysis for patients with recurrent ovarian cancer.[36,] In this setting, HIPEC did not significantly improve PFS (HR, 0.968; 95% CI, 0.542 to 1.728) or OS (HR, 1.010; 95% CI, 0.663 to 1.539).

Zhang et al (2019; see previous indication) also included results for patients with recurrent ovarian cancer.[37,] In this subgroup, HIPEC had significantly improved OS (HR, 0.45; 95% CI, 0.24 to 0.83) compared with groups that did not receive HIPEC; however, PFS (HR, 0.55; 95% CI, 0.27 to 1.11) was not significantly improved.

Wang et al (2019; see previous indication) also provided a subgroup analysis of patients with recurrent ovarian cancer.[38,] In this population, the HIPEC group had significantly improved OS (HR, 0.48; 95% CI, 0.24 to 0.96; p <.01) but not DFS (HR, 0.59; 95% CI, 0.33 to 1.08; p=.09).

Randomized Controlled Trials
Zivanovic et al (2021) reported on a multi-center RCT of 117 women who had platinum-sensitive recurrent ovarian cancer. [43,] There was a median follow-up of 39.5 months, and the median PFS in the CRS plus HIPEC group versus the control group was 12.3 and 15.7 months, respectively (p=.05). There was no reported significant difference in median OS between the two groups (p=.31).

Spiliotis et al (2015) reported on a single-center RCT of 120 women who had recurrent stage IIIC or IV ovarian cancer after surgery and systemic chemotherapy.[42,] In Kaplan-Meier survival analysis, mean OS was 26.7 months in the CRS plus HIPEC group and 13.4 months in the non-HIPEC group (p=.006)

However, completeness of cytoreduction and PCI score were associated with survival, and these measures were not comparable between groups. Treatment-related morbidity and mortality were not reported.

Tables 14 and 15 below summarize key characteristics and results of these studies.

Table 14. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Zivanovic et al (2021) [43]	US	4	2014-2019	117 women undergoing secondary CRS with first recurrence of high-grade epithelial ovarian cancer after completion of first-line platinum-based chemotherapy	CRS plus HIPEC	CRS plus systemic chemotherapy
Spiliotis et al (2015) [42]	EU	1	2006-2013	120 women with advanced (stage IIIC or IV) recurrent epithelial ovarian cancer	CRS plus HIPEC	CRS plus systemic chemotherapy

CRS: cytoreductive surgery; EU: European Union; HIPEC; hyperthermic intraperitoneal chemotherapy; RCT: randomized controlled trial; US: United States

Table 15. Summary of Key RCT Results

Study	Disease Recurrence or Death, n (%)	Median RFS, mo	Mortality , n (%)	Median OS, mo	Grade 3 or 4 AEs, %
Zivanovic et al (2021) [43]					
N	117				
CRS plus systemic chemotherapy		15.7		59.7	20
CRS plus HIPEC		12.3		52.5	24
HR (95% CI)		1.54 (1 to 2.37)		1.39 (0.73 to 2.67)	
p		.05		.31	.81
Spiliotis et al (2015) [42]					
N	120				
CRS plus systemic chemotherapy				13.4	
CRS plus HIPEC				26.7	
p				.006	

AE: adverse event; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; OS: overall survival; RCT: randomized controlled trial; RFS: relapse-free survival (disease recurrence or progression or death).

Limitations in relevance and design and conduct are noted in Tables 16 and 17. For the Spiliotis et al (2015) study, baseline between-group differences in the stage of disease and completeness of cytoreduction, which is a prognostic indicator for survival, limit interpretation of the trial results.

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Zivanovic et al (2021) [43]			3. More patients in the control group had complete cytoreduction (94% vs. 82%).		
Spiliotis et al (2015) [42]	3. The HIPEC group had more patients with stage IIIC disease (68% vs. 60%)		3. More patients in the HIPEC group had complete cytoreduction (65% vs. 55%).		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
HIPEC: hyperthermic intraperitoneal chemotherapy.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 17. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Zivanovic et al (2021) [43,]		1-3. Not blinded				
Spiliotis et al (2015)[42,]		1-3. Not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Recurrent Stage IIIC or IV Ovarian Cancer

Cytoreductive surgery plus HIPEC has been studied in RCTs of patients with recurrent stage IIIC or IV ovarian cancer. For recurrent disease (second-line setting), evidence from an RCT indicated that CRS plus HIPEC improved survival compared with CRS without HIPEC. Treatment groups in this RCT were unbalanced at baseline and in the completeness of cytoreduction, which has consistently been shown to be associated with survival. Another RCT reported that CRS plus HIPEC resulted in significant benefit in median PFS compared to CRS without HIPEC for patients with platinum-sensitive recurrent disease, however there was no significant difference in median OS.

