Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Techniques

10

Salvatore Virzì, Domenico Rosario Iusco, Serena Bonomi, and Antonio Grassi

10.1 Introduction

Peritoneal carcinomatosis has long been considered a terminal condition and constitutes a difficult therapeutic challenge given the dismal prognosis associated with this entity and the debilitating effect it exerts on affected patients. Over the past decade, novel therapeutic approaches to peritoneal surface malignancies have emerged. These new approaches are all based on a strong rationale: most frequently, peritoneal carcinosis is a locoregional condition that should be approached with locoregional treatments, such as cytoreductive surgery and peritonectomy procedures for macroscopic disease in combination with perioperative intraperitoneal chemotherapy for microscopic residual disease. In order to take advantage of this synergistic effect, different devices and techniques have been developed. Perioperative intraperitoneal chemotherapy is a milestone of the combined approach to peritoneal surface malignancy. Two main modalities for administering chemotherapeutic agents have been described: intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), and early postoperative normothermic; the former has gained greater acceptance among peritoneal surface malignancy centers.

10.2 Intraoperative Hyperthermic Intraperitoneal Chemotherapy

Intraoperative administration of intraperitoneal hyperthermic chemotherapy has been described using multiple names. The term HIPEC was adopted as the

S. Virzì (✉)
General Surgery Unit, Bentivoglio Hospital, Bentivoglio (BO), Italy
e-mail: st.virzi@gmail.com

A. Di Giorgio, E. Pinto (Eds), *Treatment of Peritoneal Surface Malignancies*, Updates in Surgery
DOI: 10.1007/978-88-470-5711-1_10, © Springer-Verlag Italia 2015

standardized acronym for this procedure during the fourth workshop on peritoneal surface malignancy held in Madrid in 2004 [1, 2]. HIPEC combines the pharmacokinetic advantage inherent to the intracavitary delivery of certain cytotoxic drugs, which results in regional dose intensification, with the direct cytotoxic effect of hyperthermia. Hyperthermia alone, in fact, has a selective cell-killing effect on malignant cells, potentiates the cytotoxic effect of certain chemotherapeutic agents, and enhances tissue penetration of the administered drug. In order to take advantage of this synergistic effect, different devices and techniques have been developed.

10.3 Perfusion Technology

Basically, all devices for administering certain chemotherapeutic agents are composed of a closed, continuous circuit, with a pump, a heater with a heat exchanger, and a real-time temperature monitor. Different temperature probes are positioned in different sites of the circuit and abdominal cavity to secure a constant temperature: heat generator, inflow and outflow drains, bladder, liver, and mesentery. A computerized, continuous recording of thermal data that may be displayed in situ for monitoring during the procedure and then exported or printed with different formats is usually included with the device. This adds security and comfort for the patient, avoids the need to create written records, and allows efficient data recording for clinical research [3].

Numerous compact HIPEC machines, approved by the US Food and Drug Administration or with a CE marking have been developed and commercialized since the late 1990s. The choice of a specific HIPEC device should be based upon certain characteristics, such as its ability to achieve adequate hyperthermia in a short period, adjustable flow rate, user-friendliness, ease of assembly, ease of reading, and continuous registration of temperatures, availability of technical support, and affordability of the machine itself and the disposable circuit tubing kits.

10.4 Perfusion Techniques

HIPEC can be conducted in various ways, without clear proven advantage of one method over the others. Four major perfusion techniques are described in the literature: open-abdomen technique(coliseum technique) closed-abdomen technique, peritoneal cavity expanders (PCE), and semiopen techniques . Procedure duration varies from 30 to 120 min according to the surgeon's discretion and drug used [4, 5].

