

Medical Policy



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

Professional

Original Effective Date: April 3, 2009
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Institutional

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DESCRIPTION

Peritoneal carcinomatosis of gastrointestinal origin, typically colorectal, occurs in 10% to 15% of such patients and is associated with a poor prognosis, with a median survival of 6 months. In a further subset of these patients, tumor recurrence is confined to the peritoneal surface. Surgical cytoreduction in conjunction with hyperthermic intraperitoneal chemotherapy has been proposed for these patients. The cytoreduction is designed to remove visible tumor deposits, and the intraperitoneal chemotherapy is designed 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 initially involves mobilization of the liver, exploration of the diaphragm, mobilization of the stomach and lesser sac, exploration of the bilateral abdominal gutters, pelvic recesses, and mobilization of the large and small bowel with examination for tumor deposits along their entire length. Surgical resection can be extensive, depending on the extent of disease, but may include partial gastrectomy, splenectomy, and resection of the tail of the pancreas, omentectomy, multiple small bowel resections, ileocecal resection, rectosigmoid resection, uterine resection, and multiple peritonectomy procedures. 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

Cytoreduction and intraperitoneal hyperthermic chemotherapy has been investigated for the past 15 years, with many single institution case series and phase II trials reported. However, the 2 key pieces of data are a retrospective multi-institutional case series involving 28 institutions and 506 patients (1) and the results of a randomized study. (2) These 2 studies are reviewed in depth and form the basis of this policy.

Multi-institutional Case Series (1)

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, with mitomycin C the most commonly used. 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 commonly used. 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 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.

Randomized Study (2)

While the cited studies were considered promising, patient bias could not be excluded, particularly since patients with better prognoses might be preferentially recruited for an aggressive surgical approach. To address these issues, 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. Patients with other sites of metastases were excluded, i.e., lung or liver. The cytoreductive procedure consisted of stripping the parietal peritoneum and resection of infiltrated viscera, if possible. Most often this consisted of

resection of the gall bladder, parts of the stomach, and spleen. 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 and cytoreduction group was 12.6 months compared to 22.4 months, respectively. 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.

While these results were statistically significant, several issues still remain. In a letter to the editor, Markman points out that the reported survival benefit may be related primarily to the cytoreduction, with the added chemotherapy only contributing to increased morbidity. (3) In another letter, Hildebrandt raises the same issue, focusing on whether the hyperthermia adds any benefit to the intraperitoneal chemotherapy. (4) Finally, new targeted systemic treatment options have emerged for colon cancer, specifically cetuximab and bevacizumab, which offer additional palliative options for colon cancer.

Aside from the issues of the trial structure, the results of the trial present complicated risk benefit questions that are not adequately addressed. If the main rationale for the 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 are 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. (5) The Functional Assessment of Cancer Therapy focusing on colon cancer (FACT-C), activities of daily living, the brief pain inventory, and depression scales composed 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 post-

surgery, 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.

2006–2007 Update

A literature search was conducted through February 2007. The published studies report on case series treated with this technique but without results from comparable control groups. European investigators reported results on treating 120 patients with peritoneal carcinomatosis from colorectal cancer with this technique. (6) Most received cisplatin and mitomycin-C. Three-year survival was 25.8%, but was 33.5% in those who could be “cytoreduced.”

Some studies have evaluated factors that may help to predict better prognosis for patients who have this procedure. DaSilva and colleagues reported that a limited volume of carcinomatosis observed at cytoreduction and negative lymph nodes at the time of primary operation were associated with a favorable long-term result. (7) However, none of the studies address the concerns discussed previously

Of note, guidelines from the National Comprehensive Cancer Network (2008) state that the NCCN colon cancer guidelines panel does not recommend cytoreductive resection of disseminated carcinomatosis with hyperthermic and intraperitoneal chemotherapy outside of a clinical trial. (8)

In a study somewhat similar to this approach, European investigators concluded that adjuvant fluorouracil-based regional chemotherapy (intraperitoneal or intraportal) did not add further benefit to that obtained with systemic chemotherapy alone in patients with stage II-III colorectal cancer. (9) In this study, overall 5-year survival was 72.3% for those who received regional and systemic chemotherapy compared with 72.0% for those who received only systemic chemotherapy.

2008 Update

The published literature continues to report on uncontrolled series, many from specialized centers. For example, van Leeuwen reported on the experience in a Swedish series of 103 patients treated from between 2003 and 2006. (10) 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%. Gusani reported results for a series of 122 patients who underwent this treatment for peritoneal carcinomatosis between 2002 and 2005. (11) Patients had a number of malignancies including ovarian cancer (13%) and peritoneal mesothelioma (12%). Overall morbidity was 56%, major morbidity was 30%, and 30-day mortality was 1.6%. Abdominal complications were the most common major morbidity; this included abscess, fistula, and anastomotic leak. The most favorable diagnosis was appendiceal cancer with a reported

2-year survival of 67%. The authors note that controlled studies are needed to help define the role of this procedure in patients with peritoneal carcinomatosis.

