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Safety Monitoring of the Coliseum Technique for Heated Intraoperative Intraperitoneal Chemotherapy With Mitomycin C

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Background: Treatment of carcinomatosis may involve the use of heated intraperitoneal chemotherapy; the cytotoxic solution is administered in the operating room with the abdomen open so that manual distribution results in uniform treatment. The potential risk of this procedure to the operating room personnel has not been previously investigated.

Methods: Mitomycin C was perfused through the peritoneal cavity, which was partially covered by a plastic sheet. Large volumes of air were suctioned from 5 and 35 cm above the abdominal skin edge. Urine from the surgeon and from the perfusionist were assayed. Sterile gloves worn in the operating room for manipulating the viscera during treatment were assayed for their permeability to mitomycin C. All samples were analyzed by high-performance liquid chromatography.

Results: Analysis of samples of operating room air and urine from 10 procedures showed no detectable levels of mitomycin C. Six tests of three different types of gloves showed a 10-fold range of mitomycin C penetration. The least permeable gloves leaked a mean of 3.8 parts per million over 90 minutes.

Conclusions: No detectable safety hazard to the surgeon or other operating room personnel was demonstrated.

Key Words: Safety monitoring—Operating room—Hyperthermia—Intraperitoneal chemotherapy—Mitomycin C—Latex gloves.

Gastrointestinal and gynecologic malignancies frequently disseminate to the peritoneal surfaces. Prevention or adequate treatment of disease at this anatomical site would improve the survival of patients if dissemination did not occur elsewhere in the body. For patients with distant metastases, eradication of cancer on abdominal and pelvic surfaces would result in a quality of life advantage because intestinal obstructions would occur much less frequently.[1] One method currently used at this institution in >450 patients to treat the peritoneal surface component of these malignancies is heated intraoperative intraperitoneal chemotherapy.[2] Heat synergizes the cytotoxic effects of chemotherapy.[3] In addition, heat increases the penetration of chemotherapy solution into cancer nodules.[4] To improve penetration of tumor nodules by chemotherapy, the size of tumor nodules is maximally cytoreduced before the heated chemotherapy treatments. In the methodology described by Sugarbaker et al.,[2] access to the abdomen and pelvis is maintained during the chemotherapy treatment so that the surgeon can distribute the heat and the chemotherapy solution uniformly. This resulted in a decreased morbidity associated with the procedure and is likely to improve its effectiveness.[5] With an increasing number of institutions adopting this strategy to treat and prevent peritoneal surface malignancy, there has been a growing concern regarding the safety of this technique for operating room personnel.

The most common chemotherapy agent used in heated intraoperative intraperitoneal chemotherapy procedures is mitomycin C. It was suitable for this study because it is highly soluble in methanol and because it is rapidly absorbed and excreted unchanged in the urine.[6] Mitomycin C can also be accurately assayed by established high-performance liquid chromatography (HPLC) techniques.[7–9] The purpose of this study was to assay in 10 patients for any detectable level of mitomycin C in the

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operating room environment and to determine levels of this drug in the urine of the attending surgeon who was manipulating the patient's viscera and in the urine of the perfusionist who was circulating the heated chemotherapy during the 90-minute procedure. In addition, the permeability of latex gloves to this drug was assessed.

METHODS

Technique for Heated Intraoperative Intraperitoneal Chemotherapy

After the cytoreductive surgery was completed, the edges of a sheet of plastic were incorporated into the running suture that suspended the skin of the abdominal wall on a self-retaining retractor. A generous cruciate incision in this plastic sheet allowed the surgeon's double-gloved hand access to the abdomen and pelvis. Manipulation of every millimeter of peritoneal surface and continued efforts at cytoreduction of small-bowel surfaces during the heated chemotherapy treatments required wide access to the abdomen and pelvis throughout the 90 minutes of heated chemotherapy. The surgeon was double gloved and was required to wear operating room–quality eye protection. Large-bore tubing connected to a smoke-evacuating device (Stackhouse, El Secunda, CA) was placed beneath the plastic sheet. It removed approximately 30 L of air per minute and forced it through a charcoal filter pack. When the smoke evacuator was placed on maximal suction, a flow of air from around the open abdomen and into the vacuum tube was created. The adequacy of this evacuation system for the evacuation of chemotherapy-contaminated air was a crucial aspect of this study.

