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

**Professional**
Original Effective Date: April 3, 2009
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<th>Interventions</th>
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<td>Comparators of interest are: Cytoreductive surgery, Systemic chemotherapy</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
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<td>Interventions of interest are: Cytoreductive surgery plus perioperative intraperitoneal chemotherapy</td>
<td>Comparators of interest are: Cytoreductive surgery, Systemic chemotherapy</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
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**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 hyperthermic chemotherapy, 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 evaluate whether cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improve health outcomes in individuals with intra-abdominal and pelvic malignancies.
BACKGROUND

Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy

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 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 hyperthermic intraperitoneal chemotherapy (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.

Pseudomyxoma Peritonei

Pseudomyxoma peritonei is a clinicopathologic entity 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. 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 fortuitously discovered on imaging or during a laparotomy performed for another reason, to advanced cases with a distended abdomen, bowel obstruction, and starvation. The conventional treatment of pseudomyxoma peritonei is surgical debulking repeated as necessary to alleviate pressure effects. However, repeated debulking surgeries become ever more difficult due to progressively thickened intra-abdominal adhesions, and this treatment is palliative, leaving visible or occult disease in the peritoneal cavity. Five-year OS depends on tumor histology and ranges from 6% for high-grade (HG) tumors to 75% for low-grade (LG) tumors.

Gastrointestinal Cancers (Colorectal, Gastric) and Peritoneal Carcinomatosis

Peritoneal dissemination develops in approximately 10% to 15% of patients with colon cancer and, despite the use of increasingly effective regimens of chemotherapy and biologic agents in the treatment of advanced disease, peritoneal metastases are associated with a median survival of 6 to 7 months.

Peritoneal carcinomatosis is detected in more than 30% of patients with advanced gastric cancer and is a poor prognostic indicator. Median survival is 3 months, and 5-year survival is less than 1%. Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis. Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for cure.
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 (DMPM) are registered every year, accounting for 10% to 30% of all-type mesothelioma. DMPM has traditionally been considered as 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 occurs as a result of locoregional progression within the abdominal cavity. In historical case series, treatment by palliative surgery, systemic/intraperitoneal chemotherapy, and abdominal irradiation resulted in a median survival of approximately 12 months.

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, prior 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 ovary; epithelial carcinoma is the most common type, 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 approximately 65% of the incidence rate.

Current management of advanced epithelial ovarian cancer is CRS followed by combination chemotherapy. Treatment guidelines recommend intraperitoneal chemotherapy for patients with optimally debulked (<1 cm) stage 2 disease (pelvic extension of tumor) or stage 3 disease (peritoneal extension of tumor). Estimated median OS is 66 months with and 37 to 49 months without intraperitoneal chemotherapy, respectively. Tumor recurrences are common, and prognosis for recurrent disease is poor.

CRS/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.
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.¹³

Several peritoneal lavage systems (Product Code LGZ) have been FDA-cleared to provide “warmed, physiologically compatible sterile solution” (eg, Performer® HT perfusion system; Rand Srl, Medolla, Italy¹⁴). 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 Inc., Minneapolis, MN¹⁵; Belmont Instrument Corp., Billerica, MA¹⁶).

POLICY
A. Cytoreductive surgery plus perioperative intraperitoneal chemotherapy may be considered medically necessary for the treatment of:
   1. pseudomyxoma peritonei; and
   2. invasive epithelial ovarian cancer; and
   3. diffuse malignant peritoneal mesothelioma

B. 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 types of ovarian cancer not meeting the above; and
   3. all other indications, including goblet cell tumors of the appendix

RATIONALE
The most recent MEDLINE literature review was performed through June 6, 2017.