Appendiceal Goblet Cell Tumors

Clinical Context and Therapy Purpose

The purpose of CRS plus HIPEC in individuals with appendiceal goblet cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with appendiceal goblet cell tumors.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9,] It may be followed by the infusion of intraperitoneal chemotherapy, commonly mitomycin C or a platinum agent. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

Comparators

The following therapies are currently being used to treat appendiceal goblet cell tumors: CRS alone and systemic chemotherapy.

Outcomes

The general outcomes of interest are OS, disease-specific survival (e.g., PFS), QOL, treatment-related mortality, and treatment-related morbidity.

Morbidity and mortality from the procedure are measured in the early postoperative period. Survival outcomes (PFS and OS) should be measured out to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Cohort Studies

Sluiter et al (2020) analyzed a propensity score-matched cohort of 44 patients with peritoneally-metastasized goblet cell carcinoids, comparing survival outcomes in patients receiving CRS plus HIPEC versus surgery alone (see Tables 18 and 19).[44,] In this observational analysis, CRS plus HIPEC was associated with improved median OS compared to surgery alone (39 months vs. 12 months). Surgery without HIPEC was correlated with poor OS in a multivariate model (HR, 2.77; 95% CI, 1.06 to 7.26), as was high age and the presence of ovarian metastases. This analysis is limited by the sample size and observational design; although propensity score matching was used to reduce selection bias, differences between patient groups likely remained and confounding by treatment indication cannot be ruled out. It is unclear how many patients attained complete cytoreduction in each treatment group, and differences in the rate of complete cytoreduction may have influenced outcomes.

Table 18. Summary of Key Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	CRS plus HIPEC	Surgery alone	Follow-Up
Sluiter et al (2020)[44,]	Propensity score-matched cohort	Netherlands and Belgium	2003-2016	Patients with confirmed peritoneal metastases of goblet cell carcinoids	22	22	Mean, 21.2 months

CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy.

Table 19. Summary of Key Observational Comparative Study Results

Study	Median OS, mo
Sluiter et al (2020)[44,]	
CRS plus HIPEC	39
Surgery alone	12
p	.017
HR (95% CI), p	2.77 (1.06 to 7.26), p =.038

CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; OS:overall survival.

Noncomparative retrospective cohort studies have reported on additional outcomes with CRS plus HIPEC in patients with appendiceal goblet cell tumors. In a multicenter, retrospective cohort study, McConnell et al (2014) studied appendiceal goblet cell tumors (n=45) and compared outcomes for CRS plus HIPEC with those in nonmucinous (n=52) and low-grade (n=567) and high-grade (n=89) mucinous appendiceal tumors.[45,] All patients had peritoneal malignancy due to advanced disease but none was identified as having pseudomyxoma peritonei. With a median follow-up of 49 months, patients with goblet cell tumors had better survival outcomes than those in patients with low-grade mucinous tumors and similar outcomes to those in patients with high-grade mucinous tumors: 3-year OS rates in patients with goblet cell, low-grade mucinous, high-grade mucinous, and nonmucinous tumor were 63%, 81% (p=.003), 40% (p=.07), and 52% (p=.48), respectively. In 489 (65%) patients who achieved complete cytoreduction, the pattern of 3-year DFS outcomes was similar: 43%, 73% (p<.001), 44% (p=.85), and 44% (p=.82), respectively (p values for rates vs. goblet cell tumors).

Treatment-related adverse events were not reported. Grade 3 or 4 surgical complications occurred in approximately 20% of patients in each group.

A noncomparative, single-center retrospective cohort study by Zambrano-Vera et al (2020) reported outcomes in 20 patients with peritoneal carcinomatosis from appendiceal goblet cell carcinoma who successfully underwent CRS plus HIPEC.[46,] Complete cytoreduction was achieved in 75%. Grade 3 postoperative complications were reported in 15%. With a median follow-up time of 70 months, 1-, 3-, and 5-year OS rates were 100%, 75%, and 65%, respectively. Median OS was not reached at 5 years. Rates of 1-, 3-, and 5-year PFS were 94%, 67%, and 59%, respectively, with a median PFS of 97 months.

