Hyperthermic Intraoperative Intraperitoneal Chemotherapy (HIIC) with Mitomycin C

PAUL H. SUGARBAKER, M.D., F.A.C.S., DIRECTOR, SURGICAL ONCOLOGY
ANDREW M. AVERBACH, M.D., GASTROINTESTINAL ONCOLOGY CLINICAL FELLOW
PIERRE JACQUET, M.D., GASTROINTESTINAL ONCOLOGY RESEARCH FELLOW
O. ANTHONY STUART, RESEARCH LABORATORY COORDINATOR
ARVIL D. STEPHENS, DIRECTOR, RESEARCH & DEVELOPMENT
GASTROINTESTINAL ONCOLOGY PROGRAM
WASHINGTON CANCER INSTITUTE
WASHINGTON, D.C.

Dedrick et al. published a mathematical model in 1978 that described the theoretical rationale for intraperitoneal administration of chemotherapeutic agents.[1] Numerous authors have provided substantial clinical and experimental evidence supporting Dedrick's model. Lukas et al.[2] and Torres et al.[3] have described the pharmacokinetics involved in the transport of drugs from the peritoneal cavity into the portal and systemic circulation. These investigations and others gave birth to the pharmacologic concept known as the peritoneal plasma barrier (PPB). The PPB has been described as a complex diffusion barrier, consisting of the endothelium, the mesothelium, and the intervening interstitium, along with the fluid in the blood and the dialysate.[4] This physiologic barrier limits the resorption of hydrophilic drugs such as mitomycin C, doxorubicin, and cisplatin from the peritoneal cavity into the blood.

The basic goal of all regional chemotherapy, including intraperitoneal chemotherapy, is to increase the total amount of drug delivered to the tumor while decreasing the amount of drug reaching the systemic circulation.[5,6] A pharmacokinetic advantage exists for larger, water soluble and ionized molecules when administered by the intraperitoneal route.[3] These molecules exit more slowly from the peritoneal cavity than small, lipid-soluble and unionized compounds.

An important route of clearance from the peritoneal cavity is by portal circulation. Some drugs, such as 5-fluorouracil, are then metabolized into nontoxic forms during the first pass through the liver. Hepatic metabolism on the first pass adds an additional pharmacokinetic advantage. All of these factors work to increase the intraperitoneal exposure while maintaining tolerable systemic levels of drugs.[5] This phenomenon is particularly advantageous when the maximum cytotoxicity of the drug occurs at a higher concentration than the maximum tolerated systemic dose. Also, systemically delivered neutralizing agents may be administered to minimize the toxic side effects of intraperitoneal chemotherapy.[5]

Penetration of chemotherapy into tumors occurs by two mechanisms. When drugs are administered intravenously, they are delivered by capillary flow. When drugs are delivered intraperitoneally, they reach the tumor by direct surface absorption and capillary flow. Penetration of chemotherapy into tumors by surface

absorption is extremely limited.[7,8] Experiments suggest that penetration may be a few cell layers (for doxorubicin) to perhaps 2 to 3 mm (for cisplatin).

As a result of limited penetration, the greatest clinical benefit of intraperitoneal administration, over systemic administration, will occur in patients having the smallest possible tumor nodules. Ideally all gross and microscopic tumor will be resected prior to chemotherapy delivery. From a pharmacologic and a practical basis, the perioperative period is best for intraperitoneal chemotherapy delivery. The logical benefits of administering chemotherapy in the perioperative period are as follows. The tumor volume is minimized at this point. Residual tumor cells in the tumor bed or free cancer cells may be destroyed before postoperative changes in tumor cell kinetics occur. Perioperative intraperitoneal chemotherapy also promotes favorable drug access to peritoneal surfaces at risk for recurrence before cancer cells are entrapped by wound healing. Finally, cell-cycle specific drugs (i.e., 5-fluorouracil) may be repeatedly administered over the first 5 to 7 postoperative days before an adhesive process causes nonuniform drug distribution.

In all of these studies with intraperitoneal chemotherapy, the volume of fluid used has been kept large. The limiting volume with awake patients is between 2 and 3 L of fluid. In the early postoperative period, when patients have an abdominal incision, the limit is 1 to 2 L. In order to maximize drug distribution and uniformity of exposure, the volume is increased until patient tolerance is reached.