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

Pseudomyxoma Peritonei
Relevant studies on pseudomyxoma peritonei, some of which are discussed next, are summarized in Table 1. We divide our discussion into primary treatment and treatment for recurrence.
Table 1. Summary of Studies of CRS and HIPEC in Pseudomyxoma Peritonei

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Postoperative Mortality/Morbidity, %</th>
<th>Median OS, m</th>
<th>5-Year OS, %</th>
<th>Median PFS, m</th>
<th>5-Year PFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Jimenez et al (2014)</td>
<td>17</td>
<td>0/16</td>
<td>90</td>
<td>56</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>125 HG</td>
<td></td>
<td></td>
<td>47</td>
<td>41</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>77 LG</td>
<td></td>
<td></td>
<td>Not reached</td>
<td>83</td>
<td>NR</td>
<td>58</td>
</tr>
<tr>
<td>Marcotte et al (2014)</td>
<td>58</td>
<td>2/40</td>
<td>NR</td>
<td>77</td>
<td>NR</td>
<td>50</td>
</tr>
<tr>
<td>Glehen et al (2010)</td>
<td>255</td>
<td>4/40</td>
<td>&gt;100</td>
<td>73</td>
<td>78</td>
<td>56</td>
</tr>
<tr>
<td>Vaira et al (2009)</td>
<td>60</td>
<td>0/45</td>
<td>NR</td>
<td>94</td>
<td>NR</td>
<td>80</td>
</tr>
<tr>
<td>Elias et al (2008)</td>
<td>105</td>
<td>8/68</td>
<td>NR</td>
<td>80</td>
<td>NR</td>
<td>68</td>
</tr>
<tr>
<td>Yan et al (2007)</td>
<td></td>
<td></td>
<td>NR</td>
<td>51-156</td>
<td>52-96</td>
<td>NR</td>
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<tr>
<td><strong>Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sardi et al (2013)</td>
<td>26</td>
<td>0/42</td>
<td>NR</td>
<td>34</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lord et al (2015)</td>
<td>35</td>
<td>NR</td>
<td>129.5</td>
<td>79.0</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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.

Primary Treatment

Jimenez et al (2014) retrospectively reviewed a prospective database of patients with peritoneal carcinomatosis as maintained by a medical center in Baltimore.17 Two hundred two patients with peritoneal carcinomatosis from appendiceal cancer who underwent cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (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 1. In the high-grade (PMCA) group, Peritoneal Cancer Index (PCI) score, 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 that evaluated toxicity and prognostic factors after CRS plus HIPEC and/or unheated intraperitoneal chemotherapy for 5 days postoperatively.19 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 (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).25 CRS was achieved 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%. Postoperative mortality was 4% and morbidity, 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 survival rate was 54.8%. Median survival 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 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. 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 survival rate of 75%. Median progression-free survival was 40 months with 1-, 3-, and 5-year progression-free survival rates of 71%, 51%, and 38%, respectively. Factors influencing OS included histopathologic type of tumor (p=0.002), with best survival in patients with disseminated peritoneal adenomucinosis, and worst survival in patients with peritoneal mucinous carcinomatosis. Other factors influencing survival were use of both HIPEC and unheated postoperative intraperitoneal chemotherapy, completeness of cytoreduction, and severe morbidity.

Vaira et al (2009) reported a single institution’s experience managing pseudomyxoma peritonei with CRS and HIPEC in 60 patients, 53 of whom had final follow-up data. 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).

In 2008, Elias et al reported on the results of 105 consecutive patients with pseudomyxoma peritonei treated between 1994 and 2006 with CRS plus HIPEC. 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 was 67.6%. The median follow-up was 48 months, and 5-year OS and DFS rates were 80% (95% confidence interval [CI], 68% to 88%) and 68% (95% CI, 55% to 79%), respectively. On multivariate analysis, 2 factors that had a negative influence on DFS were identified: serum carbohydrate
antigen 19-9 level (a marker of biliopancreatic malignancy) greater than 300 units/mL and nondisseminated peritoneal adenomucinosis tumor histology.

In 2007, Yan et al conducted a systematic review of all relevant studies from 1996 to 2006 on the efficacy of CRS and intraperitoneal chemotherapy using HIPEC and/or early postoperative intraperitoneal chemotherapy for pseudomyxoma peritonei. They found no randomized controlled trials (RCTs) or comparative studies. Ten studies were included (total N=863 patients); all were uncontrolled, observational studies. Two studies had relatively long-term follow-up (48 months and 52 months) while median follow-up in the remaining studies was less than 3 years (range, 19-35 months). Median survival across all studies ranged from 51 to 156 months. One-, 2-, 3-, and 5-year survival rates varied from 80% to 100%, 76% to 96%, 59% to 96%, and 52% to 96%, respectively. Overall mortality rates varied from 0% to 18% and morbidity from 33% to 56%.