Section Summary: Appendiceal Goblet Cell Tumors

Evidence is limited to retrospective cohort studies of patients with goblet cell tumors of the appendix. A propensity score-matched analysis found that CRS plus HIPEC was associated with improved median survival compared to surgery alone. However, this analysis was limited by the retrospective nature of the data and small sample size (N=44). Rates of complete cytoreduction were not reported or accounted for in this study, so between-group differences in this or other variables may have influenced the observed outcomes. Noncomparative retrospective studies have found 3-year survival rates of 63% to 75% with CRS plus HIPEC, and 1 study reported a 5-year survival rate of 65%.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In 2022, the American Society of Clinical Oncology published recommendations for the treatment of metastatic colorectal cancer.[47,] The guidelines recommend cytoreductive surgery (CRS) plus systemic chemotherapy for select patients. However, they recommend against CRS with oxaliplatin-based hyperthermic peritoneal chemotherapy based on evidence that this combination results in worse adverse events than CRS plus chemotherapy and little or no survival benefit.

American Society of Colon and Rectal Surgeons

In 2022, the practice guidelines on the treatment of colon cancer by the American Society of Colon and Rectal Surgeons stated that "in patients with resectable colorectal cancer peritoneal metastases, cytoreductive surgery with or without intraperitoneal chemotherapy should be considered as part of a multimodality treatment plan (strong recommendation based on moderate quality evidence, 1B)".[48,]

In 2019, the American Society of Colon and Rectal Surgeons guidelines on the management of appendiceal neoplasms stated that "in selected patients with appendiceal epithelial neoplasms, intraperitoneal chemotherapy may offer additional benefit for reducing peritoneal disease recurrence compared with CRS alone." The guidelines mention that HIPEC performed concurrently with CRS is the most common method of delivering this intraperitoneal chemotherapy.[49,]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines include the following relevant recommendation for colon cancer (v.2.2023): "The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. However, the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach very controversial."[50,]

The NCCN guidelines on gastric cancer (v.1.2023) 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."[6,] The NCCN guidelines on uterine neoplasms (v.2.2023) and rectal cancer (v.2.2023 do not discuss cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC). [51,52,]

The NCCN guidelines on ovarian cancer (v.1.2023) state that "select patients with low-volume residual disease after surgical cytoreduction for stage II or III invasive epithelial ovarian or peritoneal cancer are potential candidates for intraperitoneal therapy" and "HIPEC with cisplatin (100 mg/m^2) can be considered at the time of interval debulking surgery for stage III disease."[53,]

Chicago Consensus Working Group

In 2020, the Chicago Consensus Working Group for the Management of Peritoneal Surface Malignancies published a consensus statement on the management of ovarian neoplasms.[54,] The consensus statement mentions HIPEC, and includes it in its management pathway for patients with peritoneal metastasis from epithelial ovarian cancer. However, the authors also state that "level I evidence is lacking for HIPEC at the time of primary CRS or for stage IV disease" and "similarly, no level I evidence exists for HIPEC use in patients with rare ovarian histologies." Other consensus statements from this group on appendiceal neoplasms, peritoneal mesothelioma, gastric metastases, and colorectal metastases include CRS plus intraperitoneal chemotherapy or CRS +/- intraperitoneal chemotherapy in their management pathways; however, they do not specify whether this intraperitoneal chemotherapy should be HIPEC or another form of intraperitoneal chemotherapy.[55,56,57,58,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing or unpublished trials that might influence this review are listed in Table 20.

Table 20. Summary of Key Trials

NCT No.	Title	Enrollment	Completion Date
Ongoing			
Colorectal and appendiceal cancer			
NCT01815359	ICARuS Post-operative Intraperitoneal Chemotherapy (EPIC) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) After Optimal Cytoreductive Surgery (CRS) for Neoplasms of the Appendix, Colon or Rectum With Isolated Peritoneal Metastasis	282	Sep 2023
NCT02614534	Multicentre, Randomized Clinical Trial to Evaluate Safety and Efficacy of Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) With Mitomycin C Used During Surgery for Treatment of Locally Advanced Colorectal Carcinoma	200	Mar 2024
Gastric cancer			
NCT05300945	HIPEC Combined Gastrectomy in Patients With Advanced Gastric Cancer Received Neoadjuvant Chemotherapy	200	Dec 2028
NCT01882933	GASTRICHIP : D2 Resection and HIPEC (Hyperthermic Intraperitoneal Chemoperfusion) in Locally Advanced Gastric Carcinoma. A Randomized and Multicentric Phase III Study	367	May 2026
Ovarian cancer			
NCT05827523	Phase III Randomized Trial of HIPEC in Primary Stage Three & Four Ovarian Cancer After Interval Cytoreductive Surgery (FOCUS)	520	Dec 2027
NCT05316181	Randomized Phase III Trial of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Platinum-Resistant Recurrent Ovarian Cancer	140	Dec 2024
NCT01767675	A Phase II Randomized Study: Outcomes After Secondary Cytoreductive Surgery With or Without Carboplatin Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Followed by Systemic Combination Chemotherapy for Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	99	Jan 2024
NCT02124421	Phase II Randomized Study: Cytoreductive Surgery (CRS) With/Without Carboplatin Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Followed by Adjuvant Chemotherapy as Initial Treatment of Ovarian, Fallopian Tube, & Primary Peritoneal Cancer	48	Apr 2028
NCT01376752	A Phase III Randomized Study Evaluating Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in the Treatment of Relapse Ovarian Cancer	415	May 2025
NCT04473339	A Randomized Prospective Trial of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Recurrent Ovarian Cancer Patients With Mutations in Homologous Recombination Repair (HRR) Genes	280	Dec 2023
NCT03772028	Phase III Randomized Clinical Trial for Stage III Epithelial Ovarian Cancer Randomizing Between Primary Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy	538	Apr 2026
Unpublished			
Gastric cancer			
NCT02240524	A Phase III Study of Hyperthermic Intraperitoneal Chemotherapy in the Treatment of Locally Advanced Gastric Cancer After radical Gastrectomy With D2 Lymphadenectomy	582	July 2019 (unknown)

