Title: Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy for the Treatment of Peritoneal Carcinomatosis of Gastrointestinal Origin

**Professional**
- Original Effective Date: April 3, 2009
- Revision Date(s): August 11, 2009; October 19, 2009; January 28, 2011; March 7, 2011; February 28, 2014
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**DESCRIPTION**
Peritoneal dissemination of tumors of gastrointestinal origin, from either the appendix or colon, represent two distinct clinical entities.

Pseudomyxoma peritonei is a clinicopathologic entity characterized by the production of mucinous ascites and mostly originates from epithelial neoplasms of the appendix. As the tumor grows, the narrow lumen of the appendix becomes obstructed and subsequently leads to appendiceal perforation. The neoplastic cells progressively colonize the peritoneal cavity and copious mucin production builds up in the peritoneal cavity.
Appendix tumors causing pseudomyxoma peritonei range from a benign pathologic appearance (disseminated peritoneal adenomucinosis), to malignant pathologic findings (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. (1)

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 6 to 7 months.

Surgical cytoreduction in conjunction with hyperthermic intraperitoneal chemotherapy is designed to remove visible tumor deposits with intraperitoneal chemotherapy to address remaining microscopic disease. By delivering chemotherapy intraperitoneally, drug exposure to the peritoneal surface is increased some 20-fold compared to systemic exposure. In addition, prior animal and in vitro studies have suggested that the cytotoxicity of mitomycin C is enhanced at temperatures greater than 39 degrees Celsius. Cytoreduction consists of numerous surgical procedures including visceral and parietal peritonectomy and different organ resections, depending on the extent of intraabdominal tumor dissemination. (2) The surgical procedure is 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 the temperature. The skin is then temporarily closed during the chemotherapy perfusion, which typically runs for 1 to 2 hours.

POLICY

Cytoreduction and hyperthermic intraperitoneal chemotherapy may be considered medically necessary for the treatment of peritoneal carcinomatosis when clinically confined to the peritoneal cavity.

RATIONALE

Pseudomyxoma peritonei

Elias and colleagues report a large case series treating pseudomyxoma peritonei with cytoreductive surgery and intraperitoneal chemotherapy. (3) Their multicenter study included 301 patients treated between 1993 and 2007. Complete cytoreductive surgery was achieved in 219 patients (73%), and hyperthermic intraperitoneal chemotherapy was performed in 255 (85%). The primary tumor site was the appendix in 91% of patients, the ovary in 7%, and the origin was
unknown in 2%. Tumor histology was disseminated peritoneal adenomucinosis in 51%, intermediate in 27%, and peritoneal mucinous carcinomatosis in 22%. Postoperative mortality was 4% and morbidity 40%. Mean follow-up was 88 months. The overall 1-, 3-, and 5-year survival (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 be longer than 100 months. The disease-free survival (DFS) rate was 56% at 5 years and the median duration of DFS was 78 months. A multivariate analysis identified 5 prognostic factors: the extent of peritoneal seeding (p=0.004), the center (p=0.0004), the pathologic grade (p=0.03), gender (p=0.02), and the use of hyperthermic intraperitoneal chemotherapy (p=0.04). When only the 206 patients with complete cytoreductive surgery were considered, the extent of peritoneal seeding was the only significant prognostic factor (p=0.004).

Vaira and colleagues report their experience managing pseudomyxoma peritonei with cytoreduction and hyperthermic intraperitoneal chemotherapy in a single institution in 60 patients for whom 53 had final follow-up data. (4) 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 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).

Chua and colleagues report the long-term survival of 106 patients with pseudomyxoma peritonei treated between 1997 and 2008 with cytoreductive surgery and intraperitoneal chemotherapy. (5) Sixty-nine percent of patients had complete cytoreduction. Seventy-three patients had disseminated peritoneal adenomucinosis, 11 had peritoneal mucinous carcinomatosis, and 22 had mixed tumors. The mortality rate was 3% and severe morbidity rate was 49%. The median follow-up was 23 months (range: 0–140 months). The overall median survival was 104 months with a 5-year survival rate of 75%. The progression-free survival was 40 months with 1-, 3-, and 5-year progression-free survival rates of 71%, 51%, and 38%, respectively. Factors influencing survival included histopathological type of tumor, with the best survival in patients with disseminated peritoneal adenomucinosis and the worst in patients with peritoneal mucinous carcinomatosis (p=0.002), and completeness of cytoreduction (p=0.002).