Recurrence
From the same Baltimore medical center database studied by Jimenez et al (previously described), Sardi et al (2013) identified 26 patients who underwent repeat CRS plus HIPEC for peritoneal carcinomatosis recurrence. Sixteen (62%) patients had high-grade PMCA and 10 (38%) patients had low-grade DPAM. 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 (scale range, 0-39) 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 second procedure, 1-, 3-, and 5-year OS rates were 91%, 53%, and 34%, respectively. After 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. Thirty-five (26%) of 137 patients who recurred 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 of 47 to 156 months and 5-year OS rates of 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
Systematic Reviews
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.\textsuperscript{26} 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; $\hat{I}^2=0\%$, 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%).

Previously in 2013, de Cuba et al published a systematic review and meta-analysis of studies of colorectal cancer patients with both peritoneal and liver metastases who received CRS plus HIPEC and curative resection.\textsuperscript{27} Reviewers compared the results of studies in this population with those of patients without liver metastases who received modern systemic chemotherapy only (irinotecan, oxaliplatin, and a biologic) or CRS plus HIPEC or unheated intraperitoneal chemotherapy for 5 days postoperatively. The median OS ranged from 6 to 36 months in patients with liver metastases; from 10 to 24 months in patients (without liver metastases) who received systemic chemotherapy only; and from 19 to 63 months in patients (without liver metastases) who received CRS plus HIPEC or unheated postoperative intraperitoneal chemotherapy. Patients with liver metastases had a 24% greater risk of death than those without liver metastases who received CRS plus HIPEC or unheated postoperative intraperitoneal chemotherapy (pooled HR=1.24; 95% CI, 0.96 to 1.60; p not reported). Reviewers observed that comparisons across studies were impaired by lack of standardization of the HIPEC or unheated postoperative intraperitoneal chemotherapy procedures (exposure techniques, drugs and doses used, durations of exposure, temperatures, flow rates). In 2013, the American Society of Peritoneal Surface Malignancies, a consortium of cancer centers performing CRS with HIPEC, published recommendations for standardizing the delivery of HIPEC in colorectal cancer patients with peritoneal dissemination treated in the United States.\textsuperscript{28} Closed HIPEC using mitomycin C 40 mg at 42°C for 90 minutes was recommended.

Two systematic reviews published in 2014 examined quality of life (QOL) outcomes in patients with peritoneal carcinomatosis who underwent CRS plus HIPEC.\textsuperscript{29,30} Both reviews included studies that used structured QOL scales; Shan et al included 15 studies (total N=1583 patients),\textsuperscript{29} 14 of which appeared in the review of 20 studies (n=1181 respondents) by Seretis et al.\textsuperscript{30} 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 ($\hat{I}^2=38\%$) and emotional health ($\hat{I}^2=41\%$) showed statistically significant improvements compared with baseline,
but physical ($I^2=60\%$), social ($I^2=0\%$), and functional ($I^2=74\%$) health did not.\textsuperscript{29} Improvements were small to medium (standardized mean difference, $<0.4$ for all outcomes). Although this evidence suggested 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. This trial, reported in 2003 by Verwaal et al, 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.\textsuperscript{31} 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 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.\textsuperscript{32} 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 progression-free survival 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 several systematic reviews have been published. A 2016 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. A limitation of the RCT is that systemic chemotherapy regimens did not use currently available biologic agents.

**Peritoneal Carcinomatosis of Gastric Origin**

**Systematic Reviews**

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. 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, RCT in 17 patients from several U.S. centers who had gastric cancer metastatic to the liver and lung and peritoneal carcinomatosis. 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 with 5-fluorouracil, leucovorin, oxaliplatin, plus irinotecan (FOLFOXIRI; n=8) or to systemic chemotherapy plus gastrectomy and CRS plus 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 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.

