Protocol

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

(20307)

Medical Benefit		**Effective Date**: 07/01/15	**Next Review Date**: 03/19
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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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With pseudomyxoma peritonei	Interventions of interest are: • Cytoreductive surgery plus perioperative intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With peritoneal carcinomatosis of colorectal origin	Interventions of interest are: • Cytoreductive surgery plus perioperative intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With peritoneal carcinomatosis of gastric origin	Interventions of interest are: • Cytoreductive surgery plus perioperative intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With peritoneal carcinomatosis of endometrial origin	Interventions of interest are: • Cytoreductive surgery plus perioperative intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With peritoneal mesothelioma	Interventions of interest are: • Cytoreductive surgery plus perioperative intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy • Radiotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With ovarian cancer	Interventions of interest are: • Cytoreductive surgery plus perioperative intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With appendiceal goblet cell tumors	Interventions of interest are: • Cytoreductive surgery plus perioperative intraperitoneal chemotherapy	Comparators of interest are: • Cytoreductive surgery • Systemic chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity

Description

Cytoreductive surgery (CRS) comprises peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination. CRS may be followed intraoperatively by infusion of intraperitoneal chemotherapy with or without heating, which is intended to improve the tissue penetration of the chemotherapy. When heated, this is referred to as hyperthermic intraperitoneal chemotherapy (HIPEC). CRS and HIPEC have been proposed for a number of intra-abdominal and pelvic malignancies such as pseudomyxoma peritonei and peritoneal carcinomatosis from colorectal, gastric, or endometrial cancer.

Summary of Evidence

For individuals who have pseudomyxoma peritonei who receive CRS plus perioperative intraperitoneal chemotherapy, the evidence includes cohort studies and a systematic review. Relevant outcomes are overall survival (OS), disease-specific survival, quality of life, and treatment-related mortality and morbidity. Uncontrolled studies of primary treatment of pseudomyxoma peritonei with CRS plus HIPEC have reported a median and a five-year OS ranging from 47 to 156 months and 41% to 96%, respectively. One retrospective study of 26 patients, who underwent CRS plus HIPEC for recurrence, indicated five-year OS rate of 34%. Procedure-related morbidity and mortality have decreased over time. Controlled studies are needed to draw conclusions about the efficacy and safety of CRS plus HIPEC compared with standard treatment (CRS alone). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal carcinomatosis of colorectal origin who receive CRS plus 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 six 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 two 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 two 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 one year but not at two or three 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 (e.g., CRS alone or systemic chemotherapy alone) are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peritoneal mesothelioma who receive CRS plus 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 five-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 (i.e., 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.

Policy

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

- pseudomyxoma peritonei; and

- diffuse malignant peritoneal mesothelioma.

Cytoreductive surgery plus perioperative intraperitoneal chemotherapy are 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 Plus Hyperthermic Intraperitoneal Chemotherapy

CRS comprises peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[1] CRS may be followed intraoperatively by the infusion of intraperitoneal chemotherapy, most commonly mitomycin C. The intraperitoneal chemotherapy may be heated, which is intended to improve the tissue penetration, and this is referred to as HIPEC. Inflow and outflow catheters are placed in the abdominal cavity, along with probes to monitor temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for one to two hours.

Psuedomyxoma 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.[2] As mucin-producing cells of the tumor proliferate, the narrow lumen of the appendix becomes obstructed and subsequently leads to appendiceal perforation. Neoplastic cells progressively colonize the peritoneal cavity and produce copious mucin, which collects in the peritoneal cavity. Pseudomyxoma peritonei ranges from benign (disseminated peritoneal adenomucinosis) to malignant (peritoneal mucinous carcinomatosis), with some intermediate pathologic grades. Clinically, this syndrome ranges from early pseudomyxoma peritonei, 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.[3] Five-year overall survival depends on tumor histology and ranges from 6% for high-grade tumors to 75% for low-grade tumors.[4, 5]

Gastrointestinal Cancers and Peritoneal Carcinomatosis

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

Peritoneal carcinomatosis is detected in more than 30% of patients with advanced gastric cancer and is a poor prognostic indicator. The median survival is three months, and five-year survival is less than 1%.[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 are registered every year, accounting for 10% to 30% of all-type

mesothelioma.[9] Diffuse malignant peritoneal mesothelioma has traditionally been considered 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 results from locoregional progression within the abdominal cavity. In historical case series, treatment by palliative surgery, systemic or intraperitoneal chemotherapy, and abdominal irradiation has resulted in a median survival of 12 months.[9]

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, accounting for 90% of malignant ovarian tumors. Epithelial ovarian cancer is the fifth most common cause of cancer death in women in the United States. Most ovarian cancer patients (> 70%) present with widespread disease, and annual mortality is 65% of the incidence rate.

Current management of advanced epithelial ovarian cancer is CRS followed by combination chemotherapy. Treatment guidelines recommend intraperitoneal chemotherapy for patients with optimally debulked (less than 1 cm) stage 2 disease (pelvic extension of tumor) or stage 3 disease (peritoneal extension of tumor).[10] The estimated median overall survival is 66 months with, and 37 to 49 months without intraperitoneal chemotherapy, respectively.[11, 12] Tumor recurrences are common, and the prognosis for recurrent disease is poor.

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

Regulatory Status

Mitomycin, carboplatin, and other drugs used for 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 regularly used for this purpose.[13]

Several peritoneal lavage systems (FDA 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, Italy[14]). None have received marketing approval or clearance to administer chemotherapy. FDA has issued warnings 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, MN[15]; Belmont Instrument, Billerica, MA[16]).

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.**

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

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