Air Sampling

During the 90 minutes of heated intraoperative intraperitoneal chemotherapy, air sampling lines were positioned strategically above the operating field to sample a large volume of air in the immediate vicinity of the open abdomen. One air sampler was attached at the level of the self-retaining retractor at approximately 5 cm above the plastic sheet. The other was positioned at the level of the surgeon's mask, at approximately 35 cm above the patient's open abdomen. Each air-sampling line was attached to a canister containing 500 mL of methanol and then to wall suction with a negative pressure of 200 mm Hg. Air was continuously and vigorously suctioned through the methanol at $>$30 L/minute throughout the 90-minute procedure. Because mitomycin C is highly soluble in methanol, any mitomycin C vapors in the vicinity of the peritoneal cavity and in the operating room environment would be trapped in the canisters.

Mitomycin C Extraction From the Smoke-Evacuation System

During the 90 minutes of heated intraoperative intraperitoneal chemotherapy treatment, a large-bore smoke-evacuation system was operative. In a single patient after the mitomycin C chemotherapy treatment, the filter was removed and washed with 250 mL of 50% methanol in isopropanol. This methanol/isopropanol wash was repeated twice. The combined organic extracts were concentrated and analyzed by HPLC as with the other mitomycin C samples. Also, the air pulled through the smoke-evacuating device that was located beneath the plastic sheet was analyzed on three occasions. The air was pulled through 500 mL of methanol in a suction extraction procedure. Mitomycin C extracted from this large volume of air bubbled through the methanol was analyzed.

Urine Samples

Before the start and at the end of each heated intraoperative intraperitoneal chemotherapy procedure, a urine sample was obtained from the surgeon who was directly involved with the procedure and who was in closest contact with the heated chemotherapy solution for the entire 90 minutes of treatment. Urine samples were also obtained from the perfusionist who performed the treatment. No urine sample was obtained at different times during the chemotherapy perfusion.

Mitomycin C Quantitation

Mitomycin C levels were determined with HPLC procedures as described by Tjaden et al.[7] The HPLC system consisted of a Shimadzu (Kyoto, Japan) LC7A™ instrument equipped with an SPD-6AV™ (ultraviolet to visible) detector set (Shimadzu) at 365 nm-uv and a C-R6A™ data processor (Shimadzu). A reversed-phase column (250 $\times$ 4.6 mm) of 300 angstrom 5-μm silica bonded to C_{18} was used coupled to a guard column of the same chemical consistency (Rainin Instruments, Emeryville, CA). The mobile phase consisted of methanol in .01 M of phosphate buffer, pH 6.0. The ratio of methanol to phosphate buffer was 32 to 68 for methanol samples and 30 to 70 for urine samples. Flow rate in either case was set at 1 mL/minute. Sample injections were 50 μL.

Sample Preparation

The volume of methanol remaining in each canister was determined, and a 100-mL aliquot was evaporated under reduced pressure at 45°C until all methanol was removed. The presence of atmospheric moisture in the methanol sample restricted the concentration factor 20 to 25 times. The residue was measured, and an aliquot

(approximately 500 μL) was filtered through a .2-μm syringe filter for HPLC injection. Spiked samples containing 50 ng of mitomycin C in 100 mL of methanol (.5 ng/mL) were assayed by HPLC to verify that there was no degradation of mitomycin C during the evaporation process.

For urine samples, the volume of urine collected 10 minutes after the 90-minute procedure was determined. An aliquot of 1 mL was diluted with 500 μL of .1 M phosphate buffer (pH 7.5) and filtered through a .2-μm syringe filter before injection into the HPLC system. Sample injections were 50 μL in all cases. Urine samples collected after exposure to chemotherapy were compared with control samples collected before chemotherapy exposure and with control samples spiked with known amounts of mitomycin C. It should be noted that both solid-phase extraction techniques and liquid-liquid extraction techniques were used in an effort to concentrate urine samples.[8,9] Neither of these methods adequately removed components of urine that gave chromatographic peaks close to the mitomycin C peak. These components were further exaggerated by concentration and tended to obliterate the area of the mitomycin C peak.

