Medical Policy

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

Professional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With pseudomyxoma peritonei	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With peritoneal carcinomatosis of colorectal origin	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With peritoneal carcinomatosis of gastric origin	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With peritoneal carcinomatosis of endometrial origin	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With peritoneal mesothelioma	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy • Radiotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With newly diagnosed stage III ovarian cancer	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With recurrent stage IIIC or IV ovarian cancer	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With appendiceal goblet cell tumors	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

Cytoreductive surgery (CRS) comprises peritonectomy (ie, peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal

tumor dissemination. The surgical procedure may be followed intraoperatively 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). CRS 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.

OBJECTIVE

The objective of this policy is to determine whether the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves the net health outcome in individuals with intra-abdominal and pelvic malignancies.

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] 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.[2]

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%.[3] Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis.[4]

Treatment

Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for cure.[5]

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.[6] Diffuse malignant peritoneal mesothelioma has traditionally been considered a rapidly lethal malignancy with limited and ineffective therapeutic options.[6] 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.[6]

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.

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 postoperatively.

CRS Plus HIPEC

CRS includes peritonectomy (ie, peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[7] 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 HIPEC have not been U.S. Food and Drug Administration (FDA)–approved for this indication. Cyclophosphamide and nitrogen mustard are FDA approved for intraperitoneal administration, but neither drug is used regularly for this purpose.[8]

Several peritoneal lavage systems (Product Code LGZ) have been cleared for marketing by FDA through the 510(k) process to provide "warmed, physiologically compatible sterile solution" (eg, Performer® HT perfusion system; Rand Srl). 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 (eg, ThermaSolutions[9], Belmont Instrument[10]).

POLICY

A. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of surgery may be considered **medically necessary** for the treatment of:

1. pseudomyxoma peritonei;

2. diffuse malignant peritoneal mesothelioma.

B. 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:

1. The patient has stage III disease (see Policy Guidelines); and

2. The patient 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); and

3. It is expected that complete or optimal cytoreduction can be achieved at time of the interval debulking surgery (see Policy Guidelines).

C. 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 **experimental / investigational.**

D. Cytoreductive surgery plus perioperative intraperitoneal chemotherapy is considered **experimental / investigational** for:

1. peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer; and

2. all other indications, including goblet cell tumors of the appendix

Policy Guidelines

1. Ovarian cancer staging is as follows:

IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
IB	Tumor involves both ovaries otherwise like IA.
IC	Tumor limited to 1 or both ovaries
IC1	Surgical spill
IC2	Capsule rupture before surgery or tumor on ovarian surface.
IC3	Malignant cells in the ascites or peritoneal washings.
IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues

IIIA	(Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)
IIIA1	Positive retroperitoneal lymph nodes only
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

2. Eligibility for neoadjuvant chemotherapy and interval debulking surgery is based on a high perioperative risk profile (ie, the patient is a poor candidate to withstand an aggressive initial cytoreductive procedure) or a low likelihood of achieving cytoreduction to less than 1 cm (ie, the patient has extensive disease that precludes upfront optimal cytoreduction) or surgery has been performed but was incomplete (ie, after surgery, one or more residual tumors measuring >1 cm in diameter were present).
3. Complete cytoreduction is defined as no visible disease and optimal cytoreduction as one or more residual tumors measuring 10 mm or less in diameter remaining.

RATIONALE

The most recent MEDLINE literature review was performed through September 25, 2018.

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) plus hyperthermic intraperitoneal chemotherapy (HIPEC) in patients who have pseudomyxoma peritonei is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of CRS plus HIPEC improve the net health outcome in patients with pseudomyxoma peritonei?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with pseudomyxoma peritonei.

Interventions

The combination therapy being considered is CRS plus HIPEC.

Comparators

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

Outcomes

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

Timing

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

Setting

CRS plus HIPEC is administered in an inpatient setting, with follow-up in an outpatient setting.

Primary Treatment

Table 1 summarizes the relevant studies on pseudomyxoma peritonei, some of which are discussed next.

