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

Description

Cytoreductive surgery (CRS) comprises peritonectomy (i.e., 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 hyperthermic chemotherapy, most commonly mitomycin C. Inflow and outflow catheters are placed in the abdominal cavity, along with temperature probes to monitor temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours. This procedure is referred to as hyperthermic intraperitoneal chemotherapy (HIPEC).

Background

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%. (6) Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis. (7) Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for cure. (8)

**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. (9) DMPM has traditionally been considered as a rapidly lethal malignancy with limited and ineffective therapeutic options. (9) 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 results in a median survival of approximately 12 months. (9)

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 to 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 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. New cases and deaths from ovarian cancer in 2014 are estimated at 21,980 and 14,270, respectively. (10) 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). (11) Estimated median OS is 66 months with and 37 to 49 months without intraperitoneal chemotherapy, respectively. (12, 13) However, 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. (14)

Several peritoneal lavage systems (Product Code LGZ) have been FDA-cleared to provide “warmed, physiologically compatible sterile solution” (eg, Performer® HT perfusion system; RanD S.R.L. [Medolla, Italy]) (15). 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, MN] (16) and Belmont Instrument Corporation [Billerica, MA]) (17).

Related Policies
None

Policy
*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Cytoreductive surgery and perioperative intraperitoneal chemotherapy may be considered medically necessary for the treatment of:

- Pseudomyxoma peritonei; and
- Diffuse malignant peritoneal mesothelioma

Cytoreductive surgery and perioperative intraperitoneal chemotherapy is considered investigational for:

- peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer; ovarian cancer; and
- all other indications, including goblet cell tumors of the appendix.
Rationale

Pseudomyxoma Peritonei

Studies discussed next and other studies are summarized in Table 1.

Table 1. Summary of Studies of CRS and HIPEC in Pseudomyxoma Peritonei

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Postoperative</th>
<th>Median OS, m</th>
<th>5-y OS, %</th>
<th>PFS, m</th>
<th>5-y PFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jimenez 2014 (18)</td>
<td>202</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>NR</td>
<td>Not reached</td>
<td>83</td>
<td>NR</td>
</tr>
<tr>
<td>Marcotte 2014(19)</td>
<td>58</td>
<td>2/40</td>
<td>NR</td>
<td>77</td>
<td>NR</td>
<td>50</td>
</tr>
<tr>
<td>Glehen 2010 (20)</td>
<td>255</td>
<td>4/40</td>
<td>&gt;100</td>
<td>73</td>
<td>78</td>
<td>56</td>
</tr>
<tr>
<td>Chua 2009 (21)</td>
<td>106</td>
<td>3/49</td>
<td>104</td>
<td>75</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Vaira 2009 (22)</td>
<td>60</td>
<td>0/45</td>
<td>NR</td>
<td>94</td>
<td>NR</td>
<td>80</td>
</tr>
<tr>
<td>Elias 2008 (3)</td>
<td>105</td>
<td>8/68</td>
<td>NR</td>
<td>80</td>
<td>NR</td>
<td>68</td>
</tr>
<tr>
<td>Yan 2007 (23) (SR)</td>
<td>NR</td>
<td>NR</td>
<td>51-156</td>
<td>52-96</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sardi 2013 (24)</td>
<td>26</td>
<td>0/42</td>
<td>NR</td>
<td>34</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

HG: high-grade tumor (peritoneal mucinous carcinomatosis); LG: low-grade tumor (disseminated peritoneal adenomucinosis); m: months; N: number of patients; NR: not reported; OS: overall survival; PFS: progression-free survival; SR: systematic review; y: year

a Median overall survival (OS) not reached with mean follow-up of 36 months.
b 5-year disease-free survival.
c Results after second procedure shown.

Primary Treatment

Jimenez et al (2014) conducted a retrospective review of a prospective database of patients with peritoneal carcinomatosis maintained by Mercy Medical Center in Baltimore. (18) Two hundred two patients with peritoneal carcinomatosis from appendiceal cancer who underwent cytoreductive surgery (CRS)/HIPEC (hyperthermic intraperitoneal chemotherapy) were included; 125 patients (62%) had high-grade (HG) tumors (peritoneal mucinous carcinomatosis [PMCA]), and 77 patients (38%) had low-grade (LG) tumors (disseminated peritoneal adenomucinosis [DPAM]). Results for the entire cohort and for subgroups defined by tumor histology are shown in Table 1. In the HG (PMCA) group, Peritoneal Cancer Index (PCI), completeness of cytoreduction, and lymph node status were significantly associated with survival; in the LG (DPAM) group, completeness of cytoreduction was significantly associated with survival.

In 2010, Glehen et al published a retrospective, multicenter cohort study to evaluate toxicity and prognostic factors after CRS and HIPEC and/or unheated intraperitoneal chemotherapy for 5 days postoperatively. (20) Patients had diffuse peritoneal disease from malignancies of multiple different histologic origins. Exclusion criteria were perioperative chemotherapy performed more than 7 days after
surgery and the presence of extra-abdominal metastases. The study included 1290 patients from 25 institutions who underwent 1344 procedures between 1989 and 2007. HIPEC was performed in 1154 procedures. Postoperative mortality was 4.1%. The principal origin of peritoneal carcinomatosis was pseudomyxoma peritonei in 301 patients. Median overall survival (OS) for patients with pseudomyxoma peritonei was not reached (median OS for all patients, 34 months.)