Penetration of Mitomycin C Through Latex Gloves

A solution of 10 mg of mitomycin C in 1 L of 1.5% dextrose peritoneal dialysis solution (Baxter Healthcare Corporation, Deerfield, IL) was placed in a 2-L Medi-Vac™ canister (Allegiance Healthcare Corporation, McGaw Park, IL). This concentration was similar to the concentration used during the heated intraoperative intraperitoneal chemotherapy procedure. The solution was adjusted to a pH of 7.4, similar to that attained in the peritoneal cavity during the intraperitoneal chemotherapy procedure. A large magnetic stirring bar was placed in the canister, which was then placed in a water bath. The entire apparatus was placed on a heater/magnetic stirrer and heated until the temperature in the water bath reached 43°C. This was the inflow temperature for the heated chemotherapy perfusion. The magnetic stirrer was then turned on to obtain constant agitation of the chemotherapy solution inside the canister (Fig. 1). Before the lid of the canister was secured, a glove to be tested was introduced through an opening in the lid so that the palm and fingers were suspended inside the canister with the cuff protruding above the lid. The lid of the canister was then secured, with the glove suspended in the mitomycin C solution. By using a long-stemmed funnel, 250 mL of .9% sodium chloride solution was introduced into the glove. This volume adequately filled the fingers and palm of size 7½ gloves. For uniformity, size 7½ gloves were used for all types tested. The cuff of the glove was folded over the raised lip of the opening and held in place by a tight-fitting cap. After 90 minutes of constant moderate agitation with the temperature of the chemotherapy solution at approximately 43°C, the canister was removed from the water bath. Without removing the main lid of the canister, the cap over the cuff of the glove was raised, and a 10-mL sample of saline was pipetted from within the glove for analysis. By using solid-phase extraction techniques combined with HPLC, the mitomycin C levels in each 10-mL sample were determined. Six gloves of each type were tested. Three commercially available types of gloves were tested: the Ultrafree™ and Protegrity™ gloves (Allegiance Healthcare Corporation) and the Biogel™ glove (Regent Medical, Norcross, GA).

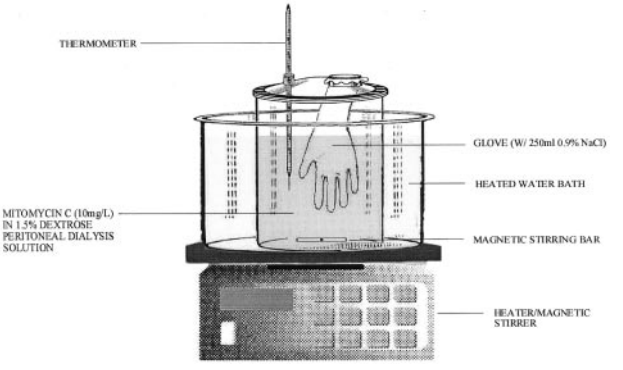

FIG. 1. Apparatus for testing the mitomycin C penetration of latex sterile gloves.

The regulatory groups authorized to control the safety of the operating room environment were contacted. All printed information was tabulated, and relevant guidelines for use of chemotherapy in the operating room were proposed.

RESULTS

Results from air and urine sampling during 10 heated intraoperative intraperitoneal chemotherapy procedures with mitomycin C are listed in Table 1. The average total mitomycin C used for the perfusion was 18.5 ± 5.2 mg in approximately 3 L of peritoneal dialysis solution. The average total volume of methanol in each canister was reduced by evaporation from 500 mL to approximately 300 mL at the end of the 90-minute procedure. The level of detection of mitomycin C was determined to be .5 ng/mL for methanol samples and 25 ng/mL for urine samples. All samples were below the levels of detection.

Methanol samples containing aerosols from the smoke-evacuating device located just beneath the plastic sheet were collected during three heated intraoperative intraperitoneal chemotherapy treatments. These samples

TABLE 1. *Summary of mitomycin C contamination of operating room air and urine of operating room personnel*[a]

Type of sample	Total volume of sample (mL)	Mitomycin C concentration (ng/mL)	Total mitomycin C in sample (μg)
Methanol from air sampler at 5-cm level	302 ± 12	<.5	<.15
Methanol from air sampler at 35-cm level	298 ± 16	<.5	<.15
Surgeon's urine after chemotherapy exposure	70 ± 6	<25	<1.75
Perfusionist's urine after chemotherapy exposure	56 ± 11	<25	<1.5

[a] Each data point is a collection of 10 different determinations. The surgeon in these experiments used Biogel gloves.

all had traces of mitomycin C. An average total of .18 ± .06 μg of chemotherapy was recovered from each procedure. In addition, at the end of one 90-minute procedure, the filter from the smoke-evacuation apparatus was removed and extracted with two 250-mL volumes of a solution of 50% methanol in isopropanol. The combined organic extracts were concentrated and analyzed by HPLC as with the methanol samples. A total of .26 μg of mitomycin C was recovered.