Jimenez et al (2014) retrospectively reviewed a prospective database of patients with peritoneal carcinomatosis maintained by a U.S. medical center.[11] 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 1. In the high-grade peritoneal mucinous carcinomatosis group, Peritoneal Cancer Index (PCI) score (scale range, 0-39), 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.[12] Patients had diffuse peritoneal disease from malignancies of multiple different histologic origins. Exclusion criteria were perioperative chemotherapy performed more than seven 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 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).[13] CRS 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 morbidity rate, 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 ($p=0.004$), institution ($p<0.001$), pathologic grade ($p=0.03$), sex ($p=0.02$), and use of HIPEC ($p=0.04$). 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 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.[14] 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, 0-140 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 ($p=0.002$), 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.[15] 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<0.003) and in those with histologic type disseminated peritoneal adenomucinosis compared with those with peritoneal mucinous carcinomatosis (p<0.014).

Elias et al (2008) reported on the results of 105 consecutive patients with pseudomyxoma peritonei treated between 1994 and 2006 with CRS plus HIPEC.[2] 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. 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 1. 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, m	5-Year PFS, %
Primary treatment						
Jimenez et al (2014)[11]	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)[16]	58	2/40	NR	77	NR	50[b]
Glehen et al (2010)[12]	301	4/40	34	73	78	56
Chua et al (2009)[14]	106	3/49	104	75	40	38
Vaira et al (2009)[15]	60	0/45	NR	94	NR	80
Elias et al (2008)[2]	105	8/68	>100	80	NR	68
Yan et al (2007)[17] (SR)	NR	NR	51-156	52-96	NR	NR
Recurrence						
Lord et al (2015)[18,c]	35	NR	129.5[e]	79	NR	NR
Sardi et al (2013)[19,d]	26	0/42	NR	34	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] 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.[19] 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 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.[18] 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=0.001). 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
Large, retrospective cohort studies and systematic reviews have reported median survival ranging from 47 to 156 months and 5-year OS rates range 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%. Procedure-related morbidity and mortality have generally decreased over time.

Peritoneal Carcinomatosis of Colorectal Origin
Clinical Context and Therapy Purpose
The purpose of CRS plus HIPEC in patients who have peritoneal carcinomatosis of colorectal origin is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of CRS plus HIPEC improve the net health outcome in those with peritoneal carcinomatosis of colorectal origin?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with peritoneal carcinomatosis of colorectal origin.

Interventions
The combination therapy being considered is CRS plus HIPEC.

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

Outcomes
The general outcomes of interest are PFS, OS, and postoperative morbidity.

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

Setting
CRS plus HIPEC is administered in an inpatient setting, with follow-up in an outpatient setting.

Systematic Reviews
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, 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 (eg, 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 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=0.423). The mean morbidity rate was 19.8% in the CRS plus HIPEC group and 20.5% in the traditional treatment group (p=0.815). In all 76 studies, the mean mortality rate was 2.8% and mean morbidity rate was 33%.

Two systematic reviews published in 2014 examined quality of life (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 (total N=1583 patients),[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, 5-216 patients), response rates (most <85%), primary cancers (eg, 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 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 would suggest improvements from baseline in some QOL domains, the absence of parallel control groups limits interpretation of the results.

Randomized Controlled Trials
One RCT has been published. A trial by Verwaal et al (2003), who randomized 105 patients with peritoneal carcinomatosis to standard treatment with systemic chemotherapy (fluorouracil and leucovorin) and palliative surgery, if necessary (ie, treatment of bowel obstruction), or to CRS plus HIPEC followed by standard systemic chemotherapy.[23] Patients with other sites of metastases (ie, lung or liver) were excluded.

The primary end point 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). 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 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.[24] 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 plus HIPEC arm after recurrent disease 30 months postrandomization. The median disease-specific survival was 12.6 months in the standard arm and 22.2 months in the CRS plus HIPEC arm (p=0.028). Median PFS was 7.7 months in the standard arm and 12.6 months in the CRS plus HIPEC arm (p=0.02).