Additional information about the subgroup of patients with pseudomyxoma peritonei was provided by Elias et al. (25) CRS was achieved in 219 patients (73%), 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. The 1-, 3-, and 5-year OS rates were 89.4%, 84.8%, and 72.6%, respectively. The 10-year survival rate was 54.8%. Median survival had not yet been reached but will exceed 100 months. Disease-free survival (DFS) was 56% at 5 years, and median duration of DFS was 78 months. A multivariate analysis identified 5 prognostic factors: the extent of peritoneal seeding (p=0.004), institution (p<0.001), pathologic grade (p=0.03), sex (p=0.02), and the 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 and HIPEC and/or unheated intraperitoneal chemotherapy for 5 days postoperatively. (21) Sixty-nine percent of patients had complete cytoreduction. Eighty-three patients (78%) had HIPEC intraoperatively, 81 patients (76%) had unheated postoperative intraperitoneal chemotherapy, and 67 patients (63%) had both. Seventy-three patients had disseminated peritoneal adenomucinosis, 11 had peritoneal mucinous carcinomatosis, and 22 had mixed tumors. Mortality rate was 3%, and severe morbidity rate was 49%. Median follow-up was 23 months (range, 0-140 months). Median OS was 104 months with a 5-year survival rate of 75%. Median progression-free survival (PFS) was 40 months with 1-, 3-, and 5-year PFS 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. Factors influencing survival include histopathologic type of tumor, the use of both HIPEC and unheated postoperative intraperitoneal chemotherapy, completeness of cytoreduction, and severe morbidity.

Vaira et al (2009) reported their experience managing pseudomyxoma peritonei with CRS and HIPEC in a single institution in 60 patients, 53 of whom had final follow-up data. (22) 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 one-half of the patients with adenocarcinoma had received previous systemic chemotherapy. Five- and 10-year OS rates were 94% and 85%, respectively, and 5- and 10-year DFS were 80% and 70%, respectively. Significant differences in improved OS were observed in patients who experienced complete surgical cytoreduction (p<0.003) and in those with histologic type disseminated peritoneal adenomucinosis versus those with peritoneal mucinous carcinomatosis (p<0.014).
In 2008, Elias et al reported the results of 105 consecutive patients with pseudomyxoma peritonei treated between 1994 and 2006 with CRS and HIPEC. (3) The primary tumor was the appendix in 93 patients, ovary in 3, urachus in 1, pancreas in 1, and indeterminate in 7. Tumor histology was disseminated peritoneal adenomucinosis in 48% of patients, intermediate in 35% and peritoneal mucinous carcinomatosis in 17%. At the end of surgery, 72% of patients had no visible residual peritoneal lesions. Postoperative mortality was 7.6% and morbidity 67.6%. Median follow-up was 48 months, and 5-year OS and DFS were 80% (95% confidence interval [CI], 68% 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 (CA19.9) 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 for pseudomyxoma. (23) There were no randomized controlled trials (RCTs) or comparative studies. Ten studies were included (863 patients); all were uncontrolled, observational studies. Two studies had relatively long-term follow-up of 48 and 52 months, and 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 Mercy Medical Center database studied by Jimenez et al (previously described), Sardi et al (2013) identified 26 patients who underwent repeat CRS/HIPEC for peritoneal carcinomatosis recurrence. (24) Sixteen patients (62%) had high-grade (HG) PMCA, and 10 patients (38%) had low-grade (LG) DPAM. Patients eligible for repeat CRS/HIPEC had Eastern Cooperative Oncology Group performance status 0 to 1. The proportion of patients who had a preoperative PCI score less than 20 (scale of 0-39) was 35% before second procedure and 75% before third procedure (1 of 4 patients). There were no 30-day postoperative deaths; postoperative morbidity was 42% after second procedure and 50% after third procedure. After second procedure, 1-, 3-, and 5-year OS was 91%, 53%, and 34%, respectively. After third procedure, 1-year OS was 75%.

Lord et al (2014) reported a retrospective cohort study of 512 patients with perforated appendiceal tumors and pseudomyxoma peritonei who received CRS/HIPEC at a single center in the UK and achieved complete cytoreduction. (26) Thirty-five (26%) of 137 patients who recurred underwent repeat CRS/HIPEC; median time to recurrence was 26 months. Complete cytoreduction was achieved (again) in 20 patients (57%). Mean OS in patients without recurrence (n=375), patients who recurred and had repeat CRS/HIPEC (n=35), and patients who recurred but did not have repeat CRS/HIPEC (n=102) was 171 months (95% CI, 164 to 178), 130 months (95% CI, 105 to 153) and 101 months (84 to 119), respectively (log-rank test, p=0.001). Five-year survival was 91%, 79%, and 65%, respectively. The incidence of complications was similar between primary and repeat procedures.
Section Summary: Pseudomyxoma Peritonei
Large, retrospective cohort studies have consistently shown median and 5-year OS as 47 to 156 months and 41% to 96%, respectively, for patients with pseudomyxoma peritonei who are treated with CRS/HIPEC. One retrospective study of 26 patients who underwent CRS/HIPEC for recurrence indicated 5-year OS of 34%. Procedure-related morbidity and mortality have generally decreased over time to acceptable levels (16% to 49% and 0% to 4%, respectively, in recent studies).