Mitomycin C levels detected in the latex glove penetration study are listed in Table 2. For each type of glove tested, two sets of results are presented. One column presents the total amount of mitomycin C absorbed in 250 mL of saline. The second column expresses this amount as parts per million in relation to the total amount of mitomycin C exposure (10 mg). The highest levels of mitomycin C were found in the saline from the Ultrafree gloves, with a mean total absorption of .21 ± .07 μg of drug. The saline in the Protegrity gloves absorbed a mean total of .06 ± .01 μg, and the saline in the Biogel gloves absorbed a mean total of .04 ± .02 μg of mitomycin C. These data are graphically summarized in Fig. 2.

The regulatory agencies consulted through published information regarding chemotherapy safety are listed in Table 3. The recommendations appropriate for heated intraoperative intraperitoneal chemotherapy are included. All guidelines for the safe administration of cancer chemotherapy were fulfilled by the heated intraoperative intraperitoneal chemotherapy procedure.

DISCUSSION

This study showed no evidence of mitomycin C in the operating room environment in areas immediately above and surrounding the field of operation during the 90-minute heated intraoperative intraperitoneal chemotherapy procedure. No detectable levels of mitomycin C were found in urine samples from the perfusionist or from the surgeon; these individuals had maximal contact with the heated chemotherapy solution. These data did not provide any evidence to suggest a health hazard to the attending surgeon or to other operating room personnel when precautions were taken.

The presence of mitomycin C in the aerosols suctioned through the smoke-evacuating device indicates that there is some chemotherapy contamination beneath the plastic sheet protector. This may be due to condensation droplets or to droplets generated by splashing during the surgeon's manipulations of the viscera. These findings support the necessity for an adequate air-evacuation system immediately above the heated chemotherapy solution and also support the need for a protective cover, such as the plastic sheet used in this operative technique.

Currently at the Washington Hospital Center, approximately 100 procedures per year are performed for the administration of heated intraoperative intraperitoneal chemotherapy. Before January 1995, all treatments were given in

TABLE 2. *Total mitomycin C penetrating through three commercially available latex sterile gloves*

	Ultrafree gloves		Protegrity gloves		Biogel gloves	
Sample No.	μg	PPM	μg	PPM	μg	PPM
1	.3	30	.06	6	.03	3
2	.28	28	.08	8	.05	5
3	.12	12	.06	6	.04	4
4	.23	23	.04	4	.01	1
5	.15	15	.06	6	.05	5
6	.2	20	.06	6	.05	5
Mean	.213	21.33	.06	6	.038	3.8
SD	.071	7.09	.013	1.3	.016	1.6

PPM, parts per million.

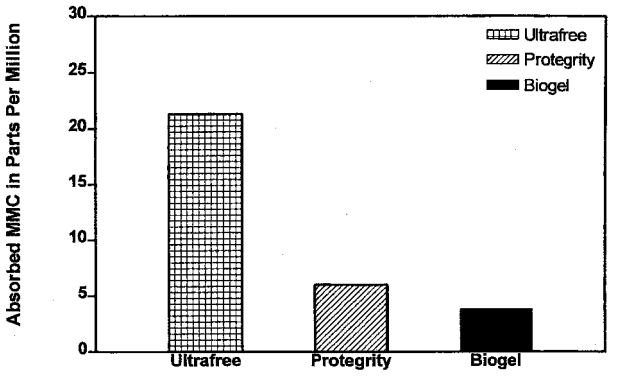

FIG. 2. Total mitomycin C (MMC) in parts per million that passed through three commercially available latex gloves.