In 2011, Yang et al randomized 68 patients (1:1) to CRS plus cisplatin HIPEC or to CRS alone. 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. 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 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.
Peritoneal Carcinomatosis from Endometrial Cancer

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.\textsuperscript{36-38} Patients varied in histopathologic subtype of cancer, prior treatment, 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 intraoperative HIPEC with cisplatin plus doxorubicin (n=19) or mitomycin (n=5). 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); 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.\textsuperscript{36} 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 is 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.\textsuperscript{9} 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 1 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 these. 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 2015 systematic review by Helm et al, 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.\textsuperscript{39}

**Observational Studies**

Relevant observational studies on peritoneal mesothelioma, some of which are discussed next, are summarized in Table 2.

**Table 2. Summary of Studies of CRS and HIPEC in Peritoneal Mesothelioma**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Postoperative, %</th>
<th>Median OS, mo</th>
<th>5-Year OS, %</th>
<th>Median PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robella et al (2014)\textsuperscript{10}</td>
<td>42</td>
<td>7</td>
<td>36</td>
<td>65</td>
<td>44</td>
</tr>
<tr>
<td>Alexander et al (2013)\textsuperscript{41}</td>
<td>211</td>
<td>2</td>
<td>30</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Glehen et al (2010)\textsuperscript{19}</td>
<td>88</td>
<td>NR</td>
<td>NR</td>
<td>41</td>
<td>NR</td>
</tr>
<tr>
<td>Yan et al (2009)\textsuperscript{42}</td>
<td>401</td>
<td>NR</td>
<td>53</td>
<td>47</td>
<td>NR</td>
</tr>
</tbody>
</table>

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 a 2009 international registry study by Yan et al, for which 401 (99%) patients had complete follow-up.\textsuperscript{42} 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.\textsuperscript{41} 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). Shetty et al (2014) similarly reported improved OS and reduced hospital stays with carboplatin HIPEC compared with mitomycin C HIPEC in 44 patients with DMPM.\textsuperscript{43}

In the 2010 retrospective, multicenter cohort study by Glehen et al (as described above in the Pseudomyxoma Peritonei section), the principal origin of the tumor was peritoneal mesothelioma in 88 patients.\textsuperscript{19} The 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 OS of 30 to 92 months and 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.

**Ovarian Cancer**

Relevant studies on ovarian cancer, some of which are discussed next, are summarized in Table 3.
Table 3. Summary of Studies of CRS and HIPEC in Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Postoperative, %</th>
<th>Median OS, mo</th>
<th>5-Year OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European studies</td>
<td>157a</td>
<td>6-8a</td>
<td>16-42a</td>
<td>35-48 NR</td>
</tr>
<tr>
<td>Bakrin et al (2014) (R)</td>
<td>184</td>
<td>2-5a</td>
<td>2-29a</td>
<td>42-58 NR</td>
</tr>
<tr>
<td>Controls</td>
<td>287</td>
<td>NR</td>
<td>NR</td>
<td>29-66a NR</td>
</tr>
<tr>
<td><strong>Randomized controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spiliotis et al (2015)</td>
<td>60</td>
<td>NR</td>
<td>NR</td>
<td>26.7c NR</td>
</tr>
<tr>
<td>Controls</td>
<td>60</td>
<td>NR</td>
<td>NR</td>
<td>13.4c NR</td>
</tr>
<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagotti et al (2012)</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
<td>68</td>
</tr>
<tr>
<td>Controls</td>
<td>37</td>
<td>NR</td>
<td>NR</td>
<td>42</td>
</tr>
<tr>
<td>Spiliotis et al (2011)</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>19.4 NR</td>
</tr>
<tr>
<td>Controls</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>11.2 NR</td>
</tr>
<tr>
<td>Muñoz-Casares et al (2009)</td>
<td>14</td>
<td>NR</td>
<td>NR</td>
<td>58</td>
</tr>
<tr>
<td>Controls</td>
<td>12</td>
<td>NR</td>
<td>NR</td>
<td>17</td>
</tr>
<tr>
<td><strong>Multitreatment settings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYPER-O Registry (2010)</td>
<td>141</td>
<td>NR</td>
<td>NR</td>
<td>30.3 25</td>
</tr>
<tr>
<td>cr: complete resection of macroscopic disease; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; NR: not reported; OS: overall survival; R: review; SR: systematic review.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In 2015, Spiliotis et al in Greece reported a single-center RCT of 120 women who had advanced (stage IIIc-IV), recurrent epithelial ovarian cancer after initial treatment with CRS or debulking surgery and systemic chemotherapy. Between 2006 and 2013, eligible women were randomized preoperatively by computer assignment to CRS plus HIPEC (using cisplatin plus paclitaxel for platinum-sensitive disease or doxorubicin plus paclitaxel or mitomycin for platinum-resistant disease) or to CRS followed by systemic chemotherapy. More patients in the CRS plus HIPEC group (65%) had complete cytoreduction compared with the non-HIPEC group (55%), and the CRS plus HIPEC group had more patients with stage IIIc disease (68%) compared with the non-HIPEC group (60%). 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). In platinum-sensitive disease, survival was 26.8 months in the CRS plus HIPEC group and 15.2 months in the non-HIPEC group (p=0.035), but in platinum-resistant disease, survival did not differ statistically between groups (26.6 months in the CRS plus HIPEC group vs 10.2 months in the non-HIPEC group; p value not reported). A statistical test for interaction (treatment × platinum sensitivity) was not reported. Completeness of cytoreduction and PCI score were associated with survival. Treatment-related morbidity and mortality were not reported. Baseline between-group differences in completeness of cytoreduction, which is prognostic for survival, limit interpretation of the trial results.
A systematic review and meta-analysis of studies on CRS plus HIPEC for treating ovarian cancer was published by Huo et al in 2015.54 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 (described above) was identified (Spiliotis et al). 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). It is important to note that most of the comparative studies were not randomized and thus subject to potential selection and observational biases. Moreover, the single RCT, as noted, had baseline between-group differences in completeness that limited conclusions on the efficacy of CRS plus HIPEC.