In 2008, Elias and colleagues reported the results of 105 consecutive patients with pseudomyxoma peritonei treated between 1994 and 2006 with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. (1) 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]: 68–88%) and 68% (95% CI: 55–79%), respectively. Two factors were identified on multivariate analysis that had a negative influence on DFS: a CA19.9 level greater than 300 units/mL and nondisseminated peritoneal adenomucinosis tumor histology.
Yan and colleagues conducted a systematic review on the efficacy of cytoreductive surgery and intraperitoneal chemotherapy for all relevant studies from 1996 to 2006. (6) There were no randomized controlled trials or comparative studies. Ten studies were included (with a total of 863 patients) and were observational without control groups. Two of the studies had relatively long-term follow-up of 48 and 52 months and the remaining studies had median follow-up times of 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 80–100%, 76–96%, 59–96%, and 52–96%, respectively. Overall mortality rates varied from 0-18% and morbidity from 33–56%.

Peritoneal carcinomatosis from colorectal cancer
Reviews from 2009 and 2010 (2,7,8) summarize the experience in the literature for treatment of colorectal peritoneal carcinomatosis with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, some of which are included below. To date, there has been a randomized controlled trial with a second publication after 8 years of follow-up (9,10), one comparative study (11) and numerous observational studies (summarized in reference 2, and references 12–14, following). Across studies, overall median survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal dissemination from colon cancer has ranged from 13 to 63 months (median approximately 18 months). The study that showed 63 months’ survival (12) may be explained by the use of more contemporary chemotherapeutic regimens in the treatment of advanced stage colon cancer compared to prior studies in which previous standard therapy was used. (2) For comparison, published studies reporting the outcome 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). (2)

A single institution study was undertaken that randomized 105 patients with peritoneal carcinomatosis to receive standard treatment with systemic chemotherapy (fluorouracil and leucovorin) and palliative surgery, if necessary (i.e., treatment of bowel obstruction), or to a second arm consisting of aggressive cytoreduction and intraperitoneal chemotherapy followed by standard systemic chemotherapy. (9) Patients with other sites of metastases, i.e., lung or liver, were excluded. The cytoreductive procedure consisted of stripping the parietal peritoneum and resection of infiltrated viscera, if possible. Most often resection of the gall bladder, parts of the stomach, and spleen were performed. The greater omentum was also routinely removed. At the completion of resection, the presence of residual tumor was assessed. Hyperthermic mitomycin C was then administered intraperitoneally for 90 minutes. The most important complications were small bowel leakage and abdominal sepsis, but a total of 24% of patients suffered from severe or life-threatening complications, such as heart failure, arrhythmias, or renal failure. A total of 8 patients (16%) died as the result of treatment at 30 days. The main endpoint was survival, measured from the time of randomization to death from any cause. After a median follow-up of 21.6 months, 20 of 51 patients in the standard therapy group were still alive compared to 30 of 54 patients in the cytoreduction group. Median survival in the control group was 12.6 months compared to 22.4 months in the cytoreduction group. Subgroup analysis revealed that survival was particularly poor among patients with either 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 only around 5 months, compared to 29 months in patients with no residual tumor.
An editorial on this randomized trial commented that while this study shows that cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with systemic chemotherapy nearly doubles survival compared to systemic chemotherapy alone, it does not show how much of this benefit is derived from the surgery and how much from the hyperthermic intraperitoneal chemotherapy. (15) and in a letter to the editor, Markman points out that the reported survival benefit may be related primarily to the cytoreduction, with added chemotherapy only contributing to increased morbidity. (16) Finally, new targeted systemic treatment options have emerged for colon cancer, specifically cetuximab and bevacizumab, which offer additional palliative options for colon cancer, whereas the chemotherapy used in the randomized trial is no longer considered standard.