Hyperthermic intraoperative intraperitoneal chemotherapy is a logical progression in the dose intensification of regional chemotherapy for peritoneal carcinomatosis. Heat alone is cytotoxic to cancer cells; particularly when the cancer is largely avascular as in the case of pseudomyxoma peritonei. Exposure to 43°C heat increases the cytotoxicity of mitomycin C 10 to 15 times over exposure at 37°C.[9] Heat also increases the penetration of drugs into tissues.[7,8] The risk of heat damage to visceral structures and systemic toxicity is minimized by close monitoring of both perfusate temperature physiologic parameters during and after administration.

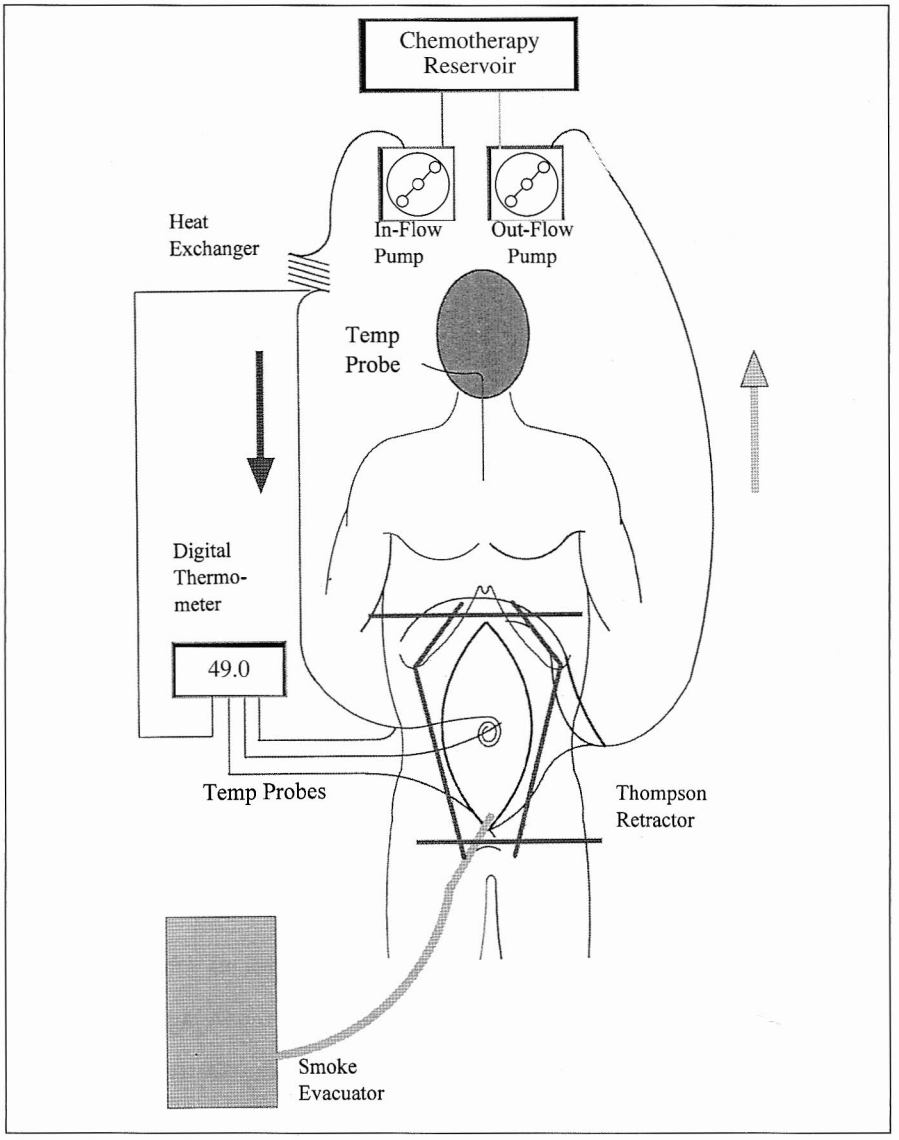

Figure 1. Hyperthermic intraoperative intraperitoneal chemotherapy equipment. Equipment required for the intraoperative administration of hyperthermic chemotherapy. Three closed suction catheters, a Tenckhoff catheter, and two esophageal temperature probes are placed through the abdominal wall. The abdominal wall is suspended from the Thompson Retractor and covered with a sterile plastic sheet. The smoke evacuator is placed beneath one edge of the plastic sheet and run at a low flow rate during the perfusion.