Peritoneal Carcinomatosis of Gastrointestinal Origin (Colorectal, Gastric)
Several authors have evaluated prognostic factors for patients undergoing CRS/HIPEC for peritoneal carcinomatosis of gastrointestinal origin. PCI (25) (a summary of both lesion size and distribution of peritoneal surface malignancy used to estimate the likelihood of complete cytoreduction; lower scores are better) (18, 27-30) and completeness of cytoreduction (18, 30-32) were consistently associated with survival.

Colorectal Cancer
Studies discussed next and other studies are summarized in Table 2.

Table 2. Summary of Studies of CRS and HIPEC in Peritoneal Carcinomatosis from Colorectal Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Postoperative Mortality/Morbidity, %</th>
<th>Median OS, mo</th>
<th>2-Year OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPSM (2014)33</td>
<td>705</td>
<td>NR</td>
<td>41</td>
<td>NR</td>
</tr>
<tr>
<td>Baratti (2014)24</td>
<td>101</td>
<td>3%/24%</td>
<td>32</td>
<td>NR</td>
</tr>
<tr>
<td>Elias (2014)27</td>
<td>139</td>
<td>6%/22%</td>
<td>39</td>
<td>39%</td>
</tr>
<tr>
<td>Huang (2014)35,a</td>
<td>33</td>
<td>0%/29%</td>
<td>14</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>29 (c)</td>
<td>6%/9%</td>
<td>9</td>
<td>12%</td>
</tr>
<tr>
<td>Nikolic (2014)28</td>
<td>61</td>
<td>NR/13%</td>
<td>51</td>
<td>59%</td>
</tr>
<tr>
<td>de Cuba (2013)26 (SR)</td>
<td>NR</td>
<td>NR</td>
<td>6-36 (with liver mets)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19-63 (no liver mets)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-24 (c, no liver mets)</td>
<td></td>
</tr>
<tr>
<td>Klaver (2013)37</td>
<td>604</td>
<td>NR</td>
<td>NR</td>
<td>83%</td>
</tr>
<tr>
<td>Glehen 2010)20</td>
<td>523</td>
<td>NR</td>
<td>NR</td>
<td>30%</td>
</tr>
<tr>
<td>2009-2010 reviews1,2,38</td>
<td>NR</td>
<td>NR</td>
<td>13-63</td>
<td>NR</td>
</tr>
<tr>
<td>Elias (2008)39</td>
<td>48</td>
<td>NR</td>
<td>63</td>
<td>NR</td>
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<tr>
<td></td>
<td>48 (c)</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Leeuwen (2009)40</td>
<td>103</td>
<td>1%/56%</td>
<td>NR</td>
<td>72%</td>
</tr>
<tr>
<td>Glehen (2004)41</td>
<td>506</td>
<td>4%/23%</td>
<td>19</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>32 (cr)/8 (no cr)</td>
<td></td>
</tr>
<tr>
<td>Verwaal (2003)42 (RCT)</td>
<td>54</td>
<td>16%/15%</td>
<td>22</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>51 (c)</td>
<td>29 (cr)/5 (no cr)</td>
<td>13</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
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<td></td>
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<tr>
<td>Williams (2014)43</td>
<td>18</td>
<td>0%/67%</td>
<td>23</td>
<td>48%</td>
</tr>
<tr>
<td>Klaver (2013)37</td>
<td>18</td>
<td>0%/17%</td>
<td>NR</td>
<td>50%</td>
</tr>
</tbody>
</table>

ASPSM: American Society of Peritoneal Surface Malignancies; c, control; cr: complete resection of macroscopic disease; CRC: colorectal cancer; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; mets: metastases; NR: not reported; OS: overall survival; RCT: randomized controlled trial; SR: systematic review.

* Nonrandomized comparative study.
Primary Treatment

De Cuba et al reported a 2013 systematic review and meta-analysis of studies of colorectal cancer (CRC) patients with both peritoneal and liver metastases who received CRS and HIPEC plus curative resection. (36) In their review, the authors 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. Median OS ranged from 6 to 36 months in patients with liver metastases, 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 hazard ratio [HR] =1.24; 95% CI, 0.96 to 1.60; p=NS). The authors observed that comparisons across studies are impaired by lack of standardization of the HIPEC or unheated postoperative intraperitoneal chemotherapy procedure (exposure technique, drugs and doses used, duration of exposure, temperature, 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 CRC patients with peritoneal dissemination treated in the United States to further research in this area. (44) Closed HIPEC using 40 mg of mitomycin C at 42°C for 90 minutes was recommended.

