

Intraperitoneal hyperthermic chemotherapy: experience at Baylor University Medical Center

JOSEPH A. KUHN, MD, JAMES M. MCLOUGHLIN, MD, DANIEL C. HARRIS, MD, LORAYE J. TALAASEN, RN, STEVEN W. SUTTON, LP, CCP, AND TODD M. MCCARTY, MD

Context: Patients with peritoneal carcinomatosis have a dismal prognosis despite systemic chemotherapy or palliative surgery. A novel strategy of complete tumor debulking with intraoperative hyperthermia with chemotherapy has been proposed to provide prolonged survival.

Objective: To retrospectively analyze the preliminary experience with this technique at Baylor University Medical Center.

Methods: All patients underwent attempted tumor debulking followed by intraperitoneal hyperthermia with 40 mg mitomycin-C over 2 hours.

Results: Patient diagnoses included nonmucinous colorectal carcinomatosis (n = 9), diffuse peritoneal adenomucinosis (n = 1), peritoneal mu-

cinous carcinomatosis (n = 2), and gastric carcinomatosis (n = 3). Tumors in most patients (13/15) were resected to ≤ 5 mm, and those in 10 of 15 were resected to no gross disease. Complications included ileus (n = 9), bowel leak (n = 2), infection (n = 1), and fistula (n = 1). One patient died of progressive gastric cancer at 1 month. Within a median follow-up of 4 months, 8 patients had no tumor by radiologic or tumor marker analysis.

Conclusion: Intraoperative hyperthermia with chemotherapy is a viable treatment for patients with isolated peritoneal carcinomatosis from colorectal or gastric origin.

Peritoneal carcinomatosis represents a common mode of tumor dissemination for malignancies arising from the colon, appendix, stomach, and ovary. The progression of the peritoneal disease generally leads to bowel obstruction, ascites, and pain. In many cases, these complications lead to a rapid demise and poor quality of life, even in cases without significant systemic disease in the liver, lungs, or bone. The outcome of patients undergoing palliative surgery for these complications of peritoneal carcinomatosis has been uniformly poor. Chu et al reported median survivals of 1, 6, 1, and 0.7 months in patients treated surgically for carcinomatosis from small bowel, colorectal, gastric, and pancreatic malignancies, respectively (1). Systemic chemotherapy has generally been ineffective due to poor peritoneal penetration and low response rates (10%–15%) (2, 3), and it rarely provides any benefit to patients with bowel obstruction or ascites.

Recognizing the need for new therapies, Weissberger and others attempted intraperitoneal infusion of chemotherapy to palliate end-stage ovarian carcinomatosis as early as 1955 (4). The theoretical advantages of intraperitoneal chemotherapy have been proposed and supported for the past 25 years. Histologically, the mesothelium is a hydrophobic cell layer separating the peritoneum from systemic circulation (5, 6). Thus, molecules with an increased size and hydrophilic nature will not penetrate the mesothelium easily, resulting in much larger concentrations in the peritoneal cavity with minimal systemic effect (7, 8). The effective peak peritoneal-to-plasma ratios for mitomycin-C, cisplatin, 5-fluorouracil, and paclitaxel are 25:1, 50:1, 500:1, and 350:1, respectively (9). In addition, the intraperitoneal chemotherapy may be metabolized by the liver to varying degrees before systemic exposure (10). It is also possible that obstruction of lymphatics due to carcinomatosis may decrease systemic absorption of the chemotherapeutic agent (11).

Early clinical trials with intraperitoneal chemotherapy reported poor results due to the delivery process. Classically, the peritoneal catheters were placed intraoperatively, and the chemotherapy was infused 1 to 2 days after the patient had recovered from surgery. In many cases, the fluid simply collected into loculated pockets in the abdomen without full distribution to the entire intraabdominal surface area. The drains were removed once the regimen was complete—usually between postoperative days 5 and 7 (12–15). This technique led to increased complications from areas of retained fluid. In addition, it was noted that adhesions formed quickly, decreasing the potential tumor exposure to the drug (16, 17). In some trials there was no attempt to debulk the tumor. In vivo studies from these early trials revealed maximal effective depth of penetration at 1.0 to 3.0 mm, explaining the poor results with retained bulky disease (9, 10).

