Medical Policy

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Title: Hyperthermic Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies

Description/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 a 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 six to seven 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 three months, and five-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. 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 a median survival of 12 months.[12]

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.

CRS 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 post-operatively.

CRS PLUS HIPEC

CRS includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[9] CRS may be followed intraoperatively by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C. 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 temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

CRS plus HIPEC is being evaluated for the following conditions:

- Pseudomyxoma peritonei;
- Peritoneal carcinomatosis of colorectal, gastric, or endometrial origin;
- Peritoneal mesothelioma;
- Ovarian cancer; and
- Appendiceal goblet cell tumors.

Regulatory Status

Mitomycin, carboplatin, and other drugs used for hyperthermic intraperitoneal chemotherapy (HIPEC) have not been FDA-approved for this indication. Cyclophosphamide and nitrogen mustard are FDA-approved for intraperitoneal administration, but neither drug is used regularly for this purpose.[10]

Several peritoneal lavage systems (Product Code LGZ) have been FDA-cleared to provide "warmed, physiologically compatible sterile solution" (e.g., Performer® HT perfusion system; RanD SRL, Medolla, Italy). None has received marketing approval or clearance to administer chemotherapy. FDA has issued warning letters 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 Chemotherapy Devices Cleared by the US FDA

Device	Manufacturer	Date Cleared	510(k) No.	Indications
MAC Medical D-Series Blanket and Solution Warming Cabinets	MAC Medical Inc.	3/5/2019	K180842	For use in hyperthermic Intraperitoneal chemotherapy
Quantum Blood and IV Fluid Infusion Warmer	Life Warmer Inc.	1/28/2019	K181775	For use in hyperthermic Intraperitoneal chemotherapy
QiF Blood and Fluid Warmer	Quality In Flow Ltd.	4/27/2018	K180154	For use in hyperthermic Intraperitoneal chemotherapy
QiF Blood and Fluid Warmer	Quality In Flow Ltd.	9/27/2017	K171215	For use in hyperthermic Intraperitoneal chemotherapy
FluidSmart	THERMEDX LLC	9/5/2017	K172048	For use in hyperthermic Intraperitoneal chemotherapy
QiF Blood and Fluid	Quality In Flow	4/20/2017	K163708	For use in hyperthermic

Warmer	Ltd.			Intraperitoneal chemotherapy
Hang&Go PAC	RanD S.r.l.	12/28/2016	K161613	For use in hyperthermic Intraperitoneal chemotherapy
QiF Blood and Fluid Warmer	Quality in Flow Ltd.	6/23/2016	K150404	For use in hyperthermic Intraperitoneal chemotherapy
The Belmont Hyperthermia Pump	Belmont Instrument Corporation	9/2/2015	K152208	For use in hyperthermic Intraperitoneal chemotherapy
Penguin In-Line Warmer	Creche Innovations	7/9/2015	K150484	For use in hyperthermic Intraperitoneal chemotherapy

Medical Policy Statement

The safety and effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) when used in combination with cytoreductive surgery (CS) have been established. It may be considered a useful therapeutic option for patients meeting patient selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:

The patient must meet ***one*** of the following criteria:

- A diagnosis of pseudomyxoma peritonei (PMP),
- A diagnosis of diffuse malignant peritoneal mesotheliomas or ovarian cancer confirmed by the treating physician.
- A newly diagnosed epithelial ovarian or fallopian tube cancer at the time of interval cytoreductive surgery.
- The patient must be able to tolerate the extensive cytoreductive surgery and hyperthermic intraperitoneal chemotherapy
- Peritoneal disease must be potentially completely resectable or significantly reduced.
- There must be no metastases to other organs or to the retroperitoneal space.

Exclusions:

- A diagnosis of peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer
- Goblet cell tumors of the appendix
- All other indications

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

96446 96547 96548 96549

Other codes related to the cytoreduction would also be billed, depending on the organs and tissues removed during the surgical debulking.

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

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, 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 one 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. RCTs 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.

PSEUDOMYXOMA PERITONEI

Discussion for this indication is divided into primary treatment and treatment for recurrence.