Reviews from 2009 and 2010 (1, 2, 38) summarized studies of colorectal peritoneal carcinomatosis with CRS and HIPEC, some of which is included in the section below. These included one RCT (discussed below) with a second publication after 8 years of follow-up (42, 45) one comparative study, (46) and numerous observational studies. Across studies, median OS after CRS and HIPEC in patients with peritoneal dissemination from colon cancer ranged from 13 to 63 months (median, ≈18 months). A 2008 study by Elias et al (39) reported OS of 63 months, which may be explained by the use of more contemporary chemotherapeutic regimens in the treatment of advanced stage colon cancer compared with earlier studies in which previous standard therapy was used. (1) For comparison, published reports of outcomes after systemic treatment of metastatic colon cancer with polychemotherapy with or without biologic agents range from 14.8 months to 22.6 months (median: 19.2 months). (1)

In the RCT by Verwaal et al (2003), the authors randomly assigned 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 aggressive CRS and HIPEC followed by standard systemic chemotherapy.42 Patients with other sites of metastases (ie, lung or liver) were excluded. 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. 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). 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 2008, Verwaal et al reported 8-year follow-up of all patients who were alive until 2007. (45) Minimum follow-up was 6 years for all patients (median, 7.8 years; range, 6-9.6). During follow-up, 1 patient crossed over from the standard arm to the CRS/HIPEC arm after recurrent disease at 30 months after randomization. At the time of this long-term follow-up, in the standard arm, 4 patients were still alive, 2 with disease and 2 without disease, and in the HIPEC arm, 5 patients were still alive, 2 with disease and 3 without disease. Median disease-specific survival was 12.6 months in the standard arm and 22.2 months in the CRS/HIPEC arm (p=0.028). Median PFS was 7.7 months in the standard arm and 12.6 months in the CRS/HIPEC arm.

In 2014, the American Society of Peritoneal Surface Malignancies evaluated a clinical tool for selecting appropriate patients for CRS/HIPEC in a retrospective review of 1013 patients. (33) Patients had peritoneal carcinomatosis from CRC and underwent CRS with (n=705) or without (n=308) HIPEC. The Peritoneal Surface Disease Severity Score (PSDSS) assesses preoperative symptoms, extent of peritoneal dissemination, and primary tumor histology and defines 4 stages by increasing disease severity (stage 1, least severe). For the CRS/HIPEC group, median OS was 41 months; 3-year and 5-year OS was 66% and 58%, respectively; median survival stratified by PSDSS prognostic group was 86, 43, 29, and 28 months for PSDSS stage 1, 2, 3, and 4, respectively; and PSDSS and Cytoreduction Score (a 4-point assessment of cytoreduction after CRS) were statistically associated with survival in multivariate logistic regression.

In the 2010 retrospective, multicenter cohort study described earlier, (20) the principal origin of peritoneal carcinomatosis was colorectal adenocarcinoma in 523 patients. Median OS for this group was 30 months. Independent prognostic indicators in multivariate analysis were institution, histologic origin of the tumor, completeness of CRS, extent of carcinomatosis, and lymph node involvement.

Quality of Life
Two systematic reviews published in 2014 examined QOL outcomes in patients with peritoneal carcinomatosis who underwent CRS plus HIPEC.(47,48) Both reviews included studies that used structured QOL scales; Shan et al included 15 studies (total N=1583 patients), (47) 14 of which appeared in the review of 20 studies (n=1181 respondents) by Seretis et al.48 No RCTs were identified. Studies were heterogeneous in sample size (median, ~60 patients; range, 5-216 patients), response rate (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 after treatment. At 1 year, QOL scores improved to baseline values or above. In random effects meta-analysis of 8 studies (n=499 patients), overall health (I2=38%) and emotional health (I2=41%) showed statistically significant improvements compared with baseline, but physical (I2=60%), social (I2=0%), and functional (I2=74%) health did not. (47) Improvements were small to medium (standardized mean difference <0.4 for all outcomes).
Although this evidence suggested improvement from baseline in some QOL domains, the absence of parallel control groups limits interpretation of the results.

In 2014, Passot et al reported on QoL in 216 patients who underwent CRS/HIPEC for peritoneal carcinomatosis at a single center in France. (49) Primary tumors were ovarian (35%), colorectal (26%), pseudomyxoma peritonei (19%), primary serous peritoneal carcinoma (4%), peritoneal mesothelioma (8%), gastric (6%), and other cancers in 1 patient each. QoL was assessed using the validated Gastro-Intestinal QoL Index questionnaire (GIQLI), which assesses symptoms, physical function, feelings, social integration, and effect of any medical intervention or treatment. The proportion of patients who returned questionnaires was 81% at baseline (preoperatively), 90% at 1 month postoperatively, 89% at 3 months and at 6 months, and 74% at 1 year. Mean GIQLI score decreased (worsened) substantially (>10%) from baseline for up to 6 months and, for 3 of 5 QoL domains assessed, returned to baseline at 12 months; mean symptoms and feelings did not return to baseline within 12 months. In multivariate analysis, factors associated with decreased QoL were cancer diagnosis at 3 months; presence of stoma at 6 months; and surgical time greater than 270 min and disease recurrence at 12 months.