Earlier reviews (Chiva et al [2015]),47 Bakrin et al [2014],48 evaluated CRS plus HIPEC as first- and second-line treatments for ovarian cancer. Chiva et al reported that, in the first-line setting, the weighted (for study sample size) median OS was 37 months (range, 27-78 months), median DFS was 14 months (range, 12-30 months), and 5-year OS was 40 months (range, 28-72 months). In the second-line setting, the weighted median OS was 36 months (range, 23-62 months) and the median DFS was 20 months (range, 11-24 months). These results were inferior to those observed in studies of second-line CRS without HIPEC (median OS, 50-60 months). Other retrospective studies in patients with recurrent ovarian cancer have reported similar survival estimates.55,56

The Bakrin (2014) review included 3 non-U.S. case-control studies that compared CRS plus HIPEC with CRS alone for recurrent ovarian cancer (total N=104 patients).50-52 Three- to 5-year survival rates ranged from 50% to 68% in the CRS plus HIPEC groups and from 17% to 42% in the CRS-only groups.

Cohort studies from Europe (total N=157 patients) have reported procedure-related morbidity and mortality of 16% to 42% and 6% to 8%, respectively, in first- and second-line settings.44-46,57 The median OS was 35 to 48 months in the first-line setting and 27 to 33 months in the second-line setting and varied by completeness of cytoreduction.

In 2005, ThermaSolutions sponsored an Internet registry of patients with epithelial ovarian cancer who were treated with HIPEC at several participating U.S. institutions.53 Initial results from 141 (85%) of 166 registered patients were published in 2010. Most patients (59%) received second-line HIPEC; others received HIPEC as first-line treatment (18%), for interval debulking (13%) or for consolidation (9%). Median follow-up was 18 months (range, <1-141 months). The median OS was 30.3 months (95% CI, 23.0 to 37.6 months), and 2-, 5-, and 10-year OS estimates were 49%, 25%, and 14%, respectively. Survival estimates adjusted for prognostic factors identified in univariate and multivariate analyses (platinum sensitivity, completeness of cytoreduction, chemotherapy agent[s] used, duration of HIPEC perfusion, duration of hospital stay) were not reported. Analysis of toxicity was not reported. The published web link to the registry (www.hyperoregistry.com) ceased to function in June 2016.