MATERIALS AND METHODS

In our current use of intraoperative intraperitoneal chemotherapy, surgery was attempted to make each patient macroscopically disease-free. At the end of the resection, closed suction catheters (Zimmer, Inc., Warsaw, Ind.) were placed through the abdominal wall, using stab incisions, to lie beneath the right and left hemidiaphragms and within the pelvis (Fig. 1). A Tenckhoff catheter (Quinton, Inc., Seattle, Wash.) was similarly placed in the abdominal cavity. The Tenckhoff catheter was placed in the area at greatest risk for recurrence and functioned as an in-flow line. The closed suction catheters were used as drainage lines. Two temperature probes (Respiratory Support Products, Inc., Irvine, Calif.) were then placed over the edge of the abdominal incision. One temperature probe was tied to the Tenckhoff catheter. The other temperature probe was tied to a closed suction drain at a distant location from the Tenckhoff. All transabdominal tubes were secured to the skin and to the peritoneum with purse string sutures to prevent fluid leakage. The Thompson retractor (Thompson Surgical Instruments, Traverse City, Mich.) was then repositioned as a frame approximately 10 cm above the open abdominal incision (Fig. 1). The skin edges are suspended to the Thompson retractor with a No. 2 running nylon suture. To prevent spillage of the chemotherapy and to control potential chemotherapy vapors, a plastic sheet was used to suspend the wound edges onto the retractor frame.

Table 1. Standardized drug doses

Drug	Day	Route	Dose
Mitomycin C	0	IP	15 mg/m² for males or 12.5 mg/m² for females in 3 L
5-Fluorouracil	1-5	IP	15 mg/kg x 5 days

Standardized dose reductions occurred as follows:
33% dose reduction for age > 65 years;
33% dose reduction for patients with compromised renal function;
50% dose reduction for prior exposure to heavy chemotherapy or radiation therapy;
Other dose reductions as deemed necessary by the Principal Investigator.

A slit incision was then made in the center of the plastic sheet to allow the surgeon access to all abdominal and pelvic contents and to control the fluid distribution manually. After the hyperthermic perfusion was complete, bowel anastomoses and other reconstructive procedures were performed.

The hyperthermic perfusion with mitomycin C was carried out for 90 minutes using a heat exchanger and a cardiopulmonary bypass pump and heater/cooler unit (Sarns, Inc., Ann Arbor, Mich.). Three liters of 1.5% dextrose peritoneal dialysis solution containing a maximum of 15 mg/m² of mitomycin C for males or 12.5 mg/m² for females were heated and infused at approximately 1 L per minute into the abdominal cavity. The perfusate was heated to approximately 43°C. Temperatures were measured with a Labcraft digital thermometer (Curtin Matheson Scientific, Jessup, Md.). The temperature at the in-flow line was approximately 44°C. The Tenckhoff temperature probe was maintained between 42 and 43°C. The temperature probes were removed at the end of the hyperthermic perfusion. The Tenckhoff catheter and closed suction drains remained in place for the administration of early postoperative intraperitoneal 5-fluorouracil.

Urine output was monitored by the anesthesiologist. At his or her discretion fluid challenge, furosemide, and renal dose dopamine were instituted to maintain a brisk diuresis. Urine output was measured every 15 minutes. It was maintained at greater than 400 cc per hour during the 90 minutes of the hyperthermic perfusion and for 1 hour thereafter.

In addition to intraoperative hyperthermic perfusion, all patients received 5 days of early postoperative intraperitoneal chemotherapy with 5-fluorouracil. These 5 days of chemotherapy were given on postoperative days 1-5. Each dose was prepared in 1000 to 2000 cc of 1.5% dextrose peritoneal dialysis solution, depending on body size. Each dose was infused as quickly as possible, allowed to dwell for 23 hours then drained for 1 hour prior to the next infusion (Table 1).

Patients were monitored for complications associated with intraperitoneal hyperthermia, including enteral complications (fistulas, anastomotic leaks), wound complications (pancreatitis, bile leaks, wound dehiscence), hematologic toxicities, prolonged ileus and line sepsis.