**Recurrence**

In 2014, Williams et al reported a case series of 18 patients from a single center in Australia who underwent second CRS with HIPEC with (n=2) or without (n=11) unheated intraperitoneal chemotherapy for 5 days postoperatively or unheated postoperative intraperitoneal chemotherapy alone (n=4) following recurrence after initial CRS at the same center. (43) One patient received no intraperitoneal chemotherapy. HIPEC followed by unheated postoperative intraperitoneal chemotherapy used mitomycin, HIPEC without unheated postoperative intraperitoneal chemotherapy used oxaliplatin, and unheated postoperative intraperitoneal chemotherapy (with or without HIPEC) used 5-fluorouracil. Results are shown in Table 2.

In 2013, Klaver et al reported a case series of 18 patients in 3 centers who had peritoneal recurrence of colorectal (13 patients) or appendiceal (5 patients) carcinomatosis and received a second CRS with HIPEC (mitomycin; 14 patients) or unheated intraperitoneal chemotherapy for 5 days postoperatively (5-fluorouracil; 3 patients) or both (1 patient). (37) Median time to recurrence after the primary procedure was 14 months (range, 1-33 months). Mean PCI score was 6.3 (scale, 0-39). No patients died within 30 days of the second procedure. During median follow-up of 10 months, 14 (78%) patients experienced a subsequent recurrence, with a median time to recurrence of 4.5 months. One- and 2-year OS were 74% and 50%, respectively.

**Section Summary: Peritoneal Carcinomatosis of Colorectal Origin**

One RCT demonstrated improved survival in patients with peritoneal carcinomatosis due to CRC who received CRS plus HIPEC and systemic chemotherapy compared with patients who received systemic chemotherapy alone. However, procedure-related morbidity and mortality were 98% and 16%, respectively, and systemic chemotherapy regimens did not use currently available biologic agents. Retrospective cohort studies have shown median and 2-year OS of 13 to 63 months and 12% to 83%, respectively. Procedure-related morbidity and mortality were 13% to 56% and 0% to 6%, respectively, similar to that observed in the American College of Surgeons National Surgical Quality Improvement
Program. QOL data from uncontrolled studies are insufficient to form conclusions. Several studies indicated that PCI score and completeness of cytoreduction are prognostic factors for survival. In 2 retrospective cohort studies of patients who underwent CRS plus HIPEC for recurrence (total N=36 patients), 2-year OS was approximately 50%. Procedure-related morbidity was 17% to 67%; there were no procedure-related deaths.

**Peritoneal Carcinomatosis of Gastric Origin**

Relevant studies on peritoneal carcinomatosis of gastric origin, some of which are discussed next, are summarized in Table 3.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Postoperative Mortality/Morbidity, %</th>
<th>Median OS, mo</th>
<th>1-Year OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudloff (2014) RCT</td>
<td>9</td>
<td>11% /100%b</td>
<td>11</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>8 (c)c</td>
<td>NA</td>
<td>4</td>
<td>0%</td>
</tr>
<tr>
<td>Yarema (2014) a,b</td>
<td>20</td>
<td>NR</td>
<td>12d</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>20 (c)c</td>
<td></td>
<td>8</td>
<td>25%</td>
</tr>
<tr>
<td>Kim (2014) a,c</td>
<td>9</td>
<td>NR</td>
<td>16</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>17 (c)e</td>
<td></td>
<td>16</td>
<td>80%</td>
</tr>
<tr>
<td>Yang (2011) RCT</td>
<td>34</td>
<td>NR</td>
<td>11g</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>34 (c)f</td>
<td></td>
<td>7</td>
<td>29%</td>
</tr>
</tbody>
</table>
| c: control; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; NA: not applicable; NR: not reported; OS: overall survival; RCT: randomized controlled trial. 
| a Nonrandomized comparative study.  
| b Ninety-day.  
| c Systemic chemotherapy only.  
| d Log-rank test vs control (p=0.004).  
| e Surgical resection.  
| f Cytoreductive surgery only.  
| g Log-rank test vs control (p=0.049).  

Coccolini et al (2014) conducted a meta-analysis of intraperitoneal chemotherapy for advanced gastric cancer in patients with or without peritoneal carcinomatosis. Literature was searched through 2012, and 20 RCTs that compared surgical treatment (primarily resection) plus intraperitoneal chemotherapy with surgical treatment alone were identified; of these, only 1 open-label RCT from Japan enrolled patients with peritoneal carcinomatosis treated with CRS plus HIPEC. Yang et al (2011) randomized 68 patients (1:1) to CRS/cisplatin HIPEC or CRS alone. Median OS was 11.0 months (95% CI, 10.0 to 11.9 months) in the CRS/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 in the CRS/HIPEC and CRS only groups were 41.2% and 29.4%, 14.7% and 5.9%, and 5.9% and 0%, respectively. Incidence of serious adverse events was similar between groups (15% in the CRS/HIPEC group vs 12% in the CRS only group).

In 2014, Rudloff et al reported results of a preliminary, open-label, Phase 3 RCT in 17 patients from several U.S. centers who had gastric cancer metastatic to liver and lung and peritoneal carcinomatosis. Eligible patients could, in the opinion of the Principal Investigator, be resected to “no evidence of disease” based on imaging studies or staging laparoscopy. Patients were randomized using a
computerized randomization algorithm to receive systemic chemotherapy with FOLFOXIRI (5-fluorouracil, leucovorin, oxaliplatin, irinotecan) (n=8) or systemic chemotherapy plus gastrectomy and CRS/oxaliplatin HIPEC (n=9). Median and 1-year OS were 4.3 months and 0%, respectively, in the control group, and 11.3 months and 78%, respectively, in the CRS/HIPEC group (statistical testing not reported). Factors associated with survival more than 1 year in the CRS/HIPEC group were complete cytoreduction and initial PCI of 15 or less. Enrollment to complete a larger planned trial was discontinued due to slow accrual.