In 1990, Sugarbaker began proposing an aggressive debulking strategy for carcinomatosis, which was then followed by postoperative peritoneal chemotherapy. His aggressive surgical approach involved 6 major peritonectomies: 1) omentectomy, splenectomy; 2) left upper-quadrant stripping; 3) right upper-quadrant stripping; 4) lesser omentectomy and cholecystectomy; 5) pelvic peritoneal stripping, hysterectomy, sigmoid colectomy; and 6) antrectomy. He reported good outcomes with these procedures only when they were combined with intraperitoneal chemotherapy. Follow-up of 1 to 8 years demonstrated that 61% of patients were alive with no evidence of disease based on radiographs and tumor markers, and 15% remained alive with disease (15, 18). Of note, the morbidity and mortality of these procedures were reported at 27% and 1.5%, respectively (19).

From the Department of Surgery, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Joseph A. Kuhn, MD, 3409 Worth Street, Suite 420, Dallas, Texas 75246 (e-mail: kuhndallas@aol.com).

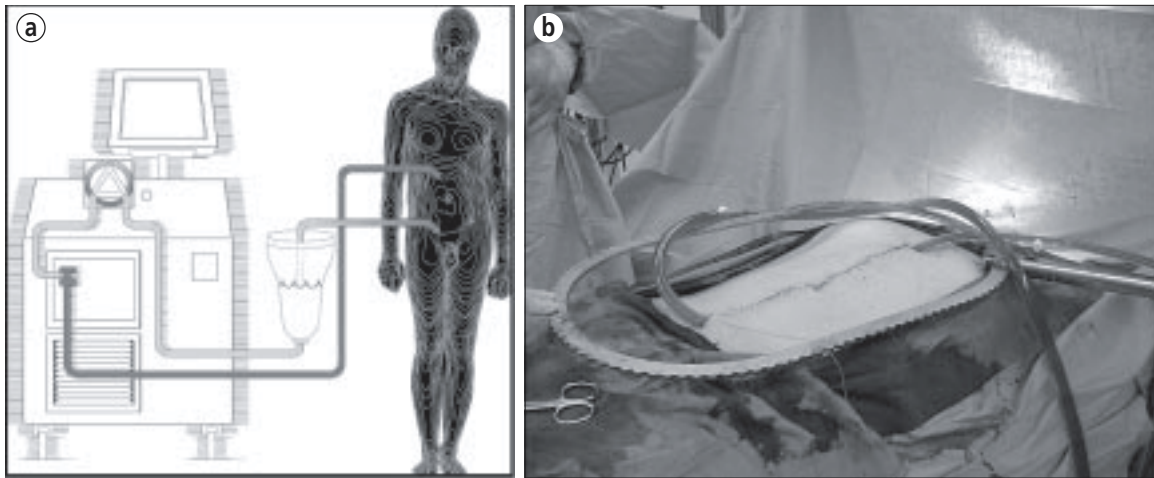


Figure. Intraperitoneal hyperthermic chemotherapy circuit. (a) Schematic reprinted with permission of ViaCirq. (b) As used in a patient.

In 1997, clinical studies with an intraoperative perfusion system were initiated. With this technique, more widespread exposure was possible throughout the peritoneal cavity once surgical debulking was complete. The filtration or flushing process may contribute to the removal of free-floating microscopic cells shed during the surgical removal, thus decreasing the opportunity for reimplantation (12). These intraoperative infusion devices can also control the temperature of the infused material. It was noted that the addition of heat had a synergistic effect on chemotherapeutics, including mitomycin-C (17, 20–22). The combination of heat and mitomycin-C was theorized to increase penetration to >3.0 mm and increase cellular accumulation (9, 23, 24). Also, with the addition of heat at 42°C, the drug was activated more quickly, previously resistant cells showed increased response (23, 25, 26), and intrinsic DNA repair mechanisms were inhibited (23).

Using a system for hyperthermia plus intraoperative chemotherapy with mitomycin-C, Loggie et al demonstrated improved survival for patients who underwent complete resection prior to the infusion (27). They noted that the site of origin was an important determinant of survival following intraperitoneal hyperthermic chemotherapy (IPHC); in particular, median survival for appendiceal cancer was better than that for colorectal and gastric cancer.