the early postoperative period on a nursing unit. The rationale and safety considerations for chemotherapy in the first postoperative week were discussed by Hallenbeck et al.[10] All subsequent chemotherapies were initiated in the operating room. Initially, the abdomen was closed and the chemotherapy perfusion administered with the patient under general anesthesia.[6] However, when methylene blue dye was infused into the closed peritoneal cavity along with the heated chemotherapy, it became obvious that there was nonuniform distribution of the heat and chemotherapy. This led to an increase in morbidity and mortality when the closed technique was compared with the current practice, which involves manual distribution of the warm chemotherapy solution.[11,12] Early on, the need for conscientious monitoring of the safety of a procedure where there was open chemotherapy in the operating room was recognized.[13] Efforts to document the safety of this new approach to the dissemination of gastrointestinal and gynecologic malignancies are contained in this article. These efforts did not reveal objective evidence for unreasonable risk to operating room personnel.

TABLE 3. *Regulatory agencies and published guidelines that are appropriate for heated intraoperative intraperitoneal chemotherapy*

OSHA Work-practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm: 43, 1193–1204, 1986	JCAHO Accreditation Manual for Hospitals, 1989.	NCI National Study Commission on Cytotoxic Exposure. Recommendations for Handling Cytotoxic Agents, 1984	WHC General Surgery/Shock Trauma/Perioperative Nursing Division Policy #504.044 "Handling and disposal of Cytotoxic Agents"
1. All personnel involved in handling cytotoxic drugs must receive an orientation regarding techniques, procedures and policies. 2. The main routes of exposure are through inhalation of drug dust or droplets, absorption through the skin, and ingestion through contact with contaminated food and cigarettes. 3. Powderless surgical latex gloves should always be used. Double-gloving is recommended if it does not interfere with technique. 4. A protective disposable gown made of lint-free, low-permeability fabric with closed front, long sleeves, and closed cuffs must be worn, with the cuffs tucked under the gloves. 5. Surgical masks do not protect against breathing of aerosols. 6. Occupational exposure to platinum salts (including cisplatin) in air must be less than 2 ug per cubic-meter in an 8-hour work period.	NR 6. Nursing department and service personnel are prepared through appropriate education and training programs for their responsibilities in the provision of nursing care. NR 7. Written policies and procedures that reflect optimal standards of nursing care guide the provision of nursing care. NR 8. As a part of the hospital's quality assurance program, the quality and appropriateness of the patient care provided by the nursing department/service are monitored and evaluated, and identified problems are resolved.	1. Disposable surgical latex gloves are recommended for all procedures involving cytotoxic drugs. Polyvinyl chloride (PVC) gloves should not be worn while handling cytotoxic agents. 2. Gloves should be routinely changed approximately every 30 minutes when working steadily with cytotoxic agents. Gloves should be changed immediately after overt contamination. 3. Double gloving is recommended for cleaning up of spills. 4. Protective barrier garments should be worn for all procedures involving the preparation and disposal of cytotoxic agents. 5. All potentially contaminated garments must not be worn outside the work area.	1. Policy guidelines should be implemented during cytotoxic therapy and for 48 hours after the last administration. 2. Nursing personnel who are pregnant or breastfeeding should not administer cytotoxic drugs or handle cytotoxic waste. 3. Unpowdered surgical gloves and a disposable, low permeability gown should always be worn. 4. Goggles and/or a respirator should be worn when the potential for exposure exists. 5. A spill kit must be kept on each unit where cytotoxic drugs are handled. 6. All laboratory specimens from patients receiving cytotoxic agents must be labeled "Chemotherapy" and placed in a zip-lock plastic bag.

OSHA,Occupational Safety and Health Administration; JCAHO, Joint Commission on Accreditation of Healthcare Organizations; NCI, National Cancer Institute; WHC, Washington Hospital Center.

The safety of this operative procedure as presented in this article is defined by the limits of detection of mitomycin C. These limits were influenced by the HPLC detection system. The limits for mitomycin C detection in air by using methanol extraction were estimated at .5 ng/mL. For the urine measurements, the limits of detection were estimated at 25 ng/mL. The authors accept that lesser quantities of drug contamination below these limits of detection are possible with this technique, which involves a covering of the abdomen by a plastic sheet but does not involve a closed system. Biogel gloves are recommended because of their low permeability to chemotherapy. Because the benefits of this technique from both a theoretical and a clinical perspective are so pronounced, this technique is recommended over the closed heated intraperitoneal chemotherapy technologies until some data suggesting chemotherapy contamination are published.