NCT No.	Title	Enrollment	Completion Date
NCT02158988	Prospective Multicenter Phase III Trial Using CRS With / Without HIPEC After Preoperative Chemotherapy in Patients With Peritoneal Carcinomatosis of Gastric Cancer Incl. Adenocarcinoma of the Esophagogastric Junction	105	June 2021
Ovarian cancer			
NCT01628380	Stage IIIC Unresectable Epithelial Ovarian/Tubal Cancer With Partial or Complete Response After 1st Line Neoadjuvant Chemotherapy (3 Cycles CBDCA+Paclitaxel): a Phase 3 Prospective Randomized Study Comparing Cytoreductive Surgery + Hyperthermic Intraperitoneal Chemotherapy (CDDP+Paclitaxel) + 3 Cycles CBDCA+Paclitaxel vs Cytoreductive Surgery Alone + 3 Cycles CBDCA+Paclitaxel	94	Jul 2018 (unknown)
NCT01539785	Surgery Plus Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) Versus Surgery Alone in Patients With Platinum-sensitive First Recurrence of Ovarian Cancer: a Prospective Randomized Multicenter Trial	158	Sep 2018 (unknown)

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - History of disease processes and treatment
  - Past and present diagnostic testing and results

  - Recurrent cancers
  - Surgery history (if applicable)
  - Chemotherapy use (if applicable)
- Radiology report(s) and interpretation (i.e., MRI, CT scan)
- Rationale for request of treatment
  - Treatment plan

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	96446	Chemotherapy administration into the peritoneal cavity via implanted port or catheter ***(Code revision effective 1/1/2024)***
	96547	Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, including separate incision(s) and closure, when performed; first 60 minutes (List separately in addition to code for primary procedure) ***(Code effective 1/1/2024)***
	96548	Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, including separate incision(s) and closure, when performed; each additional 30 minutes (List separately in addition to code for primary procedure) ***(Code effective 1/1/2024)***
	96549	Unlisted chemotherapy procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/30/2015	BCBSA Medical Policy adoption
09/01/2016	Policy revision without position change
09/01/2017	Policy revision without position change
11/01/2018	Policy revision without position change
12/01/2018	Policy title change from Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies Policy revision without position change
12/01/2019	Policy revision without position change
09/01/2023	Policy reactivated. Previously archived from 08/01/2020 to 08/31/2023.
03/01/2024	Coding update

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Hyperthermic Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies 2.03.07** **Policy Statement:** I. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of surgery may be considered **medically necessary** for the treatment of **either** of the following: A. Pseudomyxoma peritonei B. Diffuse malignant peritoneal mesothelioma II. The use of HIPEC may be considered **medically necessary** in newly diagnosed epithelial ovarian or fallopian tube cancer at the time of interval cytoreductive surgery when **all** of the following criteria are met: A. The individual has stage III disease (see Policy Guidelines) B. The individual is not eligible for primary cytoreductive surgery or surgery had been performed but was incomplete and will receive neoadjuvant chemotherapy and subsequent interval debulking surgery (see Policy Guidelines) C. It is expected that complete or optimal cytoreduction can be achieved at time of the interval debulking surgery (see Policy Guidelines) III. The use of HIPEC in all other settings to treat ovarian cancer, including but not limited to stage IIIC or IV ovarian cancer, is considered **investigational**. IV. Cytoreductive surgery plus HIPEC is considered **investigational** for: A. Peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer B. All other indications, including goblet cell tumors of the appendix