10.4.1 Open-abdomen Technique

The open method, first described by Sugarbaker, is usually performed using the "coliseum technique" (Fig. 10.1) [6]. At the end of cytoreductive phase, a Tenckhoff catheter and closed suction drains are placed through the abdominal wall. Temperature probes, secured to the skin edge, are used for intraperitoneal temperature monitoring: one in the inflow line and another one at a distance from this point (pelvis). A silastic sheet is sutured over a Thompson retractor and to the patient's skin over the abdominal incision in order to prevent the chemotherapy solution from splashing. Abdominal-wall suspension, obtained with such a suture, will create a coliseum- or soup-bowl-like container for instillation of the peritoneal perfusate. A slit in the plastic cover is made to allow access of the surgeon's double-gloved hand to the abdomen and pelvis and manual manipulation of the intra-abdominal contents, thus preventing stasis of the heated perfusate. A smoke evacuator protects operating-room (OR) personnel from aerosolized chemotherapy liberated during the procedure.

A roller pump forces chemotherapy perfusion into the abdomen through the Tenckhoff catheter and extracts it through the drains, with a flow rate ~1 L/min. A heat exchanger keeps the infused fluid at 43–45°C so that the intraperitoneal fluid is maintained at 41–43°C.

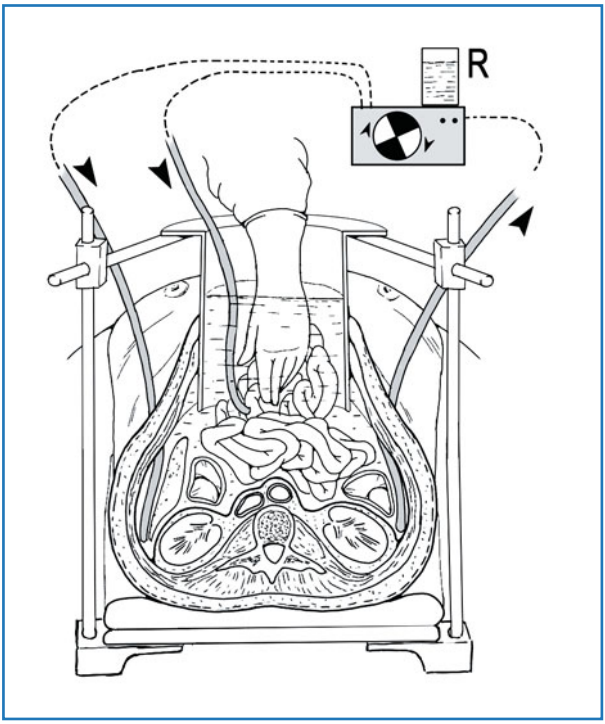

Fig. 10.1 Hyperthermic intraperitoneal chemotherapy (HIPEC): peritoneal cavity expander. (Courtesy of Prof. Angelo Di Giorgio)

The perfusate is first recirculated between the reservoir and the heat exchanger so it can be heated to an adequate temperature. At this point, full circulation of the perfusate in and out of the peritoneal cavity is established until a minimum intraperitoneal temperature of 41.5°C is achieved and maintained. The drug is then added to the circuit, at which stage the perfusion timer is started.

In centers in which bidirectional chemotherapy protocols are used, intravenous infusion of the appropriate drugs is started synchronously with peritoneal chemotherapeutic infusion, although some surgeons prefer to start it 1 h before the actual peritoneal therapy.

Use of the coliseum technique was identified by Elias et al. [7] as the best technique in terms of thermal homogeneity and spatial diffusion. Those benefits are due to the ability to manipulate the intra-abdominal viscera during perfusion, which allows homogeneous exposition of all peritoneal surfaces to the therapy. Furthermore, as excessive heating of normal tissue is associated with a more lasting postoperative ileus and increases the incidence of postoperative perforation or fistula formation, this technique theoretically avoids these complications. The disadvantages of open HIPEC are heat dissipation to the surface of the perfusate, which makes it more difficult to achieve hyperthermia, and possible increased exposure of operative personnel to the chemotherapeutic agent, even if this is as yet only a theoretical risk.

10.4.3 Closed-abdomen Technique

Basically, this technique differs from the open technique only because the skin is sutured following laparotomy so that perfusion is done in a closed, watertight circuit (Fig. 10.2). Patient position varies during perfusion, which is achieved by tilting the surgical table into a Trendelenburg or anti-Trendelenburg position and then laterally in an attempt to promote uniform heat distribution. A larger volume of perfusate is generally needed to establish the circuit compared with during the open technique, and a higher abdominal pressure is achieved during perfusion that, as noted by Jacquet et al. [8], may facilitate drug penetration into tissue.