Yarema et al (2014) conducted a retrospective review of patients who had gastric cancer with peritoneal involvement and underwent HIPEC with (n=20 patients with limited peritoneal metastases) or without (n=10 patients with diffuse peritoneal carcinomatosis and symptomatic ascites) CRS at a single center in the Ukraine. HIPEC used mitomycin-C plus cisplatin. Results were compared with contemporaneous control patients with gastric cancer who received palliative chemotherapy only (n=20 patients with limited peritoneal metastases) or best supportive care (n=10 patients with diffuse peritoneal carcinomatosis and symptomatic ascites). In 20 patients with limited disease who received CRS/HIPEC, median and 1-year OS was 12 months and 69%, respectively, compared with 8 months (log-rank test, p=0.004) and 25%, respectively, in controls. In multivariate analysis, factors statistically associated with survival were extent of peritoneal dissemination and completeness of cytoreduction. In patients with advanced disease who received HIPEC only, median OS was 3.5 months, compared with 2.4 months in controls (log-rank test, p=0.49).

In a small retrospective study at a single U.S. center, Kim et al (2014) reported no improvement in median OS (16 months) for patients with gastric cancer and peritoneal carcinomatosis who underwent surgical resection (n=17) or CRS/HIPEC (n=9). One-, 2-, and 3-year OS in the control and CRS/HIPEC groups were 80% and 73%, 49% and 39%, and 49% and 39%, respectively (statistical testing not reported).

Section Summary: Peritoneal Carcinomatosis of Gastric Origin
One small (N=17) RCT showed improved survival in patients with peritoneal carcinomatosis due to gastric cancer who received CRS/HIPEC compared with patients who received chemotherapy alone. Another small (N=68) RCT showed improved survival in patients who received CRS/HIPEC compared with CRS alone. These results were consistent with a retrospective review of 40 patients that showed improved survival with CRS/HIPEC compared with systemic chemotherapy alone, but not with a retrospective review of 26 patients that showed similar survival between CRS/HIPEC and gastric resection.

Peritoneal Carcinomatosis from Endometrial Cancer
No RCTs or nonrandomized comparative studies were identified. Three small, non-U.S. cohort studies reported outcomes with CRS plus HIPEC for primary (n=6 patients) or recurrent (confined to the peritoneum; n=18 patients) endometrial cancer with peritoneal carcinomatosis. 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 (55)); 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. (8) 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 in 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, in the absence of parallel control groups, potential bias is introduced by confounding factors, such as disease history, cancer subtype, preoperative PCI score, and treatment. Randomized trials that compare 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
Relevant studies on peritoneal mesothelioma, some of which are discussed next, are summarized in Table 4.

Table 4. Summary of Studies of CRS and HIPEC in Peritoneal Mesothelioma

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Postoperative Mortality/Morbidity, %</th>
<th>Median OS, mo</th>
<th>5-Year OS, %</th>
<th>Median PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robella (2014)*</td>
<td>42</td>
<td>7%/36%</td>
<td>65</td>
<td>44%</td>
<td>NR</td>
</tr>
<tr>
<td>Alexander (2013)*</td>
<td>211</td>
<td>2%/30%</td>
<td>38</td>
<td>41%</td>
<td>NR</td>
</tr>
<tr>
<td>Baratti (2011)*</td>
<td>427</td>
<td>0%-11%/20%-41%</td>
<td>30-92</td>
<td>33%-68%</td>
<td>7-40</td>
</tr>
<tr>
<td>Glehen (2010)*</td>
<td>88</td>
<td>NR</td>
<td>41</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yan (2009)*</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; SR: systematic review.

Alexander et al (2013) reported on 211 patients from 3 tertiary care centers in the United States who had malignant peritoneal mesothelioma and had undergone CRS plus HIPEC. (57) Results are shown in Table 4. 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 stay with carboplatin HIPEC compared with mitomycin-C HIPEC in 44 patients with DMPM. (59)
For a 2011 systematic review, Baratti et al searched the PubMed database for studies on the clinical management of DMPM. (9) The review included 14 studies with a total of 427 patients, 289 of whom underwent CRS with HIPEC and 106 with both. Studies that included patients with well-differentiated or LG types of mesothelioma were excluded. All included studies were prospective, uncontrolled case series. Mean patient age ranged from 49 to 56 years. All institutions used peritonectomy and multivisceral resection to remove visible disease. HIPEC protocols varied widely among institutions in terms of technique, drugs, carriers, timing and temperature. Operative mortality and morbidity were reported in 11 monoinstitutional series. Operative mortality 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 and HIPEC, median OS ranged from 29.5 to 92 months. 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 Baratti’s findings: pooled 1-, 3-, and 5-year survival estimates were 84%, 59%, and 42%, respectively.