Section Summary: Peritoneal Carcinomatosis of Colorectal Origin
One RCT, 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 one 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. The 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.

Peritoneal Carcinomatosis of Gastric Origin
Clinical Context and Therapy Purpose
The purpose of CRS plus HIPEC in patients who have peritoneal carcinomatosis of gastric origin is to provide a treatment option that is an alternative to or an improvement on existing therapies. The question addressed in this evidence review is: Does the use of HIPEC improve the net health outcome in those with peritoneal carcinomatosis of gastric origin?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with peritoneal carcinomatosis of gastric origin.

Interventions
The combination therapy being considered is CRS plus HIPEC.

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 PFS, OS, and postoperative morbidity.

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

Setting
CRS plus HIPEC is administered in an inpatient setting, with follow-up in an outpatient setting.

Systematic Reviews
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.[25] 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 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 a control treatment (relative risk, 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 (relative risk, 0.87; 95% CI, 0.73 to 1.04; p=0.12) or 3-year survival (relative risk, 0.99; 95% CI, 0.93 to 1.06; p=0.85).

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.[26] 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.[27] 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=0.046). 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 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 one year but there was no difference in survival rates at two or three 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 from Endometrial Cancer
Clinical Context and Therapy Purpose
The purpose of CRS plus HIPEC in patients who have peritoneal carcinomatosis of endometrial origin is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HIPEC improve the net health outcome in those with peritoneal carcinomatosis of endometrial origin?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with peritoneal carcinomatosis of endometrial origin.

Interventions
The combination therapy being considered is CRS plus HIPEC.

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 PFS, OS, and postoperative morbidity.
Timing
Morbidity and mortality from the procedure are measured in the early postoperative period. PFS and OS are should be measured out to 5 years.

Setting
CRS plus HIPEC is administered in an inpatient setting, with follow-up in an outpatient setting.

Cohort Studies

No RCTs or nonrandomized comparative studies were identified. Three small, non-U.S. cohort studies reported outcomes for CRS plus HIPEC for primary (n=6 patients) or recurrent (confined to the peritoneum; n=18 patients) endometrial cancer with peritoneal carcinomatosis.[5,28,29] Patients varied in a histopathologic subtype of cancer, prior treatment, the interval from initial treatment to CRS plus HIPEC (range, 0-120 months), preoperative PCI score (range, 3-24), and postoperative treatment. All patients underwent CRS and HIPEC. Cytoreduction was complete in 18 (75%) patients and almost complete (minimal residual disease) in 3 (12.5%) patients. Of 24 total patients, 5 (21%) died within 1 year (comparable to published survival estimates with systemic chemotherapy[29]); 3 (12.5%) died at 12 to 19 months; 11 (46%) were alive and disease-free at the time of publication (median, 34 months; range, 2-125 months); and 4 (17%) were alive with recurrent disease (median, 21 months; range, 6-28 months). (One patient was lost to follow-up.) The largest study of 13 patients with primary or recurrent disease reported a median OS of 19 months and median DFS of 11 months.[5] In all patients, grade 1 adverse events included anastomotic leak and cisplatin neurotoxicity. More severe complications occurred in 5 (21%) patients and included grade 4 septicemia and pulmonary embolism; pancytopenia and critical illness myopathy; and chronic renal failure. PCI score and completeness of cytoreduction were associated with survival.

Section Summary: Peritoneal Carcinomatosis from Endometrial Cancer

Cohort studies including 24 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, 19 months vs <12 months in published reports). However, severe complications occurred in 21% of patients. 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

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of HIPEC improve the net health outcome in those with peritoneal mesothelioma?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with peritoneal mesothelioma.

Interventions

The combination therapy being considered is CRS plus HIPEC.

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

Outcomes
The general outcomes of interest are PFS, OS, and postoperative morbidity.

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

Setting
CRS plus HIPEC is administered in an inpatient setting, with follow-up in an outpatient setting.