After hyperthermic perfusion, the abdomen is reopened and anastomoses, stoma, and drain placement are performed. The abdomen is then closed definitively in a standard manner. Otherwise, even when the closed technique is used, anastomoses and stoma are performed before abdominal wall closure. This way, there is no need to reopen the abdomen at the end of HIPEC, and catheters used for perfusion are used as drains during postoperative care.

The major advantage of the closed technique is the rapid achievement and constant maintenance of hyperthermia due to minimal heat loss. Moreover, exposure of OR personnel to aerosolized particles and contact with chemotherapeutic agents is minimized.

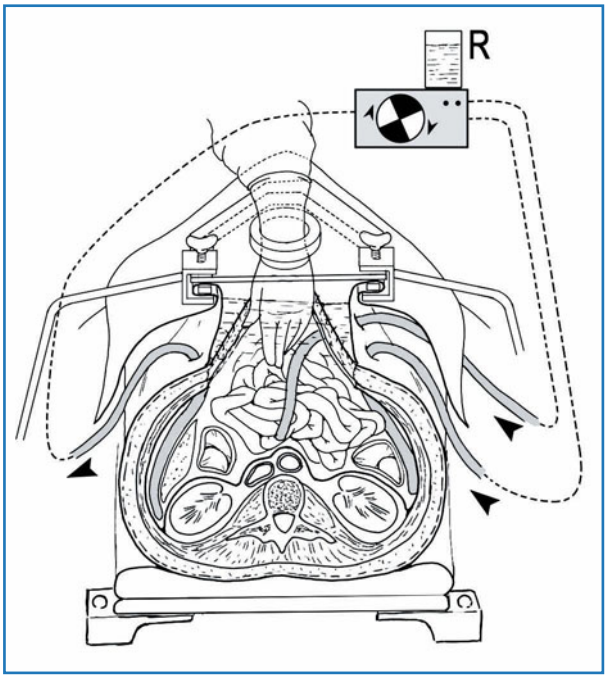

Fig. 10.2 Hyperthermic intraperitoneal chemotherapy (HIPEC): open technique. (Courtesy of Prof. Angelo Di Giorgio)

The lack of uniform distribution of the heated intraperitoneal chemotherapeutic agent is the main disadvantage of closed HIPEC. In fact, Elias et al. [7] reported an uneven distribution of methylene blue after its instillation during the procedure. Theoretically, inadequate circulation of heated intraperitoneal perfusate leads to pooling and accumulation of heat and the chemotherapeutic agent in the lower part of the body. This may result in increased systemic absorption and focal hyperthermic injury, which may prompt postoperative ileus, bowel perforation, and fistula [9]. However, no author has reported any complications that may have been caused by inadequate circulation [10].

10.4.4 Peritoneal Cavity Expander

A variation of the open HIPEC–described by Fujimura et al. and mainly used in Japan for treating or preventing gastric carcinomatosis–is the peritoneal cavity expander (PCE) technique (Fig. 10.3) [11]. The PCE is an acrylic cylinder containing inflow and outflow catheters that is secured over the wound. When filled with heated perfusate, the PCE can accommodate the small bowel, allowing the small intestine to float freely and be manually manipulated in the perfusate. The expander theoretically allows more uniform distribution com-