Section Summary: Ovarian Cancer
CRS plus HIPEC has been studied for both primary advanced ovarian cancer and recurrent disease. For recurrent disease (second-line setting), evidence from 1 RCT from Greece and 3 non-U.S. case-control studies have shown improved survival with CRS plus HIPEC compared with
Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies

CRS without HIPEC. However, treatment groups in the RCT were unbalanced at baseline in completeness of cytoreduction, which has consistently been shown to be associated with survival. Several retrospective cohort studies and systematic reviews of cohort studies did not clearly indicate that HIPEC added to CRS improved on published survival estimates in patients with ovarian cancer in the first- or second-line setting. Procedure-related morbidity and mortality estimates in the cohort studies were as high as 42% and 8%, respectively; however, these estimates are difficult to interpret with control arms (eg, CRS without HIPEC). In both the first- and second-line settings, completeness of cytoreduction, extent of peritoneal carcinomatosis, and chemosensitivity to platinum have been shown to be prognostic factors.

### 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 plus HIPEC with those in nonmucinous (n=52) and low-grade (n=567) and high-grade (n=89) mucinous appendiceal tumors. 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 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: Three-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**

A retrospective cohort study of patients with goblet cell tumors of the appendix reporting survival outcomes with CRS plus HIPEC found a 3-year survival rate of 63%.

### SUMMARY OF EVIDENCE

For individuals who have pseudomyxoma peritonei who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes cohort studies and a systematic review. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. Uncontrolled studies of primary treatment of pseudomyxoma peritonei with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have reported median and 5-year overall survival ranging from 47 to 156 months and 41% to 96%, respectively. One retrospective study of 26 patients who underwent CRS and HIPEC for recurrence indicated 5-year overall survival of 34%. Procedure-related morbidity and mortality have generally decreased over time. Controlled studies are needed to draw conclusions about the efficacy and safety of CRS and 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 perioperative intraperitoneal chemotherapy, the evidence includes a randomized controlled trial (RCT), systematic reviews, and a large number of observational studies. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A 2016 meta-analysis identified 76 studies, 15 of which were controlled. 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 rates of treatment-related morbidity. 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 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 perioperative intraperitoneal chemotherapy, the evidence includes 2 small RCTs, observational studies, and a systematic review. Relevant outcomes are OS, 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. A meta-analysis found significantly better survival in the surgery plus HIPEC group at 1 year but not at 2 or 3 years. One 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 perioperative intraperitoneal chemotherapy, the evidence includes cohort studies. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Only uncontrolled studies were available and they had small sample sizes (<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 perioperative intraperitoneal chemotherapy, the evidence includes retrospective cohort studies and systematic reviews. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Uncontrolled studies have shown median and 5-year OS ranging from 30 to 92 months and 33% to 68%, respectively, for patients with peritoneal mesothelioma who are treated with CRS plus HIPEC. Reported procedure-related morbidity and mortality were approximately 35% and 5%, respectively. 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 ovarian cancer who receive CRS plus perioperative intraperitoneal chemotherapy, the evidence includes an RCT, systematic reviews, and uncontrolled studies. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Results from an RCT with methodologic flaws, case-control studies, and cohort studies are inconsistent; the RCT and case-control studies showed improved survival with CRS plus HIPEC in the second-line setting compared with CRS without HIPEC, but retrospective cohort studies have not shown a clear survival advantage compared with current treatment in the first- or the second-line setting. Results of at least some of these studies were confounded by prognostic factors (completeness of cytoreduction, extent of peritoneal carcinomatosis, chemosensitivity to platinum). Well-designed, RCTs are needed to control for potential covariates.
and to demonstrate improvements in the net health outcome compared with current treatment approaches (ie, CRS plus systemic chemotherapy). 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 perioperative intraperitoneal chemotherapy, the evidence includes a case series. Relevant outcomes are OS, 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 in oncology include the following relevant recommendations for colon cancer (v.2.2017) and rectal cancer (v.3.2017): “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.”

NCCN guidelines for gastric cancer (v.1.2017) and for uterine neoplasms (v.2.2017) do not include cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

NCCN guidelines for ovarian cancer (v.1.2017) include recommendations for intraperitoneal chemotherapy in patients with optimally debulked (<1 cm) stage II or III (category 1 recommendation) disease. Use of hyperthermic chemotherapy is not specified.

**American Society of Colon and Rectal Surgeons**

A 2012 practice parameter on the management of colon cancer by the American Society of Colon and Rectal Surgeons stated that treatment of patients with peritoneal carcinomatosis may include surgical cytoreduction. The role of HIPEC was “insufficiently defined.”