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.[6] 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 visible disease. HIPEC protocols 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 one 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 review, aligned with Baratti's findings: pooled 1-, 3-, and 5-year survival estimates were 84%, 59%, and 42%, respectively.[30]

Observational Studies
Table 2 summarizes relevant observational studies on peritoneal mesothelioma, some of which are discussed next.

Table 2. 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)[31]	42	7	36	65	44	NR
Alexander et al (2013)[32]	211	2	30	38	41	NR
Glehen et al (2010)[12]	88	NR	NR	41	NR	NR
Yan et al (2009)[33]	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 (and included in both systematic reviews) was an international registry study by Yan et al (2009), for which 401 (99%) patients had complete follow-up.[33] 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.[32] 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.[12] 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 ranged from 30 to 92 months and from 33% to 68%, respectively, for patients with peritoneal mesothelioma 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 rates have remained relatively steady over time, at approximately 35% and 5%, respectively.

Newly Diagnosed Stage III Ovarian Cancer
Clinical Context and Therapy Purpose
The purpose of CRS plus HIPEC in patients who have newly diagnosed stage III ovarian cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HIPEC improve the net health outcome in those with ovarian cancer?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with newly diagnosed stage III ovarian cancer.
Interventions
The combination therapy being considered is CRS plus HIPEC.

Comparators
The following therapies are currently being used to treat ovarian cancer: CRS alone and systemic chemotherapy.

Outcomes
The general outcomes of interest are PFS, OS, and postoperative morbidity.

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

Setting
CRS plus HIPEC is administered in an inpatient setting, with follow-up in an outpatient setting.

Randomized Controlled Trials
One RCT has been published on CRS plus HIPEC for ovarian cancer (see Table 3). Van Driel et al (2018) reported that CRS plus HIPEC reduced mortality for patients with newly diagnosed stage III epithelial ovarian cancer (see Table 4).[34] 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=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 4 adverse events was similar in both groups (25% for surgery alone vs 27% for CRS plus HIPEC; p=0.76).

Table 3. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Van Driel et al (2018)[34]	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 4. 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 AEs, %
Van Driel et al (2018)[34]					
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	0.003		0.02		0.76

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

The purpose of the gaps tables (see Tables 5 and 6) is to display notable gaps 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 evidence supporting the position statement. The major limitation of the van Driel trial was the lack of blinding, which might be expected to have a minor effect on the objective measure of mortality.

Table 5. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Van Driel et al (2018)[34]	4. 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.
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 Gaps

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Van Driel et al (2018)[34]		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: Newly Diagnosed Stage III Ovarian Cancer

HIPEC has been studied in 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

Clinical Context and Therapy Purpose

The purpose of CRS plus HIPEC in patients who have recurrent ovarian cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HIPEC improve the net health outcome in patients with recurrent stage IIIC or IV ovarian cancer?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with recurrent stage IIIC or IV ovarian cancer.

Interventions
The combination therapy being considered is CRS plus HIPEC.

Comparators
The following therapies are currently being used to treat ovarian cancer: CRS alone and systemic chemotherapy.

Outcomes
The general outcomes of interest are PFS, OS, and postoperative morbidity.

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

Setting
CRS plus HIPEC is administered in an inpatient setting, with follow-up in an outpatient setting.

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).[35] 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][36]), 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.

Randomized Controlled Trials
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 (see Table 7).[36] 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 7. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Spiliotis et al (2015)[36]	EU	1	2006-2013	120 women with advanced (stage IIIC-IV) recurrent epithelial ovarian cancer	CRS plus HIPEC	CRS plus systemic chemotherapy

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

Table 8. 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 AEs, %
Spiliotis et al (2015)[36]					
CRS plus SC				13.4	
CRS plus HIPEC				26.7	
p				0.006	

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

Gaps in relevance and design and conduct are noted in Tables 9 and 10. For the Spiliotis study, baseline between-group differences in the stage of disease and completeness of cytoreduction, which is prognostic indicator for survival, limit interpretation of the trial results.

Table 9. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Spiliotis et al (2015)[36]	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 10. Study Design and Conduct Gaps

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Spiliotis et al (2015)[36]		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 and RCT 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 completeness of cytoreduction, which has consistently been shown to be associated with survival.