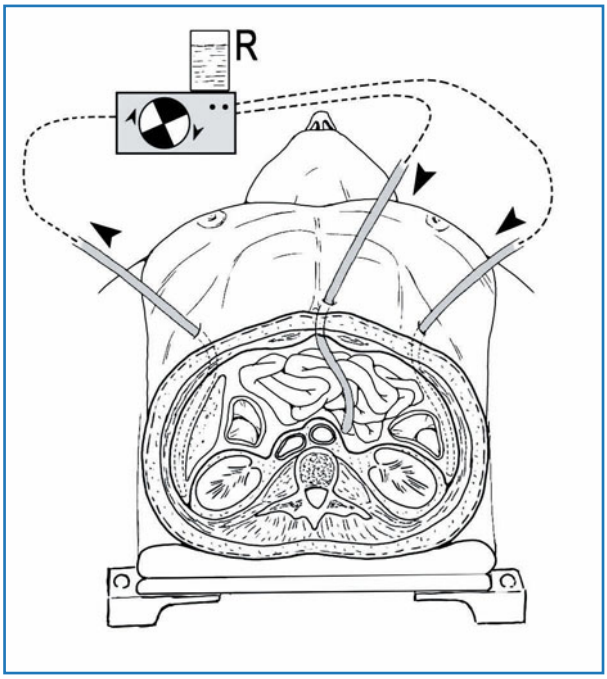

Fig. 10.3 Hyperthermic intraperitoneal chemotherapy (HIPEC): closed technique. (Courtesy of Prof. Angelo Di Giorgio)

pared with the closed technique. Its main disadvantage is the risk of OR personnel exposure to the chemotherapeutic agent, as occurs with the coliseum technique [10].

10.4.6 Semiopen (or Semiclosed) Abdominal Technique

To create a watertight environment, edges of the incision are tightly stapled with a soft abdominal cavity expander supported by a Thompson self-retaining retractor positioned over the abdomen. This permits the level of the liquid to rise above the level of the skin edges. Edges of the anterior-wall peritoneum are constantly exposed to the liquid. Large-amplitude movements become possible: the surgeon can introduce both forearms, even both arms, into the patient's abdomen without causing any liquid loss [12, 13].

10.5 Early Postoperative Intraperitoneal Chemotherapy

A second method of performing perioperative intraperitoneal chemotherapy is early postoperative intraperitoneal chemotherapy (EPIC). This approach is not favored by most surgical centers involved in treating carcinosis (Table 10.1).

Chemotherapeutic agent administration is started immediately after the operation and continued during the first 1–5 postoperative days [14]. The EPIC system is composed of a Tenckhoff catheter or a subcutaneous port placed through the abdominal wall in the approximate area at greatest risk of recurrence following cytoreductive surgery. Closed suction drains are placed in dependant areas in the pelvis and below each hemidiaphragm. EPIC has the advantages of administering multiple chemotherapy cycles and increased exposure of tumor cells to therapy, as the chemotherapeutic drug is not drained for at least 24 h. However, there is greater opportunity for significant systemic absorption and its resultant adverse effects, as the chemotherapeutic agents remains in the peritoneal cavity for such a long period. Using drugs with a high first-pass effect after portal absorption—such as 5-fluorouracil (5-FU), the most common drug used with this technique—partially overcomes this problem [7]. Moreover, other complications related to long-term catheters (infections, bowel obstruction) are reported: EPIC significantly increased the rate of postoperative complications in the large, multicentric retrospective study of 504 patients with colorectal carcinomatosis treated with cytoreductive surgery combined with perioperative intraperitoneal chemotherapy [15].

EPIC efficacy is limited by adhesion formation, which can cause pooling of the chemotherapeutic agent in limited parts of the abdomen, with consequent systemic toxicity; also, this treatment is not performed with hyperthermia. In fact, heat is cytotoxic in vitro at 42.5°C [16], and hyperthermia enhances the antitumor effect of agents such as oxaliplatin, mitomycin, doxorubicin, and cisplatin by augmenting cytotoxicity and increasing drug penetration into tissue [17–19]. Elias et al. compared two similar groups of patients with colorectal peritoneal carcinomatosis, one treated with EPIC using 5-FU and mitomycin C, and one treated with HIPEC using oxaliplatin at 43.8°C (43°C). Mortality, morbidity, peritoneal recurrence, and overall survival rate all favored the HIPEC group. In particular, peritoneal recurrence was reported as being doubled in EPIC group compared with the HIPEC group [20].

Thus, the only acceptable use of EPIC seems to be for treating microscopic residual peritoneal disease following HIPEC. An increased risk of postoperative complications must therefore be taken in account if this combined approach is chosen.

