Protocol

Hyperthermic Intraperitoneal Chemotherapy for Select Intra-Abdominal and Pelvic Malignancies

(20307)

Medical Benefit		**Effective Date**: 04/01/19	**Next Review Date**: 01/21
Preauthorization	Yes	**Review Dates**: 01/11, 01/12, 01/13, 01/14, 01/15, 03/15, 03/16, 03/17, 03/18, 01/19, 01/20	

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 hyperthermic intra-peritoneal 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 hyperthermic intra-peritoneal 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 hyperthermic intra-peritoneal 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 hyperthermic intra-peritoneal 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 hyperthermic intra-peritoneal 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 newly diagnosed stage III ovarian cancer	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intra-peritoneal 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 recurrent stage IIIC or IV ovarian cancer	Interventions of interest are: • Cytoreductive surgery plus hyperthermic intra-peritoneal 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 hyperthermic intra-peritoneal 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) includes 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 HIPEC, the evidence includes cohort studies and a systematic review. Relevant outcomes are overall survival, 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 overall survival ranging from 47 to 156 months and 41% to 96%, respectively. Two small retrospective studies, who underwent CRS plus HIPEC for recurrence, indicated five year overall survival rates ranging from 34% to 79%. 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.

Although no randomized trials or comparative studies have been published, uncontrolled study data have shown consistent, long-term overall survival with use of this technique. Procedure-related morbidity and mortality have decreased over time. Because the prevalence of pseudomyxoma peritonei is very low, conducting high-quality trials is difficult. For these reasons, CRS plus HIPEC may be considered medically necessary for this indication.

For individuals who have peritoneal carcinomatosis of colorectal origin who receive CRS plus HIPEC, the evidence includes a randomized controlled trial (RCT), systematic reviews, and a large number of observational

studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. 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 treatment-related morbidity rates. 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 rates 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 HIPEC, the evidence includes two small RCTs, observational studies, and a systematic review. Relevant outcomes are overall survival, 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. The meta-analysis found significantly better survival in the surgery plus HIPEC group at one year but not at two or three years. An 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 HIPEC, the evidence includes cohort studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Only uncontrolled studies with small sample sizes were available (less than 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 HIPEC, the evidence includes retrospective cohort studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Uncontrolled studies have shown median and five year overall survival ranging from 30 to 92 months and 33% to 68%, respectively, for patients who had peritoneal mesothelioma treated with CRS plus HIPEC. Reported procedure-related morbidity and mortality were approximately 35% and 5%, respectively. Although no RCTs or comparative studies have been published, uncontrolled study data have shown reasonable rates of overall survival with the use of this technique. Procedure-related morbidity and mortality have remained steady over time. Because the prevalence of peritoneal mesothelioma is very low, conducting high-quality trials is difficult. Thus, although the evidence is insufficient to determine the effects of the technology on health outcomes, for the reasons discussed above, CRS plus HIPEC may be considered medically necessary for this indication.

For individuals who have newly diagnosed stage III ovarian cancer who receive CRS plus HIPEC, the evidence includes an RCT. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. For patients with newly diagnosed stage III ovarian cancer who had received neoadjuvant chemotherapy, HIPEC increased the time to disease recurrence and reduced mortality. HIPEC did not increase serious adverse events compared with surgery alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent stage IIIC or IV ovarian cancer who receive CRS plus HIPEC, the evidence includes an RCT and systematic review. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. For recurrent stage IIIC or IV disease (second-line setting), evidence from an RCT indicated that CRS plus HIPEC improved survival compared with CRS without HIPEC. However, interpretation of this study is limited because treatment groups in this RCT were unbalanced at baseline

(variation in the completeness of cytoreduction), which has been shown to be associated with survival. 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 HIPEC, the evidence includes a case series. Relevant outcomes are overall survival, 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 hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of surgery may be considered **medically necessary** for the treatment of:

- pseudomyxoma peritonei; and
- diffuse malignant peritoneal mesothelioma.

The use of HIPEC may be considered **medically necessary** in newly diagnosed epithelial ovarian or fallopian tube cancer at the time of interval cytoreductive surgery when ALL of the following criteria are met:

- The patient has stage III disease (see Policy Guidelines);
- The patient is not eligible for primary cytoreductive surgery or surgery had been performed but was incomplete and will receive neoadjuvant chemotherapy and subsequent interval debulking surgery (see Policy Guidelines); and
- It is expected that complete or optimal cytoreduction can be achieved at time of the interval debulking surgery (see Policy Guidelines).

The use of HIPEC in all other settings to treat ovarian cancer, including but not limited to stage IIIC or IV ovarian cancer, is considered **investigational**.

Cytoreductive surgery plus HIPEC are considered **investigational** for:

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

POLICY GUIDELINES

Ovarian cancer staging is as follows:

- Stage I: The cancer is confined to the ovary or fallopian tube.
- Stage II: The cancer involves one or both ovaries with pelvic extension.
- Stage III: The cancer has spread within the abdomen.
- Stage IV: The cancer is widely spread throughout the body.