Appendiceal Goblet Cell Tumors
Clinical Context and Therapy Purpose
The purpose of CRS plus HIPEC in patients who have appendiceal goblet cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HIPEC improve the net health outcome in those with appendiceal goblet cell tumors?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with appendiceal goblet cell tumors.

Interventions
The combination therapy being considered is CRS plus HIPEC.

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 PFS, OS, and postoperative morbidity.

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

Setting
CRS plus HIPEC is administered in an inpatient setting, with follow-up in an outpatient setting.
Cohort Studies
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.[37] 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=0.003), 40% (p=0.07), and 52% (p=0.48), respectively. In 489 (65%) patients who achieved complete cytoreduction, the pattern of 3-year DFS outcomes was similar: 43%, 73% (p<0.001), 44% (p=0.85), and 44% (p=0.82), 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.

Section Summary: Appendiceal Goblet Cell Tumors
Evidence is limited to a retrospective cohort study of patients with goblet cell tumors of the appendix. This study found a 3-year survival rate of 63% for CRS plus HIPEC.

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, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Uncontrolled studies of primary treatment of pseudomyxoma peritonei with CRS plus HIPEC have reported a median and a 5-year overall survival ranging from 47 to 156 months and 41% to 96%, respectively. Two small retrospective studies, who underwent CRS plus HIPEC for recurrence, indicated 5-year overall survival rates ranging from 34% to 79%. Procedure-related morbidity and mortality have decreased over time. Controlled studies are needed to draw conclusions about the efficacy and safety of CRS plus HIPEC compared with standard treatment (CRS alone). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal carcinomatosis of colorectal origin who receive CRS plus HIPEC, the evidence includes an RCT, systematic reviews, and a large number of observational studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, 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 overall survival, disease-specific survival, quality of life, 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. An

RCT found better survival in patients who received CRS plus HIPEC compared with an alternative treatment. 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 overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Only uncontrolled studies with small sample sizes were available (<25 patients). Randomized trials that compare CRS plus HIPEC with standard treatment (eg, 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 overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Uncontrolled studies have shown median and 5-year overall survival ranging from 30 to 92 months and 33% to 68%, respectively, for patients who had peritoneal mesothelioma treated with CRS plus HIPEC. Reported procedure-related morbidity and mortality were approximately 35% and 5%, respectively. Although no RCTs or comparative studies have been published, uncontrolled study data have shown reasonable rates of overall survival with the use of this technique. Procedure-related morbidity and mortality have remained steady over time. Because the prevalence of peritoneal mesothelioma is very low, conducting high-quality trials is difficult. Thus, although the evidence is insufficient to determine the effects of the technology on health outcomes, for the reasons discussed above, CRS plus HIPEC may be considered medically necessary for this indication.

For individuals who have newly diagnosed stage III ovarian cancer who receive CRS plus HIPEC, the evidence includes an RCT. Relevant outcomes are overall survival, disease-specific survival, quality of life, 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 review. Relevant outcomes are overall survival, disease-specific survival, quality of life, 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 a case series. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. One retrospective series was identified. Additional studies—preferably controlled and ideally RCTs—are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines include the following relevant recommendations for colon cancer (v.2.2018) and rectal cancer (v.2.2018): "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. The panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities."[38,39]

NCCN guidelines on gastric cancer (v.2.2018) and for uterine neoplasms (v.2.2018) do not discuss cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC).[40,41]

NCCN guidelines on ovarian cancer (v.2.2018) state that "patients with low volume residual disease after surgical debulking for stage II or II invasive epithelial ovarian or peritoneal cancer are candidates for intraperitoneal (IP) chemotherapy."[42] Use of HIPEC is not specified.