Aside from the issues of the trial methodology, the results of the trial present complicated risk benefit questions that are not adequately addressed. If the main rationale for cytoreductive surgery is to provide a curative option, data regarding disease recurrence would be important. It is not known whether the survivors in either group are alive with or without disease. If the main rationale for the therapy is palliation in terms of prolonging life or relieving specific symptoms (e.g., related to ascites or bowel obstruction), it is important to determine the quality of life associated with the 10-month improvement in median survival. Quality of life data were not reported in this randomized trial; however, the high incidence of major complications, and the reported mean length of hospitalization of 29 days suggest that this aggressive surgical approach has a significant impact on quality of life. Quality of life was addressed in a separate case series of 64 patients undergoing cytoreductive surgery and intraperitoneal chemotherapy. (17) The Functional Assessment of Cancer Therapy - Colon (FACT-C), activities of daily living, the brief pain inventory, and depression scales comprised the quality of life instruments used. A total of 48 patients completed the assessment prior to and at a mean of 12 days after surgery; 16 of the original 64 patients did not complete the survey either due to death (n=11) or missed appointments. By 6 months' follow-up, only 39 patients were available, either due to death or continuing dropout. Among the respondents, the overall quality of life decreased significantly from baseline to postsurgery, but improved to greater than baseline at 3 months. However, these data are difficult to interpret without a control group, and owing to the large number of dropouts due to death.

The randomized study (9) reported an 8-year follow-up of all patients still alive until 2007. (10) This update had a minimum follow-up of 6 years for all patients (median: 94 months; range: 72–115 months). During the follow-up, 1 patient crossed over from the standard arm to the hyperthermic intraperitoneal chemotherapy arm after recurrent disease at 30 months after randomization (the standard arm being systemic chemotherapy only and the hyperthermic intraperitoneal chemotherapy arm including systemic chemotherapy, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy). 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 hyperthermic intraperitoneal chemotherapy arm, 5 patients were still alive, 2 with disease and 3 without disease. Disease-specific survival was reported as 12.6 months in the standard arm and 22.2 months in the hyperthermic intraperitoneal chemotherapy arm (p=0.028), and progression-free survival was 7.7 months in the standard arm and 12.6 months in the hyperthermic intraperitoneal chemotherapy arm (p=0.02).

Elias and colleagues compared 48 patients in the French Multicentric Database with peritoneal carcinomatosis arising from colon cancer who received palliative systemic oxaliplatin or
irinotecan-based chemotherapy to 48 patients who underwent additional cytoreduction and hyperthermic intraperitoneal chemotherapy. (12) The chemotherapeutic regimen and the duration of systemic chemotherapy were comparable in both groups. The results showed a significant improvement of long-term survival after complete macroscopic cytoreduction followed by hyperthermic intraperitoneal chemotherapy compared to systemic treatment alone. The median survival was 23.9 months in the control group versus 62.7 months in the hyperthermic intraperitoneal chemotherapy group. The 5-year survival rates were 13% and 51%, respectively.

vanLeeuwen and colleagues reported on the experience in a Swedish series of 103 patients treated from between 2003 and 2006. (13) This study was to explore factors associated with postoperative morbidity and survival. While postoperative mortality in this center was less than 1%, postoperative morbidity was 56%. Tumor type and optimal cytoreduction influenced survival. In this uncontrolled series, at 2 years, overall survival was estimated at 72% and disease-free survival was 34%.

Glehen and colleagues reported on a retrospective multi-institutional case series involving 28 institutions and 506 patients (14) The study population consisted of patients with peritoneal carcinomatosis related to colorectal cancer who underwent the procedure between 1987 and 2002. Patients with extra-abdominal metastases were excluded. A variety of protocols for intraperitoneal operative chemotherapy were used; mitomycin C was the most common. Some patients also received intraperitoneal chemotherapy in the early postoperative procedure, sometimes after a prior operative infusion. In the early postoperative setting, fluorouracil was most common. A total of 20 patients (4%) died postoperatively. Major complications occurred in 116 patients (22.9%); digestive fistula was the most common major complication, occurring in 8.3% of patients, and was the cause of death in the 7 of the 20 patients who died. At a mean follow-up of 53 months, the morbidity and mortality rates were 22.9% and 4%, respectively, with a median survival of 19.2 months. Subgroup analysis of outcomes based on the completeness of resection reported that patients with complete resection of macroscopic disease had a median survival of 32.4 months compared to only 8 months in those cases for which complete resection was not possible. The completeness of resection was the most significant prognostic indicator. The overall recurrence rate was 73.3%, with peritoneal recurrences noted in 41.9% of patients. The authors concluded that these results echoed those reported in small case series.

**National Comprehensive Cancer Network (NCCN) guidelines and National Cancer Institute (NCI) Physician Query Database (PDQ)**

NCCN clinical practice guidelines in oncology for colon cancer (v.1.2011) consider the treatment of disseminated carcinomatosis with cytoreductive surgery and perioperative hyperthermic intraperitoneal chemotherapy to be investigational and do not endorse such therapy outside of a clinical trial. (18) NCCN guidelines specifically addressing the treatment of appendiceal tumors and pseudomyxoma peritonei were not identified.