The largest study in both systematic reviews was a 2009 international registry study by Yan et al, for which 401 (99%) patients had complete follow-up. (58) Of these patients, 92% received HIPEC. Median and 1-, 3-, and 5-year survival rates were 53 months, 81%, 60%, and 47%, respectively.

In the 2010 retrospective, multicenter cohort study by Glehen et al described above, the principal origin of tumor was peritoneal mesothelioma in 88 patients. (20) 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 has 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 5.

#### Table 5. Summary of Studies of CRS and HIPEC in Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Postoperative Mortality/Morbidity, %</th>
<th>Median OS, mo</th>
<th>5-Year OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary treatment</strong></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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European studies</td>
<td>157</td>
<td>6%-8% / 16%-425</td>
<td>35-48</td>
<td>NR</td>
</tr>
<tr>
<td>Chiva (2015) (SR)</td>
<td>248</td>
<td>0%-7% / 255</td>
<td>37</td>
<td>40%</td>
</tr>
<tr>
<td>Bakrin (2014) (R)</td>
<td>184</td>
<td>2%-5% / 5%-295</td>
<td>42-58</td>
<td>NR</td>
</tr>
</tbody>
</table>
In 2014, 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. (70) Between 2006 and 2013, eligible women were randomized preoperatively by computer assignment to CRS/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/HIPEC group had complete cytoreduction compared with the non-HIPEC group (65% vs 55%), and the CRS/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/HIPEC group versus 13.4 months in the non-HIPEC group (statistical tests not reported, p=0.006). In platinum-sensitive disease, survival was 26.8 months in the HIPEC group versus 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 HIPEC group vs 10.2 months in the non-HIPEC group; p value not reported). A statistical test for interaction (treatment x 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. (71) The authors selected studies that included more than 10 patients with primary or recurrent ovarian cancer who were treated with CRS plus HIPEC. A total of 37 studies were identified, 9 comparative studies and 28 uncontrolled studies. Only 1 RCT (described above) was identified (Spiliotis et al66). In a pooled analysis of 8 studies comparing CRS/HIPEC to CRS with non-
HIPEC chemotherapy found significantly higher 1-year survival in the CRS/HIPEC group (odds ratio [OR], 4.24; 95% CI, 2.17 to 8.30). There were similar findings on 3-year survival (pooled OR=4.31; 95% CI, 2.11 to 8.11). It is important to note that most of the comparative studies were not randomized and thus were subject to potential selection and observational biases. Moreover, the single RCT, as noted, had baseline between-group differences in completeness that limited conclusions on efficacy of CRS/HIPEC.

Earlier reviews (Chiva et al [2015]), (64) Bakrin et al [2014], (65) evaluated CRS plus HIPEC for first- and second-treatment of ovarian cancer. Chiva et al reported that in the first-line setting, 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, weighted median OS was 36 months (range, 23-62 months) and 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. (72,73)

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). (67-69) Three- to 5-year survival ranged from 50% to 68% in the CRS/HIPEC groups versus 17% to 42% in the CRS only groups. Cohort studies from Europe (total N=157 patients) reported procedure-related morbidity and mortality of 16% to 42% and 6% to 8%, respectively, in first- and second-line settings.61-63,74 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 Inc. sponsored an internet registry of patients with epithelial ovarian cancer who were treated with HIPEC at several participating U.S. institutions. (70) 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). 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) is not functional as of 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 showed improved survival with CRS plus HIPEC compared with 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 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

Goblet cell carcinoid tumors of the appendix comprise a small proportion of appendiceal tumors (14%-19%). Goblet cell tumors are aggressive, often presenting with peritoneal and ovarian metastases. Treatment commonly comprises appendectomy, right-sided hemicolecotomy, and lymphadenectomy followed by chemotherapy. Five- and 10-year OS with this approach are 76% and 60%, respectively. (75)

In a multicenter, retrospective cohort study, McConnell et al (2014) studied appendiceal goblet cell tumors (n=45) and compared outcomes with CRS plus HIPEC to those in nonmucinous (n=52) and LG (n=567) and HG (n=89) mucinous appendiceal tumors. (76) 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 LG mucinous tumors and similar outcomes to those in patients with HG mucinous tumors: Three-year OS rates in patients with goblet cell, LG mucinous, HG 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 are rates compared with goblet cell tumors). Adverse events/complications of treatment were not reported. Grade 3/4 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 reported survival outcomes with CRS plus HIPEC that were reduced compared with published 5- and 10-year survival estimates.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.
Table 6. 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>NCT01815359</td>
<td>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</td>
<td>220</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>NCT01226394</td>
<td>Trial Comparing Simple Follow-up to Exploratory Laparotomy Plus &quot;in Principle&quot; (Hyperthermic Intraperitoneal Chemotherapy) HIPEC in Colorectal Patients (ProphylloCHIP)</td>
<td>130</td>
<td>Jun 2019</td>
</tr>
<tr>
<td>NCT02231086</td>
<td>Adjuvant HIPEC in High Risk Colon Cancer (COLOPEC)</td>
<td>176</td>
<td>Jan 2022</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>NCT02158988</td>
<td>Cytoreductive Surgery (CRS) With/Without HIPEC in Gastric Cancer With Peritoneal Carcinomatosis (GASTRIPEC)</td>
<td>180</td>
<td>Sep 2017</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>NCT01683864</td>
<td>Randomized Controlled Trial to Prevent Peritoneal Seeding in Gastric Cancer (HIPEC_Stomach)</td>
<td>60</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>NCT01882933</td>
<td>D2 Resection and HIPEC (Hyperthermic Intraperitoneal Chemoperfusion) in Locally Advanced Gastric Carcinoma (GASTRICHIP)</td>
<td>322</td>
<td>May 2021</td>
</tr>
<tr>
<td>NCT01767675</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 IIIC Epithelial Ovarian Cancer (CHORINE)</td>
<td>94</td>
<td>Jul 2018</td>
</tr>
<tr>
<td>NCT01539785</td>
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<td>NCT02124421</td>
<td>Outcomes in CRS/HIPEC as Initial Treatment of Ovarian, Fallopian Tube and Primary Peritoneal Cancer</td>
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NCT: national clinical trial.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology for colon cancer (v.2.2016) and for rectal cancer (v.2.2016) consider the treatment of disseminated carcinomatosis with CRS and HIPEC to be investigational and do not endorse such therapy outside of a clinical trial. (77, 78)
NCCN guidelines for gastric cancer (v.2.2016) and for uterine cancer (v.2.2016) do not include CRS plus HIPEC. (79, 80)