Clinical Context and Therapy Purpose

The purpose of cytoreductive surgery (CRS) hyperthermic intraperitoneal chemotherapy (HIPEC) in patients who have peritoneal malignances is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest are individuals with pseudomyxoma peritonei.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Cytoreductive surgery includes peritonectomy (ie, 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 therapy is currently used to treat pseudomyxoma peritonei: CRS alone.

Outcomes

The general outcomes of interest are progression-free survival (PFS), overall survival (OS) and post-operative morbidity and mortality.

Morbidity and mortality from the procedure are measured in the early postoperative period. PFS and OS should be measured out to five years.

Review of Evidence

Primary Treatment

Table 2 summarizes the relevant studies on pseudomyxoma peritonei, some of which are discussed next.

Jimenez et al (2014) conducted a retrospective review of a prospective database of patients with peritoneal carcinomatosis maintained by Mercy Medical Center in Baltimore.[10] Two hundred two patients with peritoneal carcinomatosis from appendiceal cancer who underwent CRS/HIPEC were included; 125 (62%) patients had high-grade tumors (peritoneal mucinous carcinomatosis [PMCA]) and 77 (38%) patients had low-grade tumors (disseminated peritoneal adenomucinosis [DPAM]). Results for the entire cohort and for subgroups defined by tumor histology are shown in Table 2. In the HG (PMCA) group, Peritoneal Cancer Index (PCI), completeness of cytoreduction, and lymph node status were significantly associated with survival; in the low-grade (DPAM) group, completeness of cytoreduction was significantly associated with survival.

In 2010, Glehen et al published a retrospective, multicenter cohort study to evaluate toxicity and prognostic factors after CRS and HIPEC and/or unheated early 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. HIPEC was performed in 1154 procedures. Postoperative mortality was 4.1%. The principal origin of peritoneal carcinomatosis was pseudomyxoma peritonei in 301 patients. Median overall survival (OS) for patients with pseudomyxoma peritonei was not reached (median OS for all patients, 34 months.)

Additional information about the subgroup of patients with pseudomyxoma peritonei was provided by Elias et al.[12] CRS was achieved in 219 patients (73%), and hyperthermic intraperitoneal chemotherapy was performed in 255 (85%). The primary tumor site was the appendix in 91% of patients, the ovary in 7%, and the origin was unknown in 2%. Tumor histology was disseminated peritoneal adenomucinosis in 51%, intermediate in 27%, and peritoneal mucinous carcinomatosis in 22%. Postoperative mortality was 4% and morbidity, 40%. Mean follow-up was 88 months. The 1-, 3-, and 5-year OS rates were 89.4%, 84.8%, and 72.6%, respectively. The 10-year survival rate was 54.8%. Median survival had not yet been reached but will be longer than 100 months. The disease-free survival (DFS) rate was 56% at 5 years, and the median duration of DFS was 78 months. A multivariate analysis identified five prognostic factors: the extent of peritoneal seeding (p=0.004), the center (p=0.0004), the pathologic grade (p=0.03), gender (p=0.02), and the use of hyperthermic intraperitoneal chemotherapy (p=0.04). When only the 206 patients with complete CRS were considered, the extent of peritoneal seeding was the only significant prognostic factor (p=0.004).

Chua et al (2009) reported the long-term survival of 106 patients with pseudomyxoma peritonei treated between 1997 and 2008 with CRS and HIPEC and/or EPIC.[13] Sixty-nine percent of patients had complete cytoreduction. Eighty-three patients (78%) had HIPEC intraoperatively, 81 patients (76%) had EPIC postoperatively, and 67 patients (63%) had both. Seventy-three patients had disseminated peritoneal adenomucinosis, 11 had peritoneal mucinous carcinomatosis, and 22 had mixed tumors. Mortality rate was 3% and the severe morbidity rate was 49%. Median follow-up was 23 months (range: 0–140 months). The overall median survival was 104 months with a 5-year survival rate of 75%. PFS was 40 months with 1-, 3-, and 5-year PFS rates of 71%, 51%, and 38%, respectively. Factors influencing survival included histopathologic type of tumor, with the best survival in patients with disseminated peritoneal adenomucinosis and the worst in patients with peritoneal mucinous carcinomatosis (p=0.002), and completeness of cytoreduction (p=0.002), with best survival in patients with disseminated peritoneal adenomucinosis and worst survival in patients with peritoneal mucinous carcinomatosis. Factors influencing survival include histopathologic type of tumor, the use of both HIPEC and EPIC, completeness of cytoreduction, and severe morbidity.