RESULTS

The temperatures recorded in a representative patient at three different anatomic sites and at the in-flow line are shown in Figure 2. The heat rapidly dissipates within the peritoneal cavity as high blood flow in viscera transmits the heat to

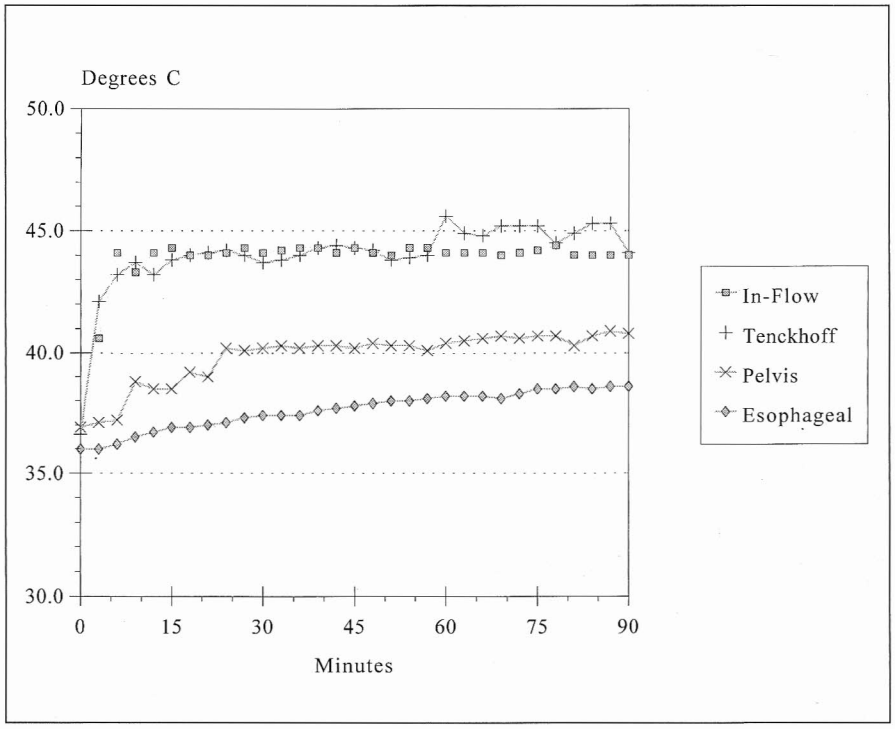

Figure 2. Patient temperatures at three anatomic sites and at the in-flow line. Intra-abdominal and esophageal temperatures for a single patient. Data presented are typical temperatures observed during the hyperthermic perfusion. Note the differences in area under the temperature curves between in-flow and Tenckhoff lines (at resection site), pelvis (distant intra-abdominal site) and esophageal (core body) temperatures. This figure demonstrates the localized administration of heat with this procedure.

other portions of the body. A temperature probe at a distant site in relation to the inflow demonstrated the temperature gradient within the abdomino-pelvic cavity. Core temperatures, recorded here as esophageal temperatures, were monitored and at no time reached critical levels. The highest core temperature recorded for any patient in these series was 40.0°C. The differences in AUC of heat between the Tenckhoff, pelvis, and esophageal temperatures demonstrate the regional administration of heat by this technique.

A semilog plot of the absorption of mitomycin C from the peritoneal fluid is shown in Figure 3. This suggests that a simple diffusion model accounts for drug clearance. The amount of drug excreted in the urine was highly dependent on the urine volume produced during each 15 minute period.

Hyperthermic mitomycin C demonstrated a mean half-life of 58.4 ± 10.3 minutes in the peritoneal fluid. Drug absorption was 14.34 ± 2.69 mg (70.2 ± 12.0 % of the dose) during the 90-minute perfusion. The mean peak plasma concentration was 0.198 ± 0.046 μg/mL and occurred at 47 ± 20 minutes. The mean AUC for perfusate and plasma was 340.1 ± 138.5 μg/mL x min and 15.1 ± 4.0 μg/mL x min respectively. The mean peritoneal fluid:plasma AUC ratio was 23.5, with a range of 14.7 - 46.0. The maximum concentration of mitomycin C in urine was 1.144 ± 0.553 μg/mL and occurred at 58 ± 20 minutes into the perfusion. Mean cumulative mitomycin C excretion through the urine during the 90-minute perfusion was 704 ± 330 μg or 3.3% of the mean dose.

Pharmacokinetics of early postoperative intraperitoneal 5-FU were not altered by administration of HIIC (Fig. 4). The half-life of 5-FU in the peritoneal fluid was 282 ± 123 minutes. Area under the peritoneal fluid curve was 35,256 ± 16,854 μg/mL x min. Area under the plasma curve was 15.1 ± 3.0 μg/mL x min. The peritoneal fluid/plasma ratio was 23.5 ±10.3 μg/mL x min.