NCCN guidelines for ovarian cancer (v.1.2016) include recommendations for intraperitoneal chemotherapy in patients with optimally debulked (<1 cm) stage 2 or 3 (category 1 recommendation) disease. (81) Use of hyperthermic chemotherapy is not specified.

American Society of Colon and Rectal Surgeons
A 2012 practice parameter on the management of colon cancer ASCRS stated that the treatment of patients with peritoneal carcinomatosis may include surgical cytoreduction. The role of HIPEC was “insufficiently defined.” (82)

Society of Surgical Oncology
In 2007, SSO issued a consensus statement on CRS and HIPEC in the management of peritoneal surface malignancies of colonic origin. (83) Their recommendation is that patients with peritoneal carcinomatosis without distant disease, in whom complete cytoreduction is possible, undergo HIPEC before systemic therapy. As of June 2016, 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. (84)

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 Recommendation
USPSTF does not address CRS and Intraperitoneal chemotherapy.

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 cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes 1 randomized controlled trial (RCT), a systematic review, and observational studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. The RCT found significantly higher median overall survival in the CRS and HIPEC group than in the standard care group. However, the RCT had methodologic limitations including an inability to differentiate between benefits of CRS and HIPEC. Additional controlled trials reporting quality of life as well as survival outcomes are needed to evaluate the impact on the net health outcome. 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 cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes 2 small RCTs and 2 small retrospective comparative studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes. Given that patients eligible for CRS and HIPEC must be surgical candidates, the most appropriate comparator would be gastric resection with or without systemic chemotherapy administered to both treatment groups in a comparative study. The only RCT that used this design reported reduced survival in the CRS and HIPEC group, although the trial was small (N=26) and statistical testing was not reported. Additional trials are needed using the appropriate comparator and with appropriate sample sizes and statistical analysis reporting. 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 cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes cohort studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. Only uncontrolled studies were available and they had small sample sizes (<25 patients). Randomized trials that compare CRS plus HIPEC to standard treatment (eg CRS alone or systemic chemotherapy alone). The evidence is insufficient to determine the effects of the technology on health outcomes. For individuals who have peritoneal mesothelioma who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes retrospective cohort studies and systematic reviews. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. Uncontrolled studies have shown median and 5-year overall survival ranging from 30 to 92 months and 33% to 68%, respectively, for patients with peritoneal mesothelioma who are treated with CRS and 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 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 ovarian cancer who receive cytoreductive surgery and perioperative intraperitoneal chemotherapy, the evidence includes 1 RCT, systematic reviews, and uncontrolled studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. Results from 1 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 net health outcomes compared with current treatment approaches (ie, CRS with systemic chemotherapy). The evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare
There is no national coverage determination (NCD) for cytoreductive surgery or hyperthermic intraperitoneal surgery.

References


Section: Medicine  Effective Date: January 15, 2017  
Subsection: Oncology  Original Policy Date: June 7, 2012  
Subject: Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies  
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<tr>
<th>Date</th>
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<tr>
<td>June 2012</td>
<td>New Policy</td>
<td></td>
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<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search. No references added. No change to policy statements.</td>
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<tr>
<td>March 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review references 4-8, 10-14, 18-19, 24, 26-35, 43, 51-61, 63-80, and 83-85 added; references 14 and 23-24 deleted. Investigational policy statement for ovarian cancer, peritoneal carcinomatosis due to gastric cancer or endometrial cancer, and for all other indications added. Medically necessary policy statement unchanged. Title changed to “Select Intra-Abdominal and Pelvic Malignancies” to include the additional indications.</td>
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<tr>
<td>December 2016</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 73 and 84 added. Policy statements unchanged.</td>
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Keywords
Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy  
Hyperthermic Intraperitoneal Chemotherapy  
Intraperitoneal Hyperthermic Chemotherapy  
Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 2, 2016 and is effective January 15, 2017.

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