Vaira et al (2009) reported their experience managing pseudomyxoma peritonei with CRS and HIPEC in a single institution 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 were 94% and 85%, respectively, and 5- and 10-year DFS were 80% and 70%, respectively. Significant differences in improved OS were observed in patients who experienced complete surgical cytoreduction (p<0.003) and in those with histologic type disseminated peritoneal adenomucinosis versus those with peritoneal mucinous carcinomatosis (p<0.014).

In 2008, Elias and colleagues reported the results of 105 consecutive patients with pseudomyxoma peritonei treated between 1994 and 2006 with CRS and 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 surgery, 72% of patients had no visible residual peritoneal lesions. Postoperative mortality was 7.6% and morbidity, 67.6%. Median follow-up was 48 months, and 5-year OS and DFS were 80% (95% confidence interval [CI]: 68–88%) and 68% (95% CI: 55–79%), respectively. Two factors were identified on multivariate analysis that had a negative influence on DFS: a CA 19.9 level >300 units/mL and nondisseminated peritoneal adenomucinosis tumor histology.

Table 2. Primary and Recurrence Studies of CRS and HIPEC in Pseudomyxoma Peritonei

Study	N	Postoperative Mortality/Morbidity, %	Median OS, m	5-Year OS, %	Median PFS, m	5-Year PFS, %
Primary Treatment						
Jimenez et al (2014)	202	0/16	90	56	40	44
HG tumor	125	NR	47	41	26	34
LG tumor	77	NR	Not reached[a]	83	NR	58
Marcotte et al (2014)	58	2/40	NR	77	NR	50[b]
Glehen et al (2010)	255	4/40	>100	73	78	56

Chua et al (2009)	106	3/49	104	75	40	38
Vaira et al (2008)	60	0/45	NR	94	NR	80
Elias et al (2008)	105	8/68	NR	80	NR	68
Yan et al (2007) (SR)	NR	NR	51-156	52-96	NR	NR
Recurrence						
Sardi et al (2013)	26	0/42	NR	34	NR	NR
Lord et al (2015)	35	NR	129.5[e]	79.0	NR	NR

CRS: cytoreductive surgery; HG: high-grade tumor (peritoneal mucinous carcinomatosis); HIPEC: hyperthermic intraperitoneal chemotherapy; LG: low-grade tumor (disseminated peritoneal adenomucinosis); 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] Results after second procedure shown.
[d] 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.
[e] Mean OS.

Recurrence

From the same Mercy Medical Center database studied by Jimenez et al (described above), Sardi et al (2013) identified 26 patients who underwent repeat CRS/HIPEC for peritoneal carcinomatosis recurrence.[18] Sixteen patients (62%) had high-grade PMCA, and 10 patients (38%) had low-grade DPAM. Patients eligible for repeat CRS/HIPEC had Eastern Cooperative Oncology Group (ECOG) performance status 0-1. The proportion of patients who had a pre-operative PCI score less than 20 was 35% before second procedure and 75% before third procedure (1 of 4 patients). There were no 30-day post-operative deaths; post-operative morbidity was 42% after second procedure and 50% after third procedure. After second procedure, 1-, 3-, and 5-year OS was 91%, 53%, and 34%, respectively. After third procedure, 1-year OS was 75%.

Lord et al (2015) reported a retrospective cohort study of 512 patients with perforated appendiceal tumors and pseudomyxoma peritonei who received CRS/HIPEC at a single center in the U.K. and achieved complete cytoreduction.[17] Thirty-five (26%) of 137 patients who recurred underwent repeat CRS/HIPEC; median time to recurrence was 26 months. Complete cytoreduction was achieved (again) in 20 patients (57%). Mean OS in patients without recurrence (n=375), patients who recurred and had repeat CRS/HIPEC (n=35), and patients who recurred but did not have repeat CRS/HIPEC (n=102) was 171 months (95% CI, 164 to 178), 130 months (95% CI, 105 to 153) and 101 months (84 to 119), respectively (log-rank test, p=0.001). Five-year survival was 91%, 79%, and 65%, respectively. The incidence of complications were 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

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.