The primary histologic tumors that are candidates for this treatment are categorized by anatomic location and mucin production. Adenocarcinoma may arise from a colorectal, gastric, pancreatic, or primary small bowel site. An additional group of mucinous benign and malignant neoplasms has been termed pseudomyxoma peritonei. These neoplasms are usually encountered in the peritoneum following the rupture of a mucinous tumor of the appendix or ovary. The benign variant, diffuse peritoneal adenomucinosis (DPAM), is a mucin-producing peritoneal condition or dissemination. Its cells have minimal atypia, scant cellularity, and rare mitotic activity with rare lymph node involvement. Upon exploration, the abdomen may appear to be disseminated with mucin. DPAM can be controlled with repeated debulking operations, as metastases are rare. The 5-year survival rate is >80% (28, 29). The benign variant generally progresses to peritoneal mucinous carcinomatosis (PMCA), a malignant mucin-producing adenocarcinoma from appendiceal,

colonic, or small intestinal sites. Surgical exploration in patients with PMCA reveals significant carcinomatosis with invasive implants and often positive lymph nodes and parenchymal invasion. Histologically, PMCA cells demonstrate increased cellularity, increased atypia, nuclear pleomorphism, and increased mitotic figures. The 5-year survival rate is 25% after complete cytoreduction without intraperitoneal chemotherapy (30, 31).

The purpose of this study was to review our early experience with a novel technique involving complete tumor debulking followed by intraperitoneal chemotherapy with hyperthermia.

METHODS

A retrospective institutional review board–approved chart review was performed at Baylor University Medical Center. All patients who underwent IPHC were included. The operative procedure involved initial tumor debulking with an attempt to remove all gross evidence of disease. Afterwards, 2 inflow catheters were placed in the left and right hemidiaphragms. Two outflow catheters were placed, one in the deep pelvis and one in the superficial pelvis. The skin was then closed. Lactated Ringer’s solution was circulated using a roller pump at approximately 600 mL/min (Figure) (27). The fluid was gradually warmed to 42°C when the system was flowing without air pockets. Mitomycin-C 30 mg was then infused into the solution and circulated. To achieve optimal diffusion of the chemotherapy throughout the peritoneal cavity, the abdomen was continually massaged throughout the procedure. At 1 hour, an additional 10 mg of mitomycin-C was infused. After 2 hours, the abdomen was washed out with lactated Ringer’s solution, the abdomen was opened and inspected, the cannulae were removed, and the fascia and skin were reapproximated (27).

RESULTS

The Baylor experience consists of 15 patients: 10 men aged 48 to 74 years and 5 women aged 31 to 65 years. Nine patients had a diagnosis of nonmucinous colorectal carcinomatosis. There was a wide spectrum of disease, including DPAM and PMCA (Table 1).

Most of the patients had been treated with preoperative surgery, chemotherapy, or radiation. The operative findings revealed wide variation in the extent of disease: 3 patients had diffuse

Table 1. Spectrum of disease for patients receiving debulking plus intraperitoneal hyperthermic chemotherapy at Baylor University Medical Center

Diagnosis	n	Ascites
Diffuse peritoneal adenomucinosis	1	1
Peritoneal mucinous carcinomatosis	2	2
Gastric carcinomatosis	3	2
Colorectal carcinomatosis	9	0

Table 2. Postoperative resection status for patients receiving debulking plus intraperitoneal hyperthermic chemotherapy at Baylor University Medical Center

Resection status	Description*	n
R ₀	No visible tumor, negative cytology, negative margins	3
R ₁	No visible tumor, positive cytology, positive margins	7
R _{2a}	Minimal tumor, <5.0 mm	3
R _{2b}	Gross tumor, >5.0 mm to <2.0 cm	0
R _{2c}	Extensive tumor, >2.0 cm	2

*Resection status system from reference 27.

disease; 2 had disease in the upper abdomen only; 1 in the central abdomen only; 2 in the lower abdomen only; and 2 in the upper and central abdomen. In all cases, surgeons sought to completely debulk all tumor deposits. Upper abdominal disease generally required stripping of the peritoneum off the diaphragm. Lateral colonic cul-de-sac disease often required complete stripping of the peritoneum as well. Even in patients with prior omentectomy, residual tumor existed in the omental remnant. For mucinous lesions, the Cavitron Ultrasonic Dissector was used to effectively aspirate the tumor deposits until they were completely evacuated. Bowel resection was required in 12 of the 15 patients. Total operative time averaged 7 hours. The primary measure of operative success was the extent of tumor removed. Optimal results can be expected when all residual tumor is <5 mm. In our study, 13 of the patients met this goal (Table 2).

The most common complication was related to prolonged ileus (n = 9). Other complications included bowel leak (n = 2), fistula (n = 1), and infection (n = 1). One patient with refractory malignant ascites from gastric cancer died within 30 days. This was related to unresectable residual gross disease and progressive failure despite IPHC. The hospital stay averaged 14 days, with a range of 7 to 69 days. With a short follow-up of 4 months, 8 of the 15 patients had no visible disease based on radiologic follow-up and tumor marker assay.

DISCUSSION

Historically, patients with peritoneal carcinomatosis have had very few treatment options to prolong survival. IPHC has been approved by the Food and Drug Administration based on several studies reporting survival in years rather than months.