DISCUSSION

Uniform drug distribution and uniform heat administration throughout the abdomen and pelvis are the major advances that are addressed by this technique. All other plans for intraperitoneal chemotherapy distribution have areas within the abdomen and pelvis that are not exposed to the perfusate. Dependent surfaces beneath

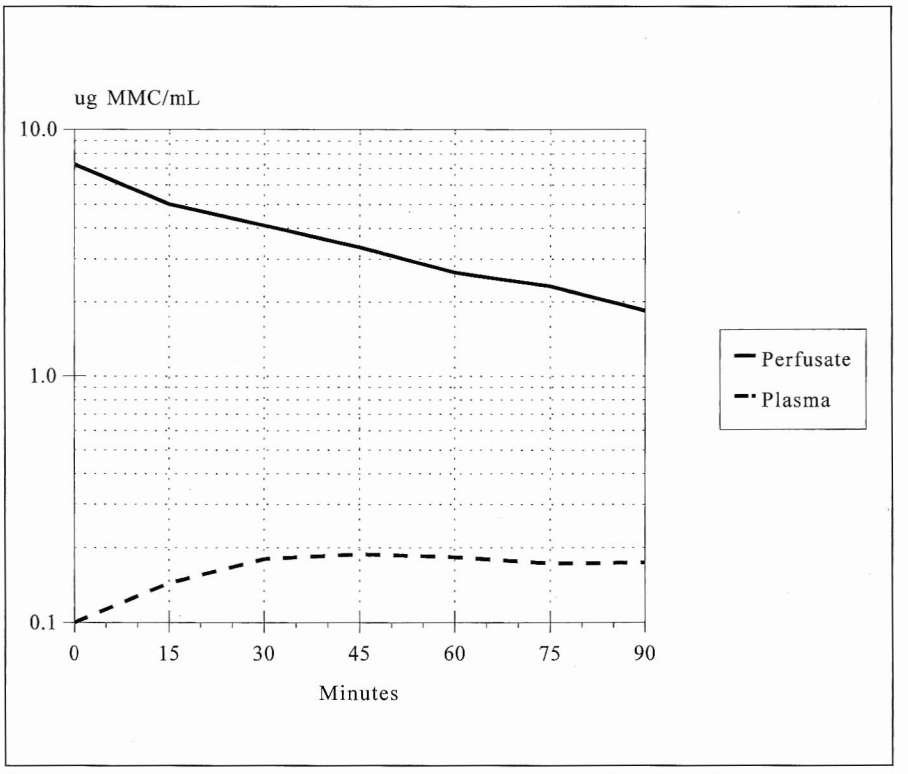

Figure 3. Perfusate and plasma levels (semilog plot). Drug clearance from the perfusate demonstrated first-order kinetics. Data presented are means from 10 patients treated with continuous-flow HIIC and 18 patients treated with cyclic-flow HIIC. No statistically significant differences in pharmacokinetics were observed between continuous-flow and cyclic-flow techniques.