In 2017, Huang et al published a systematic review and meta-analysis of studies on 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, one 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 hazard ratio [HR], 2.67, 95% CI, 2.21 to 3.23; I^2=0%, p<0.001). In sensitivity analyses, date of publication, geographic location of the study, 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% (standard deviation [SD], 3.7%) in the CRS plus HIPEC group compared with 6.2% (SD=4.2%) in the traditional treatment group (p=0.423). The mean morbidity rate was 19.8% (SD=9.2%) in the CRS plus HIPEC group and 20.5% (SD=12.3%) in the traditional treatment group (p=0.815). In all 76 studies, mean mortality rate was 2.8% (SD=2.9%) and mean morbidity rate was 33% (SD=13.4%).

Two systemic 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 included 15 studies (total N=1583 enrolled patients),[21] 14 of which appeared in the review of 20 studies (total N=1181 respondents) by Seretis et al.[22] No RCTs were identified. Studies were heterogeneous in sample size (median, ≈60, range, 5-216), response rate (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 after treatment. At 1 year, QOL scores improved to baseline values or above. In random effects meta-analysis of 8 studies (total N=499 enrolled patients), 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 suggests improvement 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)	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)					*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	0.99	0.43	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)	4. 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. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

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)	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.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[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.

In the RCT by Verwaal et al (2003), included in Huang et al (2017), who randomly assigned 105 patients with peritoneal carcinomatosis to receive standard treatment with systemic chemotherapy (fluorouracil and leucovorin) and palliative surgery, if necessary (i.e., treatment of bowel obstruction), or to an aggressive CRS and 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=0.032). 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 residual tumor measuring greater than 2.5 mm or 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.

In 2008, Verwaal et al reported 8-year follow-up on all patients alive until 2007.[25] Minimum follow-up was 6 years (median, 7.8 years; range, 6-9.6 years). During follow-up, 1 patient crossed over from the standard arm to the CRS/HIPEC arm after recurrent disease 30 months post randomization. At the 8-year follow-up, in the standard arm, 4 patients were still alive, 2 with disease and 2 without disease, and in the HIPEC arm, 5 patients were still alive, 2 with

disease and 3 without disease. Median disease-specific survival was 12.6 months in the standard arm and 22.2 months in the CRS/HIPEC arm (p=0.028). Median PFS was 7.7 months in the standard arm and 12.6 months in the CRS/HIPEC arm (p=0.02).

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 (eg, 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

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.

In 2017, Desiderio et al published a meta-analysis of controlled studies comparing CRS plus HIPEC to 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 treatment of patients with peritoneal carcinomatosis of gastric origin, reviewers identified 2 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 a control treatment (relative risk [RR], 0.67; 95% CI, 0.52 to 0.86; p=0.002). 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=0.12) or 3-year survival (RR=0.99; 95% CI, 0.93 to 1.06; p=0.85).

Randomized Controlled Trials

In 2014, Rudloff et al reported results of a preliminary, open-label, Phase 3 RCT in 17 patients from several U.S. centers who had gastric cancer metastatic to 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 randomized using a computerized randomization algorithm to receive systemic chemotherapy with FOLFOXIRI (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) (n=8) or systemic chemotherapy plus gastrectomy and CRS/oxaliplatin 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/HIPEC group (statistical testing not reported). Factors associated with survival more than 1 year in the CRS/HIPEC group were complete cytoreduction and initial PCI 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/cisplatin HIPEC or CRS alone.[29]Median OS was 11.0 months (95% CI, 10.0 to 11.9) in the CRS/HIPEC group and 6.5 months (95% CI, 4.8 to 8.2) in the CRS only group (log-rank test, p=0.046). One-, 2-, and 3-year OS in the CRS/HIPEC and CRS only groups were 41.2% and 29.4%, 14.7% and 5.9%, and 5.9% and 0%, respectively. Incidence of serious adverse events was similar between groups (15% in the CRS/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 better survival in the CRS plus HIPEC group at 1 year but not at 2 or 3 years. One small (N=17) 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 small (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 FROM ENDOMETRIAL CANCER