**Society of Surgical Oncology**

In 2007, the Society of Surgical Oncology issued a consensus statement on CRS and HIPEC in the management of peritoneal surface malignancies of colonic origin. Their recommendation is that patients with peritoneal carcinomatosis without distant disease, in whom complete cytoreduction is possible, undergo HIPEC before systemic therapy. As of January 2015, an updated consensus statement has not been published.

**Canadian HIPEC Collaborative Group**

Consensus guidelines published in 2015 specify patient selection criteria for CRS plus HIPEC to treat selected indications.

For patients with peritoneal surface malignancy of colorectal origin, eligibility criteria with the highest (A) level of consensus include ECOG Performance Status score of 0, patient age of 65 years or younger, body mass index of 35 kg/m² or less, classical I or II histologic grade, 6-month or more interval from primary tumor to peritoneal carcinomatosis, extraperitoneal disease absent,
Peritoneal Carcinomatosis Index score of 20 or less, and predicted score for completeness of cytoreduction of 0.

For patients with peritoneal surface malignancy of appendiceal origin, eligibility criteria with the highest (A) level of consensus include ECOG Performance Status score of 0 or 1, patient age of 65 years or younger, body mass index of 35 kg/m² or less, classical I or II histologic grade, Any Time Interval From Primary Tumor To Peritoneal Carcinomatosis, Extraperitoneal Disease Absent, Any Peritoneal Carcinomatosis Index, and predicted score for completeness of cytoreduction of 0 or 1.

**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 4.

**Table 4. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal and appendiceal cancer</td>
<td>ICArU5 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</td>
<td>220</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>NCT02179489</td>
<td>Trial Evaluating Surgery With Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Treating Patients With a High Risk of Developing Colorectal Peritoneal Carcinomatosis</td>
<td>300</td>
<td>Oct 2023</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Cytoreductive Surgery (CRS) With/Without HIPEC in Gastric Cancer With Peritoneal Carcinomatosis (GASTRIPEC)</td>
<td>180</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>NCT02240524</td>
<td>Efficacy of HIPEC in the Treatment of Patients With Locally Advanced Gastric Cancer</td>
<td>582</td>
<td>July 2019</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>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</td>
<td>98</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>NCT01628380</td>
<td>Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIIC Epithelial Ovarian Cancer (CHORINE)</td>
<td>94</td>
<td>Jul 2018</td>
</tr>
<tr>
<td>NCT01539785</td>
<td>Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) in Ovarian Cancer Recurrence (HORSE)</td>
<td>158</td>
<td>Sep 2018</td>
</tr>
<tr>
<td>NCT00426257</td>
<td>Secondary Debulking Surgery +/- Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer</td>
<td>280</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>NCT01376752</td>
<td>Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment (CHIPOR)</td>
<td>444</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT02124421</td>
<td>Outcomes in CRS/HIPEC as Initial Treatment of Ovarian, Fallopian Tube and Primary Peritoneal Cancer</td>
<td>48</td>
<td>Apr 2020</td>
</tr>
</tbody>
</table>

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

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-9 Diagnoses

158.8  Malignant neoplasm of retroperitoneum and peritoneum; Specified parts of peritoneum
158.9  Malignant neoplasm of retroperitoneum and peritoneum; Peritoneum, unspecified
197.6  Secondary malignant neoplasm of respiratory and digestive systems; retroperitoneum and peritoneum

ICD-10 Diagnoses (Effective October 1, 2015)

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

- 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.

REFERENCES


13. Yan TD, Cao CQ, Munkholm-Larsen S. A pharmacological review on intraperitoneal chemotherapy for peritoneal malignancy. World J Gastrointest Oncol. Feb 15 2014;6(6):1204-1214. PMID 25049365


Other References
1. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, June 29, 2009.
2. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, August 14, 2009.
3. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, August 18, 2009.
4. Blue Cross and Blue Shield of Kansas Surgery Liaison Committee, August 2015; February 2016.
5. Blue Cross and Blue Shield of Kansas OB/GYN Liaison Committee, January 2016.
6. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee, August 2017.