Two randomized Phase III trials were identified and are outlined in the following paragraphs. A Phase III randomized study of systemic chemotherapy with versus without intraperitoneal chemohyperthermia in patients undergoing surgery for peritoneal carcinomatosis originating from colorectal cancer is ongoing (NCT00769405). Primary outcome is overall survival. Secondary outcome measures include recurrence free survival, treatment toxicity, morbidity from surgical complications and prognostic factors of survival. Expected enrollment is 264, with a trial start date of February 2008.
A Phase III randomized pilot study of standard systemic therapy with versus without cytoreduction surgery and hyperthermic intraperitoneal mitomycin C in patients with advanced limited peritoneal dissemination of colon adenocarcinoma is recruiting patients. (NCT01167725) Primary outcome is overall survival. Secondary outcomes include progression-free survival, quality of life, toxicity burden of these regimens, survival according to patient's peritoneal surface tumor genotype, and comparisons of circulating tumor cells in patients treated with these regimens. Expected enrollment is 360 and trial completion date is June 2011 (estimated).

Specialty Society Recommendations
In 2007, the Society of Surgical Oncology issued a consensus statement on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin. (19) Their recommendation is that patients with peritoneal carcinomatosis without distant disease, in whom complete cytoreduction in possible, undergo hyperthermic intraperitoneal chemotherapy prior to systemic therapy.

Summary
Pseudomyxoma peritonei
Several case studies and a systematic review on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy have been published. Although no randomized trials or comparative studies have been published, the data has shown consistent, long-term disease-free and overall survival with the use of this technique as compared to historical controls.

Peritoneal carcinomatosis from colorectal cancer
Numerous studies with different levels of evidence support the safety and feasibility of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy and existing data suggest a possible improvement in long-term survival of select patients. However, prospective randomized trials are needed to compare best available systemic therapy with and without cytoreductive surgery and hyperthermic intraperitoneal chemotherapy to determine the exact effects of each step, which are currently unknown. An ongoing Phase III trial (NCT00769405) addresses this question of how much of the survival benefit is derived from the cytoreduction and how much from hyperthermic intraperitoneal chemotherapy, as patients will be randomized to hyperthermic intraperitoneal chemotherapy or no hyperthermic intraperitoneal chemotherapy after complete cytoreductive surgery.
CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT / HCPCS Codes

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<tr>
<td>77605</td>
<td>Hyperthermia, externally generated; deep (i.e. heating to depths greater than 4 cm)</td>
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<tr>
<td>77620</td>
<td>Hyperthermia generated by intracavitary probe(s)</td>
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<tr>
<td>96446</td>
<td>Chemotherapy administration into the peritoneal cavity via indwelling port or catheter</td>
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The coding for this overall procedure would likely involve codes for the surgery, the intraperitoneal chemotherapy, and the hyperthermia.

- **Cytoreduction**
  - There is no specific CPT code for the surgical component of this complex procedure. It is likely that a series of CPT codes would be used describing exploratory laparotomies of various components of the abdominal cavity, in addition to specific codes for resection of visceral organs, depending on the extent of the carcinomatosis.

- **Intraperitoneal Chemotherapy**
  - CPT code 96446 identifies “chemotherapy administration into the peritoneal cavity via indwelling port or catheter.”.

- **Hyperthermia**
  - CPT code 77605 identifies, “Hyperthermia, externally generated; deep.”

ICD-9 Diagnosis

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<td>197.6</td>
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ICD-10 Diagnosis (Effective October 1, 2014)

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REVISIONS

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<td>Revised wording From, &quot;B. Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of gastrointestinal origin is considered experimental / investigational.&quot; To &quot;Cytoreduction and</td>
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hyperthermic intraperitoneal chemotherapy may be considered medically necessary for the treatment of peritoneal carcinomatosis when clinically confined to the peritoneal cavity."

Updated Rationale and References sections.

01-28-2011
Description section updated.
Rationale section updated.
Diagnosis Code wording updated.
References section updated.

03-07-2011
In Coding section:
- Added CPT code: 96446
- Removed CPT code: 96445

02-28-2014
Description section reviewed
Rationale section reviewed
In Coding section:
- Updated Coding Information bullets
- Added ICD-10 Diagnoses Codes
References reviewed

REFERENCES


Other References:
1. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, June 29, 2009.
2. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, August 14, 2009.
3. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, August 18, 2009.