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 recurrence-free survival and OS were 23% and 34%, respectively. Factors associated with decreased recurrence-free survival were preoperative chemotherapy (p=0.027), resection of more than 3

peritoneal areas (p=0.010), cytoreduction of the supramesocolic compartment (p=0.023), HIPEC treatment with paclitaxel (p=0.013), and the presence of metastatic lymph nodes in histological analysis (p=0.029). 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<0.016).

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)	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)	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	Post-op Complications %	Post-op Morbidity / Mortality %	5-year OS %	Median OS, mo	5-year RFS %	5-Year PFS %	Median PFS mo
Navarro-Barrios et al (2020)	43	33	NR	34	NR	23	NR	NR
Cornali et al (2018)	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: recurrence-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, absent parallel control

groups, 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

Systematic Reviews

For a 2011 systematic review, Baratti et al searched the PubMed database for studies on the clinical management of DMPM.[7] The review included 14 studies with a total of 427 patients, 289 of whom underwent CRS with HIPEC, 2 with EPIC, and 106 with both. Studies that included patients with well-differentiated or low-grade types of mesothelioma were excluded. All included studies were prospective, non-randomized, uncontrolled case-series studies. Mean patient age ranged from 49 to 56 years. All the centers used peritonectomy procedures and multivisceral resections to remove all visible disease. HIPEC protocols varied widely among institutions in terms of technique, drugs, carriers, timing and temperature. Operative mortality and morbidity were reported in 11 mono-institutional series. Operative mortality ranged from 0% to 10.5%. Overall, it occurred in 11 of 373 assessable patients (3.1%). 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 and HIPEC, median overall survival ranged from 29.5 to 92 months. Median OS was not reached in 3 series, but exceeded 100 months in one of these. The 1-, 2-, 3-, and 5-year overall survival rates varied from 43% to 88%, 43% to 77%, 43% to 70%, and 33% to 68%, respectively. In 4 series, median PFS ranged from 7.2 to 40 months.

Results of a 2015 systematic review by Helm et al, 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.[30]

Observational Studies

Table 9 summarizes relevant observational studies on peritoneal mesothelioma, some of which are discussed next.

Table 9. Summary of Studies of CRS and HIPEC in Peritoneal Mesothelioma

Study	N	Postoperative, %		Median OS, mo	5-Year OS, %	Median PFS, mo
		Mortality	Morbidity			
Robella et al (2014)	42	7	36	65	44	NR
Alexander et al (2013)	211	2	30	38	41	NR
Glehen et al (2010)	88	NR	NR	41	NR	NR
Yan et al (2009)	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 study in both systematic reviews was a 2009 international registry study by Yan et al, for which 401 patients (99%) had complete follow-up.[35] Of these patients, 92% received HIPEC. Median and 1-, 3-, and 5-year survival were 53 months, 81%, 60%, and 47%, respectively.

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

In the 2010 retrospective, multicenter cohort study by Glehen et al described above, the principal origin of tumor was peritoneal mesothelioma in 88 patients.[11] Median survival for this group of patients was 41 months. Independent prognostic indicators in multivariate analysis were institution, origin of peritoneal carcinomatosis, completeness of CRS, extent of carcinomatosis, and lymph node involvement.

Section Summary: **Peritoneal Mesothelioma**
Retrospective cohort studies have shown median and 5-year overall survival of 30-92 months and 33%-68%, respectively, for patients with peritoneal mesothelioma who are treated with CRS plus HIPEC. Two studies indicated improved outcomes with platinum-containing HIPEC (cisplatin or carboplatin) compared with mitomycin-C. Procedure-related morbidity and mortality has remained relatively steady over time at approximately 35% and 5%, respectively.

