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

(20307)
(Formerly Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for the Treatment of Pseudomyxoma Peritonei, Peritoneal Carcinomatosis of Gastrointestinal Origin, and Peritoneal Mesothelioma)

Medical Benefit  Effective Date: 07/01/15  Next Review Date: 03/16
Preauthorization  Yes  Review Dates: 01/11, 01/12, 01/13, 01/14, 01/15, 03/15

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. Preauthorization is required. 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.

Description
Pseudomyxoma peritonei describes extensive mucus accumulation within the peritoneum resulting from mucin-secreting tumor cells. Peritoneal carcinomatosis from non-ovarian malignancies has long been regarded as a terminal disease with limited survival. Mesotheliomas arise from the mesothelium lining potential spaces of the body, such as the peritoneum. In an attempt to prolong survival in these diseases, aggressive locoregional therapy, such as combining cytoreductive surgery (CRS) with perioperative intraperitoneal chemotherapy, has been used.

Background
CRS and HIPEC
CRS comprises peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intraabdominal 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.\(^3\) Five-year overall survival (OS) depends on tumor histology and ranges from 6% for high-grade (HG) tumors to 75% for low-grade (LG) tumors.\(^4, 5\)

**Gastrointestinal Cancers (Colorectal, Gastric) and Peritoneal Carcinomatosis**

Peritoneal dissemination develops in approximately 10–15% 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%.\(^6\) 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.\(^8\)

**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 resulted in a median survival of approximately 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 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 two disease (pelvic extension of tumor) or stage three 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” (e.g., 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 (e.g., ThermaSolutions, Inc. [Minneapolis, MN]16 and Belmont Instrument Corporation [Billerica, MA]17).

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.

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.