American Society of Colon and Rectal Surgeons

The 2017 practice guidelines on the management of colon cancer by the American Society of Colon and Rectal Surgeons stated that treatment of patients with isolated peritoneal carcinomatosis may include cytoreductive surgery in conjunction with perioperative intraperitoneal chemotherapy, with or without hyperthermia.[43]

Society of Surgical Oncology

The Society of Surgical Oncology (2007) issued a consensus statement on cytoreductive surgery and HIPEC in the management of peritoneal surface malignancies of colonic origin.[44] The Society recommended that patients with peritoneal carcinomatosis without distant disease, in whom complete cytoreduction is possible, undergo HIPEC before systemic therapy. As of July 2018, an updated statement has not been published.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Trials

NCT Number	Title	Enrollment	Completion Date
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	Mar 2019
NCT02179489	Trial Evaluating Surgery With Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Treating Patients With a High Risk of Developing Colorectal Peritoneal Carcinomatosis	300	Oct 2023
NCT01226394	Multicentric Phase III Trial Comparing Simple Follow-up to Exploratory Laparotomy Plus "in Principle" HIPEC (Hyperthermic Intraperitoneal Chemotherapy) in Colorectal Patients Initially Treated With Surgery and Adjuvant Chemotherapy Who Have a	130	Jun 2019

NCT Number	Title	Enrollment	Completion Date
Colorectal and appendiceal cancer			
	High Risk of Developing Colorectal Peritoneal Carcinomatosis (ProphyloCHIP)		
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	Oct 2020
NCT02231086	Adjuvant Hyperthermic Intraperitoneal Chemotherapy in Patients With Colon Cancer at High Risk of Peritoneal Carcinomatosis	204	Apr 2022
Gastric cancer			
NCT02158988	Cytoreductive Surgery (CRS) With/Without HIPEC in Gastric Cancer With Peritoneal Carcinomatosis (GASTRIPEC)	180	Sep 2020
NCT02960061	D2 Radical Resection After Neoadjuvant Chemotherapy Combined With HIPEC for Advanced Gastric Cancer: a Prospective Randomized Controlled Trial	640	Dec 2019
NCT02240524	Efficacy of HIPEC in the Treatment of Patients With Locally Advanced Gastric Cancer	582	July 2019
NCT01882933	GASTRICHIP : D2 Resection and HIPEC (Hyperthermic Intraperitoneal Chemoperfusion) in Locally Advanced Gastric Carcinoma. A Randomized and Multicentric Phase III Study	322	May 2025
Ovarian cancer			
NCT01767675	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	98	Jan 2019
NCT01628380	Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer (CHORINE)	94	Jul 2018 (ongoing)
NCT01539785	Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) in Ovarian Cancer Recurrence (HORSE)	158	Sep 2018
NCT01376752	Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment (CHIPOR)	444	Dec 2020
NCT02124421	Outcomes in CRS/HIPEC as Initial Treatment of Ovarian, Fallopian Tube and Primary Peritoneal Cancer	48	Apr 2020

NCT: national clinical trial

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

CPT / HCPCS Codes

77605	Hyperthermia, externally generated; deep (ie, heating to depths greater than 4 cm)
77620	Hyperthermia generated by intracavitary probe(s)
96446	Chemotherapy administration into the peritoneal cavity via indwelling port or catheter
96549	Unlisted chemotherapy procedure

- The coding for this overall procedure would likely involve codes for the surgery, the intraperitoneal chemotherapy, and the 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 describing 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 indwelling port or catheter". When performed using a temporary catheter or performed intraoperatively, the unlisted code 96549 would be reported.
- Hyperthermia
  This procedure does not refer to external application of heat as described by CPT code 77605. There are no codes for the heating of the chemotherapy.

