Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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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 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.

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 CRS and HIPEC have reported median and five-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 five-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 one 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 two small RCTs and two 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 (e.g., 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 intra-peritoneal 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 five-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 one RCT, systematic reviews, and uncontrolled studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. Results from one 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 (i.e., CRS with systemic chemotherapy). The evidence is insufficient to determine the effects of the technology on health outcomes.

**Policy**

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.

**Background**

*Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy*

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 one to two hours. This procedure is referred to as HIPEC.

**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 overall survival (OS) depends on tumor histology and ranges from 6% for high-grade tumors to 75% for low-grade 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 six to seven months. Peritoneal carcinomatosis is detected in more than 30% of patients with advanced gastric cancer and is a poor prognostic indicator. Median survival is three months, and five-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 results from locoregional progression within the abdominal cavity. In historical case series, treatment by palliative surgery, systemic or intraperitoneal chemotherapy, and abdominal irradiation resulted in a median survival of approximately 12 months.

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

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

Regulatory Status

Mitomycin, carboplatin, and other drugs used for hyperthermic intraperitoneal chemotherapy (HIPEC) have not been approved by the U.S. Food and Drug Administration (FDA) 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 cleared for marketing by FDA through the 510(k) process to provide “warmed, physiologically compatible sterile solution” (e.g., Performer® HT perfusion system; RanD Srl, Medolla, Italy15). 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 (e.g., ThermaSolutions, Minneapolis, MN16; Belmont Instrument, Billerica, MA17).

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