NEWLY DIAGNOSED STAGE III OVARIAN CANCER

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 (range of patients, 12-122), with patients with advanced (stage IC-IV) primary ovarian cancer, were included. Groups treated with HIPEC had a better OS (HR 0.59, 95% CI 0.46- 0.72) and PFS (HR 0.41, 95% CI 0.32-0.54) 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 one 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 three 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 0.40-0.83, p=0.04) and DFS (HR 0.61, 95% CI 0.47-0.80, p<0.01) 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 HIPEC reduced mortality for patients with newly diagnosed stage III epithelial ovarian cancer .[40] Disease recurrence or death occurred in 81% of patients treated with CRS plus HIPEC compared to 89% treated with CRS alone. At 5 year follow-up, 50% of patients treated with HIPEC had died compared with 62% treated with CRS alone (p=0.02). Median OS was 45.7 months in the HIPEC group and 33.9 months in the control group. The incidence of grade 3 or grade 4 adverse events was similar in the 2 groups (25% in the surgery group and 27% in the surgery plus HIPEC group (p=0.76).

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; 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

CI: confidence interval; HR: hazard ratio; RCT: randomized controlled trial; RFS: recurrence free survival (disease recurrence or progression or death); SC: systemic chemotherapy.

The purpose of the limitations tables is to 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. 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 (eg, recurrent disease) is unknown				

The evidence gaps 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. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

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				
Van Driel et al (2018)[40,]		1-3. Not blinded				

The evidence gaps 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.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[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.

Section Summary: Ovarian Cancer
Evidence for HIPEC includes systematic reviews and an RCT in patients with newly diagnosed stage III epithelial ovarian cancer who were treated with neoadjuvant chemotherapy and had complete or optimal cytoreduction. HIPEC increased the time to disease recurrence and reduced mortality. HIPEC 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

Systematic Reviews
A systematic review and meta-analysis of studies assessing CRS plus HIPEC for treating ovarian cancer were published by Huo et al (2015).[41] Reviewers selected studies that included more than ten 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, 4.24; 95% CI, 2.17 to 8.30). There were similar findings on 3-year survival (pooled odds ratio, 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.

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 0.24-0.83) compared with groups that did not receive HIPEC, however, PFS (HR 0.55, 95% CI 0.27-1.11) 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 0.24-0.96, p<0.01) but not DFS (HR 0.59, 95% CI 0.33-1.08, p=0.09).

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 to IV ovarian cancer after surgery and systemic chemotherapy (see Table 14).[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=0.006) (see Table 8). 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.

Table 14. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Zivanovic et al (2021)	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
Spillotis et al (2015)	EU	1	2006-2013	120 women with advanced (stage IIIc-IV) recurrent epithelial ovarian cancer	CRS + HIPEC	CRS + systemic chemotherapy

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

Table 15. Summary of Key RCT Results

Study	Disease Recurrence or Death, n (%)	Median RFS, mo	Mortality at Median of 4.7 Years, n (%)	Median OS, mo	Grade 3 or 4 Adverse Events, %
Zivanovic et al (2021)					
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		0.05		0.31	0.81
Spillotis et al (2015)					
CRS + SC				13.4	
CRS + HIPEC				26.7	
p				0.006	

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

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 for survival, limit interpretation of the trial results.

Table 16. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Zivanovic et al (2021)			3. More patients in the control group had complete cytoreduction (94%		

			vs. 82%).		
Spillotis et al (2015)	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 evidence gaps 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. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 17. Study Design and Conduct Limitations

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

The evidence gaps 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.
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
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).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
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.

Section Summary: Recurrent Stage IIIC or IV Ovarian Cancer

CRS plus HIPEC has been studied in an RCT of patients with recurrent stage IIIc to 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 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

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 + HIPEC	Surgery Alone	Follow-Up
Sluiter et al (2020)	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)	39
CRS plus HIPEC	12
Surgery alone	12
p	0.017
HR (95% CI), p	2.77 (1.06 to 7.26), p=0.038