Finally, it should be mentioned that all the guidelines listed in Table 3 for the administration of antineoplastic drugs can be met with the coliseum technique for chemotherapy administration in the operating room. This includes the Occupational Safety and Health Administration guidelines and those of the Joint Commission for the American Hospital Association, the National Cancer Institute, and the Washington Hospital Center Clinical Nursing Division Policy for Handling and Disposal of Cytotoxic Agents. We must consider whether the greatest danger to hospital personnel in performing this surgical technique exists outside the operating room, in the specimens, instruments, and waste that leave the operating room. Lack of knowledge in the handling of biomedical waste is a very real consideration for specimens and for the maintenance and cleaning of an operating room. In this regard, mitomycin C is an excellent choice for a drug used in the operating room. Its complete decay over 24 hours in dilute solution and its rapid degradation on exposure to light would cause minute amounts of drug remaining on surfaces in the operating room to be rapidly detoxified. No buildup of toxic waste over time could occur.

REFERENCES

1. Sugarbaker PH, Cunliffe W, Belliveau JF, et al. Rationale for perioperative intraperitoneal chemotherapy as a surgical adjuvant for gastrointestinal malignancy. *Reg Cancer Treat* 1988;1:66–79.
2. Sugarbaker PH, Averbach AM, Jacquet P, Stephens AD, Stuart OA. A simplified approach to hyperthermic intraoperative intraperitoneal chemotherapy (HIIC) using a self retaining retractor. In: Sugarbaker PH, ed. *Peritoneal Carcinomatosis: Principles of Management.* Boston: Kluwer, 1996:415–21.
3. Urano M, Kuroda M, Nishimura Y. The clinical application of thermochemotherapy given at mild temperatures (invited review). *Int J Hyperthermia* 1999;15:79–107.
4. Jacquet P, Averbach AM, Stuart OA, Chang D, Sugarbaker PH. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism and tissue distribution in a rat model. *Cancer Chemother Pharmacol* 1998;41:147–54.
5. Stephens AD, Alderman R, Chang D, et al. Morbidity and mortality of 200 treatments with cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann Surg Oncol* 1999;6:790–6.
6. Jacquet P, Averbach A, Stephens AD, Stuart OA, Chang D, Sugarbaker PH. Heated intraoperative intraperitoneal mitomycin C and early postoperative intraperitoneal 5-fluorouracil: pharmacokinetic studies. *Oncology* 1998;55:130–8.
7. Tjaden UR, DeBruijn EA, Van Der Hoeven RAM, Jol C, Van Der Greef J, Lingeman H. Automated analysis of mitomycin C in body fluids by high performance liquid chromatography with on-line sample pre-treatment. *J Chromatogr B Biomed Appl* 1987;420:53–62.
8. Eksborgh S, Ehrsson H, Lindfors A. Liquid chromatographic determination of mitomycin C in human plasma and urine. *J Chromatogr B Biomed Appl* 1983;274:263–70.
9. Den Hartigh J, McVie JG, van Oort WJ, Pinedo HM. Pharmacokinetics of mitomycin C in humans. *Cancer Res* 1983;43:5017–21.
10. Hallenbeck P, Sanniez CK, Ryan AB, Neily B, Sugarbaker PH. Cytoreductive surgery and intraperitoneal chemotherapy. *AORN J* 1992;56:50–72.
11. Jacquet P, Stephens AD, Averbach AM, et al. Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. *Cancer* 1996;77:2622–9.
12. Sugarbaker PH, Jacquet P, Stephens AD, Stuart OA, Averbach AM. Comparison of covered versus closed technique for heated intraoperative intraperitoneal chemotherapy for peritoneal carcinomatosis from gastrointestinal cancer. In: Abe O, Inokuchi K, Takasaki K, eds. *XXX World Congress of the International College of Surgeons*. Bologna: Monduzzi Editore, 1996:389–93.
13. Stephens AD, White SK, Sugarbaker PH. Guidelines for the safe administration of perioperative intraperitoneal chemotherapy. In: Bleiberg H, Rougier P, Wilke WI, eds. *Management of Colorectal Cancer*. London: Martin Dunitz, 1998:145–52.