ICD-10 Diagnoses

C45.1	Mesothelioma of peritoneum
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C78.6	Secondary malignant neoplasm of other and unspecified respiratory organs; retroperitoneum and peritoneum

REVISIONS

08-11-2009	In Policy section: ▪ Added indication "A. Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei is considered medically necessary."
	In Coding section: ▪ Added CPT Code: 77620.
10-19-2009	In Policy section: ▪ Removed, "A. Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei is considered medically necessary." ▪ Revised wording From, "B. Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of gastrointestinal origin is considered experimental / investigational." To "Cytoreduction and hyperthermic intraperitoneal chemotherapy may be considered medically necessary for the treatment of peritoneal carcinomatosis when clinically confined to the peritoneal cavity."
	Updated Rationale and References sections.
01-28-2011	Description section updated.
	Rationale section updated.
	Diagnosis Code wording updated.
	References section updated.
03-07-2011	In Coding section: ▪ Added CPT code: 96446 ▪ Removed CPT code: 96445
02-28-2014	Description section reviewed
	Rationale section reviewed
	In Coding section: ▪ Updated Coding Information bullets

	▪ Added ICD-10 Diagnoses Codes
	References reviewed
07-23-2015	Policy published 06-23-2015 for an effective date of 07-23-2015
	Title revised from "Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy for the Treatment of Peritoneal Carcinomatosis of Gastrointestinal Origin" to "Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies".
	Description section updated
	In Policy section: ▪ In Item A "removed "peritoneal carcinomatosis when clinically confined to the peritoneal cavity" to read, "Cytoreduction and hyperthermic intraperitoneal chemotherapy may be considered medically necessary for the treatment of:" ▪ In Item A added, "1. pseudomyxoma peritonei; and 2. diffuse malignant peritoneal mesothelioma" ▪ Added Item B "Cytoreductive surgery and perioperative intraperitoneal chemotherapy is considered experimental / investigational for: 1. peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer; 2. ovarian cancer; and 3. all other indications, including goblet cell tumors of the appendix"
	Rationale section updated
	In Coding section: ▪ Added CPT Code: 96549 ▪ Removed CPT Codes: 77605, 77620 (they were not applicable to this policy). ▪ Added ICD-9 Codes: 158.8, 158.9 and the corresponding ICD-10 code. ▪ Updated Coding notations.
	References updated
02-17-2016	In Policy section: ▪ Added new Item A 2, "invasive epithelial ovarian cancer; and" ▪ Previous Item A 2 is now Item A 3. ▪ In Item B 2, added "all other types" and "not meeting the above" to read, "all other types of ovarian cancer not meeting the above"
	Updated Rationale section.
	Updated References section.
09-15-2016	Updated Description section.
	In Policy section: ▪ In Item A, added "surgery" and "perioperative" and removed "on" and "hyperthermic" to read, "Cytoreductive surgery and perioperative intraperitoneal chemotherapy may be considered medically necessary for the treatment of:"
	Updated Rationale section.
	In Coding section: ▪ Revised coding bullets.
	Updated References section.
11-15-2016	In Coding section: ▪ Added ICD-10 codes: C56.1, C56.2.
08-15-2017	Updated Description section.
	In Policy section: ▪ In Item A, added "plus" and removed "and" to read, "Cytoreductive surgery plus perioperative intraperitoneal chemotherapy may be considered medically necessary for the treatment of:"

	▪ In Item B, added "plus" and removed "and" to read, "Cytoreductive surgery plus perioperative intraperitoneal chemotherapy is considered experimental / investigational for:"
	Updated Rationale section.
	Updated References section.
04-12-2019	Policy posted to the bcbsks.com website on 03-13-2019 with an effective date of 04-12-2019.
	The title of the policy was revised from "Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies."
	Updated Description section.
	In Policy section: ▪ In Item A, removed "perioperative" and added "hyperthermic" and "(HIPEC) at the time of surgery" to read, "Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of surgery may be considered medically necessary for the treatment of:" ▪ Removed Item A 2, "invasive epithelial ovarian cancer; and" ▪ Added new Item B, "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: 1. The patient has stage III disease (see Policy Guidelines); and 2. The patient 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); and 3. It is expected that complete or optimal cytoreduction can be achieved at time of the interval debulking surgery (see Policy Guidelines)." ▪ Added new Item C, "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 experimental / investigational." ▪ Removed previous Item B 2 (currently Item D), "all other types of ovarian cancer not meeting the above; and" ▪ Updated Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 77605, 77620. ▪ ICD-9 codes were removed.
	Updated References section.

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