Prior IPHC studies have shown promising results in non-randomized pilot studies. McQuellon and Loggie evaluated the quality of life in 64 patients following debulking and IPHC. Using the Functional Assessment of Cancer Therapy–Colon (FACT-C) scale and several other subscales, they noted that most of their patients returned to normal or better by 3 months after treatment. Patients were also evaluated by the SF-36 Physical Functioning scale, showing 58% of patients with normal activity at 1 year (32). Fujimoto et al reported that the group of patients receiving debulking plus IPHC using mitomycin-C in gastric cancer had a 1-year survival rate of 80% compared with 34% for the control group (33). Finally, Loggie reported data on 84 patients treated with IPHC. Three-year survival was significantly improved for patients with no visible disease after resection (62%) compared with patients with visible disease remaining after an attempted resection (22%; $P < 0.0002$) and for patients with no ascites (44%) compared with those with ascites prior to surgery (18%) ($P < 0.0004$) (27).

The use of IPHC for gastric cancer has been more thoroughly studied in the Japanese literature. Fujimara showed improved 3-year survival with IPHC (68%) compared with intraperitoneal normothermic chemotherapy (51%) and control (23%; $P < 0.01$) for T3 or N1 gastric cancer. Koga has also shown significantly improved results with IPHC vs a normothermic control for gastric cancer (12).

Based on these studies, appropriate candidates for IPHC may include patients with mucinous or nonmucinous adenocarcinoma or DPAM who have no evidence of metastatic spread to the liver, lungs, or bones. It is not known whether physicians should offer IPHC as soon as peritoneal involvement is noted or only after all systemic treatment options have been exhausted and bulky disease with early obstruction or ascites is present. Our current follow-up period is 10 months, so survival data are not meaningful. Our data support the prior studies suggesting that this procedure is safe and well tolerated. The current treatment algorithm includes an attempt to debulk all visible disease with heated mitomycin-C at 42°C infused for 2 hours after debulking. Future clinical studies may help define the optimal dose, treatment regimen, and timing for treatment.

In conclusion, IPHC has been shown to be safe and effective in prolonging survival in many patients with peritoneal carcinomatosis. Researchers generally agree that the postoperative remaining tumor burden, the presence of ascites, and the site of origin are the most important factors contributing to long-term survival. Continued follow-up and collaborative studies are encouraged to further evaluate this treatment protocol.

1. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer* 1989;63:364–367.
2. Sugarbaker PH. Rationale for postoperative intraperitoneal chemotherapy as a surgical adjuvant for gastrointestinal malignancy. *Reg Cancer Treat* 1988;1:66.
3. Schabel FM Jr. Concepts for systemic treatment of micrometastases. *Cancer* 1975;35:15–24.
4. Weissberger AS, et al. Use of nitrogen mustard in treatment of serous effusions of neoplastic origin. *JAMA* 1955;159:1704.
5. Markman M. Intraperitoneal chemotherapy. *Semin Oncol* 1991;18:248–254.
6. Jacquet P. The peritoneal plasma barrier. In Sugarbaker P, ed. *Peritoneal Car-*