2009 Update

Pseudomyxoma peritonei is a rare cancer arising from low grade adenocarcinomas of appendiceal, ovarian, or peritoneal origin. Reported outcomes of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for this rare condition are markedly superior to that reported for cytoreduction alone and other conventional treatments for this condition. (15)

The proposed treatment is not considered investigational by the medical community in carefully selected patients, such as this patient with mucinous adenocarcinoma of the cecum. Hyperthermic chemotherapy in conjunction with complete cytoreduction results in improved survival. There will be no prospective randomized trial in this disease due to its rarity and the fact that patients will not agree to randomization. As such, there will not be any prospective randomized trials to report. (16)

According to a surgical oncology consultant, in clinical practice, the intraperitoneal hyperthermic chemotherapy is considered state of the art therapy in patients with malignant peritoneal mesothelioma, who have a complete resection of all visible peritoneal disease. It is medically indicated in that it increases post-operative survival. Use of the intraperitoneal hyperthermic chemotherapy for this patient's clinical condition, would be considered medically necessary to treat this patient's illness and is considered consistent with the treatment of this member's diagnosis. The decision to proceed with the use of intraperitoneal hyperthermic chemotherapy would be made at the time of surgery. (17)

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. (18) Their recommendation is that patients with peritoneal carcinomatosis without distant disease, in whom complete cytoreduction is possible, undergo hyperthermic intraperitoneal chemotherapy prior to systemic therapy. (18)

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 Codes

96445	Chemotherapy administration into peritoneal cavity, requiring and including peritoneocentesis
77605	Hyperthermia, externally generated; deep (i.e. heating to depths greater than 4 cm)
77620	Hyperthermia generated by intracavitary probe(s)

The coding for this overall procedure would likely involve codes for the surgery, the intraperitoneal chemotherapy, and the hyperthermia. 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.

ICD-9 Diagnosis

197.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
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REVISIONS

08-11-2009	In Policy section:
	<ul style="list-style-type: none"> ▪ Added indication "A. Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei is considered medically necessary."
10-19-2009	In Coding section:
	<ul style="list-style-type: none"> ▪ Added CPT Code: 77620.
10-19-2009	In Policy section:
	<ul style="list-style-type: none"> ▪ Removed, "A. Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei is considered medically necessary." ▪ Revised wording From, "B. Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of gastrointestinal origin is considered experimental / investigational." To "Cytoreduction and 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.

REFERENCES

1. Glehen O, Kwiatkowski F, Sugarbaker PH et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 2004; 22(16):3284-92.

2. Verwaal VJ, van Ruth S, de Bree E et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-43.
3. Markman M. Intraperitoneal hyperthermic chemotherapy as treatment of peritoneal carcinomatosis of colorectal cancer. Letter to the editor. *J Clin Oncol* 2004; 22(8):1527.
4. Hildebrandt B, Rau B, Gellermann J et al. Hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinosis. Letter to the editor. *J Clin Oncol* 2004; 22(8):1527-9.
5. McQuellon RP, Loggie BW, Fleming RA et al. Quality of life after intraperitoneal hyperthermic chemotherapy (IPHC) for peritoneal carcinomatosis. *Eur J Clin Oncol* 2001; 27(1):65-73.
6. Cavaliere F, Valle M, De Simone M et al. 120 peritoneal carcinomatoses from colorectal cancer treated with peritonectomy and intra-abdominal chemohyperthermia: a S.I.T.I.L.O. multicentric study. *In Vivo* 2006; 20(6A):747-50.
7. da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. *J Am Coll Surg* 2006; 203(6):878-86.
8. National Comprehensive Cancer Network (NCCN) Colon cancer. NCCN Clinical Practice Guidelines in Oncology. V. 1. 2008. Fort Washington, PA: NCCN; 2008.
9. Nordlinger B, Rougier P, Arnaud JP et al. Adjuvant regional chemotherapy and systemic chemotherapy versus systemic chemotherapy alone in patients with stage II - III colorectal cancer: a multicenter randomised controlled phase III trial. *Lancet Oncol* 2005; 6(7):459-68.
10. van Leeuwen BL, Graf W, Pahlman L et al. Swedish experience with peritonectomy and HIPEC. HIPEC in peritoneal carcinomatosis. *Ann Surg Oncol* 2008; 15(3):745-53.
11. Gusani NJ, Cho SW, Colovos C et al. Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. *Ann Surg Oncol* 2008; 15(3):754-63.
12. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol*. 1999;6(8):727-731.
13. Stewart JH 4th, Shen P, Levine EA. Intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: Current status and future directions. *Ann Surg Oncol*. 2005;12(10):765-777
14. Elias D, Honoré C, Ciuchendéa R, et al. Peritoneal pseudomyxoma: Results of a systematic policy of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Br J Surg*. 2008;95(9):1164-1171.
15. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, June 29, 2009.
16. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, August 14, 2009.
17. MCOP board certified General Surgeon consultant, MCOP ID 2062-4612, Reviewer ID 1042, August 18, 2009.
18. Esquivel J, Sticca R, Sugarbaker P, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology, *Ann Surg Oncol* 2007; 14(1):128-33.