Eligibility for neoadjuvant chemotherapy and interval debulking surgery is based on a high perioperative risk profile (i.e., the patient is a poor candidate to withstand an aggressive initial cytoreductive procedure) or a low likelihood of achieving cytoreduction to less than one cm (i.e., the patient has extensive disease that precludes

upfront optimal cytoreduction) or surgery has been performed but was incomplete (i.e., after surgery, one or more residual tumors measuring larger than one cm in diameter were present).

Complete cytoreduction is defined as no visible disease and optimal cytoreduction as one or more residual tumors measuring 10 mm or less in diameter remaining.

BACKGROUND

PSEUDOMYXOMA PERITONEI

Pseudomyxoma peritonei is a clinicopathologic disease characterized by the production of mucinous ascites and mostly originates from epithelial neoplasms of the appendix. Appendix cancer is diagnosed in fewer than 1,000 Americans each year; less than half are epithelial neoplasms.[1] 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, usually discovered during imaging or a laparotomy performed for another reason, to advanced cases with a distended abdomen, bowel obstruction, and starvation.

Treatment

The conventional treatment of pseudomyxoma peritonei is surgical debulking, repeated as necessary to alleviate pressure effects. However, repeated debulking surgeries become more difficult due to progressively thickened intra-abdominal adhesions, and this treatment is palliative, leaving visible or occult disease in the peritoneal cavity.[2]

PERITONEAL CARCINOMATOSIS OF COLORECTAL ORIGIN

Peritoneal dissemination develops in 10% to 15% of patients with colon cancer.

Treatment

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 OF GASTRIC ORIGIN

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%.[3] Sixty percent of deaths from gastric cancer are attributed to peritoneal carcinomatosis.[4]

Treatment

Current chemotherapy regimens are nonstandard, and peritoneal seeding is considered unresectable for cure.[5]

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.[6] Diffuse malignant peritoneal mesothelioma has traditionally been considered a rapidly lethal malignancy with limited and ineffective therapeutic options.[6] 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.[6]

Treatment

Surgical cytoreduction (resection of visible disease) in conjunction with hyperthermic intraperitoneal chemotherapy (HIPEC) is designed to remove visible tumor deposits and residual microscopic disease. By delivering chemotherapy intraperitoneally, drug exposure to the peritoneal surface is increased some 20-fold compared with systemic exposure. In addition, 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 ovaries; 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 (more than 70%) present with widespread disease, and annual mortality is 65% of the incidence rate.

Treatment

Current management of advanced epithelial ovarian cancer is cytoreductive surgery (CRS) followed by combination chemotherapy. 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.

CRS PLUS HIPEC

CRS includes peritonectomy (i.e., peritoneal stripping) procedures and multivisceral resections, depending on the extent of intra-abdominal tumor dissemination.[7] 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.

CRS plus HIPEC is being evaluated for the following conditions:

- Pseudomyxoma peritonei;
- Peritoneal carcinomatosis of colorectal, gastric, or endometrial origin;
- Peritoneal mesothelioma;
- Ovarian cancer; and
- Appendiceal goblet cell tumors.

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 is used regularly for this purpose.[8]

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). None has 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[9]; Belmont Instrument[10]).

Table 1. Hyperthermic Intraperitoneal Chemotherapy Devices Cleared by the U.S. Food and Drug Administration

Device	Manufacturer	Date Cleared	510(k) No.	Indication
MAC Medical D-Series Blanket and Solution Warming Cabinets	MAC Medical Inc.	3/5/2019	K180842	For use in hyperthermic intraperitoneal chemotherapy
Quantum Blood and IV Fluid Infusion Warmer	Life Warmer Inc.	1/28/2019	K181775	For use in hyperthermic intraperitoneal chemotherapy
QiF Blood and Fluid Warmer	Quality In Flow Ltd.	4/27/2018	K180154	For use in hyperthermic intraperitoneal chemotherapy
QiF Blood and Fluid Warmer	Quality In Flow Ltd.	9/27/2017	K171215	For use in hyperthermic intraperitoneal chemotherapy
FluidSmart	THERMEDX LLC	9/5/2017	K172048	For use in hyperthermic intraperitoneal chemotherapy
QiF Blood and Fluid Warmer	Quality In Flow Ltd.	4/20/2017	K163708	For use in hyperthermic intraperitoneal chemotherapy
Hang&Go PAC	RanD S.r.l.	12/28/2016	K161613	For use in hyperthermic intraperitoneal chemotherapy
QiF Blood and Fluid Warmer	Quality in Flow Ltd.	6/23/2016	K150404	For use in hyperthermic intraperitoneal chemotherapy
The Belmont Hyperthermia Pump	Belmont Instrument Corp.	9/2/2015	K152208	For use in hyperthermic intraperitoneal chemotherapy
Penguin In-Line Warmer	Creche Innovations	7/9/2015	K150484	For use in hyperthermic intraperitoneal chemotherapy

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