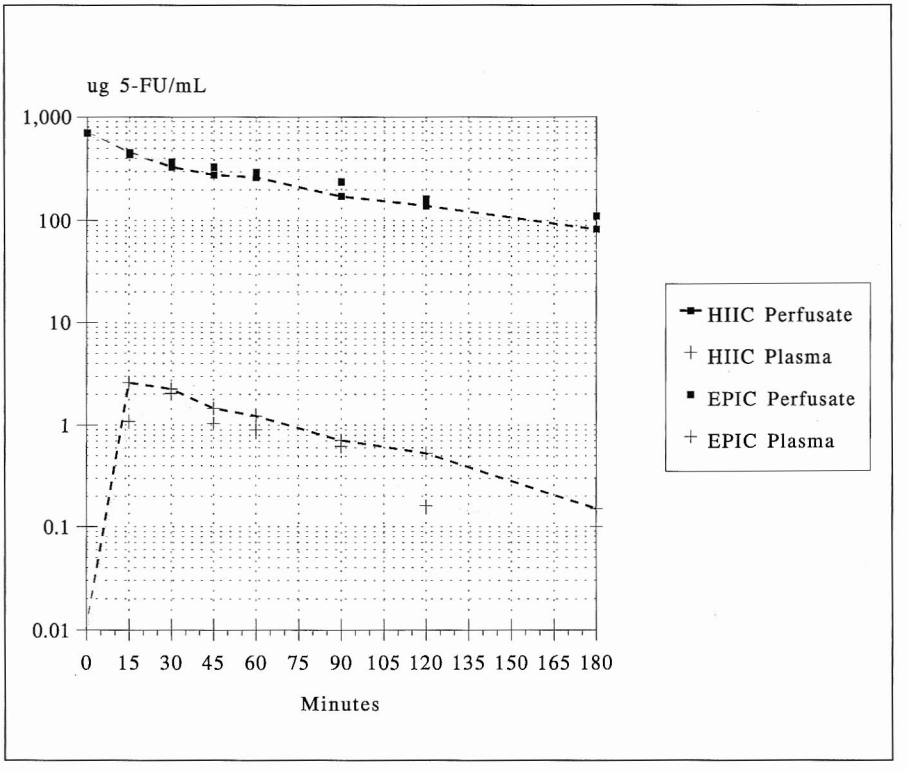

Figure 4. Pharmacokinetics of early postoperative 5-fluorouracil with and without HIIC. No significant difference was observed in 5-FU pharmacokinetics when administered after HIIC or when administered after normothermic mitomycin C as early postoperative intraperitoneal chemotherapy (EPIC). Area under the perfusate curve was 677 μg/mL and 761 μg/mL for 5-FU after normothermic mitomycin C alone and after heated intraoperative mitomycin C respectively (p=0.33). Likewise, area under the plasma curve was 2.93 and 1.76 respectively (p=0.77). No significant difference was observed between AUC ratios (perfusate/plasma) for the two groups (p=0.28).

the liver, within the pelvis, and between loops of bowel are closed off to contact with chemotherapy solution by all lavage techniques. Only when the surgeon has full access to the abdomen and pelvis can all structures be guaranteed full access to drug and to heat. The manual separation of all structures in a repetitive fashion is required for an optimal intraperitoneal chemotherapy administration. Fujimura et al. have reported on the use of a peritoneal cavity expander to improve the uniform exposure of viscera to heated mitomycin C.[10]

We have added methylene blue to the peritoneal fluid, prior to the last hyperthermic lavage cycle with the original closed technique, and the distribution assessed after reopening the abdominal incision. We observed an uneven distribution of methylene blue on the viscera of all patients, which we speculate will reflect the patterns of treatment failure in these patients.

The treatment of a wide variety of intra-abdominal malignancies may be benefitted by HIIC. Gilly has reported favorable responses from heated intraperitoneal cisplatin, given in a similar fashion to that described here, for treating patients with recurrent ovarian malignancy.[11,12] Los et al. have reported that cisplatin levels were greater within 1 to 2 mm from the periphery of intraperitoneal tumors due to drug delivery by both direct penetration and by blood circulation.[13,14] These observations provide strong support for the application of hyperthermic cisplatin for primary and recurrent ovarian cancer. Fujimoto et al. have reported encouraging results with hyperthermia and mitomycin C for gastric cancer[15,16] and rectal cancer[17] patients. Their studies have indicated an improved survival and decreased local recurrence rates without major postoperative complications. Yonemura and colleagues have reported results of prospective studies showing decreased peritoneal dissemination of disease and disappearance of ascites after treatment with hyperthermic intraperitoneal mitomycin C and cisplatin.[18]

Hyperthermic intraoperative intraperitoneal chemotherapy perfusion, as described here, allows treatment of the peritoneal surfaces with extremely cytotoxic levels of chemotherapy. To determine if this approach produces a clear survival advantage will require a prospective, randomized clinical trial. It has been demonstrated that a complete cytoreduction greatly improves the prognosis for patient survival.[19] Perhaps the combination of a complete cytoreduction and hyperthermic intraoperative intraperitoneal chemotherapy may improve the survival of patients with certain histologic grades of peritoneal carcinomatosis. The definitive assessment of this novel way to administer chemotherapy will come with continued follow-up of these patients, and with analysis of sites of treatment failure.

In summary, studies indicate that 42°C temperatures adequately potentiate cytotoxicity for single tumor cell layers in vitro or microscopic residual disease in vivo. Hyperthermic intraoperative intraperitoneal chemotherapy can be performed clinically. Several reports have demonstrated that tumor microcirculation is generally more sensitive to heat than normal tissue.[20,21] However, factors such as (1) the extent of tumor vascularization, (2) interstitial pressure within the tumor, (3) the amount of necrosis at the center of the lesion, (4) the degree of thermotolerance demonstrated, and (5) the depth of drug penetration from peritoneal and vascular compartments will influence the clinical efficacy of hyperthermic intraperitoneal chemotherapy administration. STI

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