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

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 with CRS/HIPEC with those in nonmucinous (n=52) and LG (n=567) and HG (n=89) mucinous appendiceal tumors.[45] All patients had peritoneal malignancy due to advanced disease, but none were identified as having pseudomyxoma peritonei. With a median follow-up of 49 months, patients with goblet cell tumors were found to have survival outcomes better than those in patients with LG mucinous tumors and similar to those in patients with HG mucinous tumors: Three-year OS in patients with goblet cell, LG mucinous, HG mucinous, and nonmucinous tumor was 63%, 81% (logrank test vs. goblet cell tumors, p=0.003), 40% (log-rank test vs. goblet cell tumors, p=0.07), and 52% (logrank test vs. goblet cell tumors, p=0.48), respectively. In 489 patients (65%) who achieved complete cytoreduction, the pattern of 3-year DFS outcomes was similar: 43%, 73% (log-rank test vs. goblet cell tumors, p<0.001), 44% (log-rank test vs. goblet cell tumors, p=0.85), and 44% (log-rank test vs. goblet cell tumors, p=0.82), respectively. Adverse events/complications of treatment were not reported. Grade 3/4 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%.

SUMMARY OF EVIDENCE

For individuals who have pseudomyxoma peritonei who receive CRS plus HIPEC, the evidence includes cohort studies and a systematic review. Relevant outcomes are overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related mortality and morbidity. 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 disease-free survival of 24 months). Median progression-free survival with CRS plus HIPEC as primary treatment has been reported as 40 to 78 months, with 5-year progression-free survival 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have peritoneal carcinomatosis of colorectal origin who receive CRS plus HIPEC, the evidence includes a randomized controlled trial (RCT), systematic reviews, and a large number of observational studies. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. A meta-analysis of controlled studies found that CRS plus HIPEC, compared with traditional therapy without HIPEC, was associated with significantly higher survival rates and was not associated with significantly higher treatment-related morbidity rates. The RCT, in which patients with peritoneal carcinomatosis due to colorectal cancer were followed for at least 6 years, demonstrated improved survival in patients who received CRS plus HIPEC and systemic chemotherapy compared with patients who received systemic chemotherapy alone. However, procedure-related morbidity and mortality rates were relatively high, and systemic chemotherapy regimens did not use currently available biologic agents. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal carcinomatosis of gastric origin who receive CRS plus HIPEC, the evidence includes 2 small RCTs, observational studies, and a systematic review. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality

and morbidity. A 2017 meta-analysis identified 2 RCTs and 12 controlled nonrandomized studies comparing surgery plus HIPEC with standard surgical management in patients who had peritoneal carcinomatosis due to gastric cancer. The meta-analysis found significantly better survival in the surgery plus HIPEC group at 1 year but not 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal carcinomatosis of endometrial origin who receive CRS plus HIPEC, the evidence includes cohort studies. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Only uncontrolled retrospective cohort studies were available, with the largest including only 43 patients. Randomized trials that compare CRS plus HIPEC with standard treatment (e.g., CRS alone or systemic chemotherapy alone) are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal mesothelioma who receive CRS plus HIPEC, the evidence includes retrospective cohort studies and systematic reviews. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
For individuals who have newly diagnosed stage III ovarian cancer who receive CRS plus HIPEC, the evidence includes systematic reviews and an RCT. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. For patients with newly diagnosed stage III ovarian cancer who had received neoadjuvant chemotherapy, HIPEC increased the time to disease recurrence and reduced mortality. HIPEC did not increase serious adverse events compared with surgery alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent stage IIIC or IV ovarian cancer who receive CRS plus HIPEC, the evidence includes an RCT and systematic reviews. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. For recurrent stage IIIC or IV disease (second-line setting), evidence from an RCT indicated that CRS plus HIPEC improved survival compared with CRS without HIPEC. However, interpretation of this study is limited because treatment groups in this RCT were unbalanced at baseline (variation in the completeness of cytoreduction), which has been shown to be associated with survival. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have appendiceal goblet cell tumors who receive CRS plus HIPEC, the evidence includes retrospective cohort studies. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. 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. Additional studies-preferably controlled and ideally, RCTs-are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology for colon cancer (version 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 RO 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]

NCCN guidelines on gastric cancer (v.2.2023) 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.1.2024), and rectal cancer (v.5.2023) do not discuss cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC).[51,52]

NCCN guidelines for ovarian cancer (version 2.2023) state that
Those with optimally debulked stage II disease may also receive IP chemotherapy, as the NCCN Panel has decided that many of the regimens tested in stage III–IV should also be offered to patients with stage II disease. Patients with stage II were allowed in GOG-0252 and another (small) randomized trial, although in both of these studies the IP/IV regimens did not significantly improve PFS or OS compared with IV regimens.862,870 IP chemotherapy is not recommended for stage I or IV disease.