- cinomatosis: Principles of Management*. Boston: Kluwer Academic Publishers, 1996:53–63.
7. Dedrick RL. Interspecies scaling of regional drug delivery. *J Pharm Sci* 1986; 75:1047–1052.
 8. Cho HK, Lush RM, Bartlett DL, Alexander HR, Wu PC, Libutti SK, Lee KB, Venzon DJ, Bauer KS, Reed E, Figg WD. Pharmacokinetics of cisplatin administered by continuous hyperthermic peritoneal perfusion (CHPP) to patients with peritoneal carcinomatosis. *J Clin Pharmacol* 1999;39:394–401.
 9. Los G, Mutsaers PH, van der Vijgh WJ, Baldew GS, de Graaf PW, McVie JG. Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. *Cancer Res* 1989;49:3380–3384.
 10. Dedrick RL. Theoretical and experimental bases of intraperitoneal chemotherapy. *Semin Oncol* 1985;12(3 Suppl 4):1–6.
 11. Bartlett D. Peritoneal carcinomatosis. In DeVita VT Jr, Hellman S, Rosenberg SA Jr, eds. *Cancer: Principles and Practice of Oncology*. Baltimore: Lippincott Williams & Wilkins, 2001:2561–2573.
 12. Koga S, Hamazoe R, Maeta M, Shimizu N, Murakami A, Wakatsuki T. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. *Cancer* 1988;61:232–237.
 13. Fujimura T, Yonemura Y, Fushida S, Urade M, Takegawa S, Kamata T, Sugiyama K, Hasegawa H, Katayama K, Miwa K, et al. Continuous hyperthermic peritoneal perfusion for the treatment of peritoneal dissemination in gastric cancers and subsequent second-look operation. *Cancer* 1990; 65:65–71.
 14. Fujimoto SEA. Clinical outcome of combined therapy of intraoperative hyperthermic chemotherapy and surgery for patients with peritoneal recurrence from gastric cancer. *Reg Cancer Treat* 1990;3:181.
 15. Sugarbaker PH. Cytoreductive surgery and intraperitoneal chemotherapy with peritoneal spread of cystadenocarcinoma. *Eur J Surg Suppl* 1991;561:75–82.
 16. Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. *J Natl Cancer Inst* 1997;89:480–487.
 17. Dunnick NR, Jones RB, Doppman JL, Speyer J, Myers CE. Intraperitoneal contrast infusion for assessment of intraperitoneal fluid dynamics. *AJR Am J Roentgenol* 1979;133:221–223.
 18. Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995;221:29–42.
 19. Stephens AD, Alderman R, Chang D, Edwards GD, Esquivel J, Sebbag G, Steves MA, Sugarbaker PH. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann Surg Oncol* 1999;6:790–796.
 20. van Hazel GA, Scott M, Rubin J, Moertel CG, Eagan RT, O'Connell MJ, Kovach JS. Pharmacokinetics of mitomycin C in patients receiving the drug alone or in combination. *Cancer Treat Rep* 1983;67:805–810.
 21. Sayag AC, Gilly FN, Carry PY, Perdrix JP, Panteix G, Brachet A, Bannillon V, Braillon G. Intraoperative chemohyperthermia in the management of digestive cancers. A general review of literature. *Oncology* 1993;50:333–337.
 22. Fisher GA. Enhancement of cis-platinum (II) diamminodichloride cytotoxicity by hyperthermia. *Natl Cancer Inst Monogr* 1982;61:255.
 23. Wallner KE, Banda M, Li GC. Hyperthermic enhancement of cell killing by mitomycin C in mitomycin C-resistant Chinese hamster ovary cells. *Cancer Res* 1987;47:1308–1312.
 24. Benoit L, Duvillard C, Rat P, Chaffert B. [The effect of intra-abdominal temperature on the tissue and tumor diffusion of intraperitoneal cisplatin in a model of peritoneal carcinomatosis in rats]. *Chirurgie* 1999;124:375–379.
 25. Teicher BA, Kowal CD, Kennedy KA, Sartorelli AC. Enhancement by hyperthermia of the in vitro cytotoxicity of mitomycin C toward hypoxic tumor cells. *Cancer Res* 1981;41:1096–1099.
 26. Zakris EL, Dewhirst MW, Riviere JE, Hoopes PJ, Page RL, Oleson JR. Pharmacokinetics and toxicity of intraperitoneal cisplatin combined with regional hyperthermia. *J Clin Oncol* 1987;5:1613–1620.
 27. Loggie BW, Fleming RA, McQuellon RP, Russell GB, Geisinger KR. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin. *Am Surg* 2000;66: 561–568.
 28. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to “pseudomyxoma peritonei.” *Am J Surg Pathol* 1995;19:1390–1408.
 29. Ronnett BM, Shmookler BM, Sugarbaker PH, Kurman RJ. Pseudomyxoma peritonei: new concepts in diagnosis, origin, nomenclature, and relationship to mucinous borderline (low malignant potential) tumors of the ovary. *Anat Pathol* 1997;2:197–226.
 30. Sugarbaker PH, Kern K, Lack E. Malignant pseudomyxoma peritonei of colonic origin. Natural history and presentation of a curative approach to treatment. *Dis Colon Rectum* 1987;30:772–779.
 31. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol* 1999; 6:727–731.
 32. McQuellon RP, Loggie BW, Fleming RA, Russell GB, Lehman AB, Rambo TD. Quality of life after intraperitoneal hyperthermic chemotherapy (IPHC) for peritoneal carcinomatosis. *Eur J Surg Oncol* 2001;27:65–73.
 33. Fujimoto S, Shrestha RD, Kokubun M, Kobayashi K, Kiuchi S, Konno C, Ohta M, Takahashi M, Kitsukawa Y, Mizutani M, et al. Positive results of combined therapy of surgery and intraperitoneal hyperthermic perfusion for far-advanced gastric cancer. *Ann Surg* 1990;212:592–596.