The NCCN-recommended HIPEC agent is cisplatin, 100 mg/m2 , as was used in M06OVH-OVHIPEC. Although this trial tested only one regimen for NACT and postoperative chemotherapy (carboplatin, area under the curve [AUC] 5–6 + paclitaxel, 175 mg/m2 body surface area [BSA]), other studies have used a variety of agents, and the optimal pairing of pre/postoperative regimens with HIPEC agent has not been determined. The NCCN Guidelines currently do not restrict the HIPEC.[53]

American Society of Colon and Rectal Surgeons (ASCRS)

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 state 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]

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.[55-58]

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Table 20. Summary of Key Trials

NCT Number	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	220	Sep 2023
NCT02614534	Multicenter, 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			
NCT05827523	Phase III Randomized Trial of HIPEC in Primary Stage Three & Four Ovarian Cancer After Interval Cytoreductive Surgery (FOCUS)	520	Dec 2027
NCT01882933	GASTRICHIP: D2 resection and HIPEC in locally advanced gastric carcinoma. A randomized and multicentric phase III study	322	May 2025
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-	98	Jan 2024

	sensitive ovarian, fallopian tube, or primary peritoneal cancer		
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	Phase III randomized study evaluating hyperthermic intra-peritoneal chemotherapy (HIPEC) in the treatment of relapse ovarian cancer	415	May 2025
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			
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
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

Government Regulations

National:

There is no national coverage determination for cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). However, 96446 is payable, as are the surgical codes for any organs removed.

Local:

There is no local coverage determination for cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). However, 96446 is payable, as are the surgical codes for any organs removed.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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57. Schuitevoerder D, Izquierdo FJ, Plana A, et al. The Chicago Consensus on Peritoneal Surface Malignancies: Management of Peritoneal Mesothelioma. Ann Surg Oncol. Jun 2020; 27(6): 1774-1779. PMID 32285273
58. Schuitevoerder D, Plana A, Izquierdo FJ, et al. The Chicago Consensus on Peritoneal Surface Malignancies: Management of Appendiceal Neoplasms. Ann Surg Oncol. Jun 2020; 27(6): 1753-1760. PMID 32285275

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2023, the date the research was completed.

Joint BCBSA/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/11	1/25/11	1/4/11	Joint policy established
5/1/13	2/19/13	3/4/13	Routine update
3/1/15	12/9/14	12/29/14	Routine maintenance.
7/1/16	4/19/16	5/23/16	Routine maintenance, updated references and rationale section, added endometrial cancer, ovarian cancer and goblet cell tumors to policy exclusions. Added statement “this policy does not apply to gastric cancer” to inclusion section.
10/1/16	6/21/16	6/21/16	Remove 77605 from covered codes.
7/1/17	4/18/17	4/18/17	Routine maintenance. Updated policy title per BCBSA policy.
7/1/18	4/17/18	4/17/18	Routine policy maintenance. Added reference # 26 and 33. No change in policy status.
11/1/18	9/7/18	8/28/18	Ovarian cancer added to the established MPS and deleted from the exclusion section. Rationale updated, reference # 41 added.
3/1/19	1/8/19		Reference 34 added. Policy title changed to Hyperthermic Intraperitoneal Chemotherapy for Select Intra-abdominal and Pelvic Malignancies.
3/1/20	12/17/20		Routine policy maintenance, added references 45 and 46. No change in policy status.
3/1/21	12/15/20		Updated rationale section, added references 41 and 49-53. No change in policy status.
3/1/22	12/14/21		Updated rationale section, added reference, no change in policy status.
3/1/23	12/20/22		Updated rationale section added references 8, 27 and 42. No change in policy status.
3/1/24	12/19/23		Routine policy maintenance, updated rationale, added references 19,36 and 39. Added codes 96547 & 96548 as established. Vendor Managed: N/A (ds)

Next Review Date: 4th Qtr. 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.