10.6 Drugs, Carrier Solutions, and Temperature

10.6.1 Drugs

When choosing a chemotherapeutic drug, some very important aspects must be considered. Whereas in instillation intraperitoneal chemotherapy all categories of active drugs can be used, in HIPEC procedures, a direct cytotoxic agent

(cell cycle nonspecific) is needed; the agent should lack severe direct local toxicity after intraperitoneal administration, have a well-established activity against the malignancy treated, have a heat-synergized cytotoxicity, and should not have to be metabolized systemically into its active form [21]. Intraperitoneally administered drugs inevitably have a variable, although usually limited, systemic absorption, which may, however, lead to toxicity.

Standardized drug dose and carrier-solution volume, assessed according to the patient's body surface area (BSA) (usually 1.5–2 L/m^2), are recommended in order to make exposure and toxicity predictable; drug dosage per liter of perfusate or per body weight usually prevents untoward events secondary to overdosing.

Different single-drug or combination regimens have been employed over the years, as shown in Table 10.1. A dose reduction of 33% should be considered for patients > 60 years, those previously exposed to multiple lines of systemic chemotherapy, those who require granulocyte-macrophage colony-stimulating-factor (GM-CSF) rescue for febrile neutropenia while on systemic chemotherapy, or those who have received radiation therapy to bone-marrow-bearing regions. Typically, centers that associate HIPEC and EPIC use moderate drug doses for HIPEC, whereas those that perform only HIPEC after cytoreductive surgery use much higher doses.

Elias et al. were the first to report using bidirectional HIPEC regimens (concurrent administration of intraperitoneal and IV chemotherapy). In particular, they administer 5-FU and folinic acid IV prior to performing HIPEC with oxaliplatin due to the instability of the mixture of both drugs [22]. The advantage of this strategy was demonstrated by Van der Speeten et al.: after IV administration of 5-FU in a patient undergoing intraperitoneal hyperthermia, the drug unexpectedly accumulated in the peritoneal cavity and in tumor nodules [23].

10.6.2 Carrier Solutions

Different carrier solutions with varying chemical properties have been investigated [24]: 1.5% dextrose isotonic peritoneal dialysis solution is the most commonly used in HIPEC centers rather than the regular crystalloid solutions (normal saline or 5% dextrose in water). Hetastarch (6% hydroxyethyl starch), a high-molecular-weight solution, is regularly employed as carrier for paclitaxel [25].

10.6.3 Temperature

Theoretically, what is the optimal temperature to use during HIPEC? The target range reported in the literature varies from 40° to 45.8°C; however, most

Table 10.1 Different drug regimens applied in different peritoneal surface malignancy centers. (Modified from [26])

Indication	HIPEC: dose/perfusion time	Concomitant IV therapy	EPIC	Center
Appendiceal and colorectal carcinomatosis	Mitomycin C, 15 mg/m^2 doxorubicin, 15 mg/m^2/90 min	5-FU, 400 mg/m^2; LV, 20 mg/m^2	5-FU 4 days	Washington Hospital Center, Washington, DC (USA)
	Oxaliplatin, 130 mg/m^2/60 min	5-FU, 400 mg/m^2; LV, 20 mg/m^2	5-FU 4 days	Washington Hospital Center, Washington, DC (USA)
	Oxaliplatin, 460 mg/m^2/30 min	5-FU, 400 mg/m^2; LV, 20 mg/m^2	No	Gustave Roussy Institute, Villejuif (France)
	Mitomycin C, 35 mg/m^2/60 min	No	No	National Cancer Institute, Amsterdam (The Netherlands)
	Mitomycin C, 3.3mg/m^2/L cisplatin, 25 mg/m^2/L/60 min	No	No	National Cancer Institute, Milan (Italy)
	Mitomycin C,10 mg/mL perfusate/60 minNo	No		Centre hospitalo-universitaire Lyon-sud, Lyon (France)
Gastric cancer	Cisplatin, 50 mg/m^2 doxorubicin, 15 mg/m^2/90 min	5-FU, 400 mg/m^2; LV, 20 mg/m^2	Taxol 4 days	Washington Hospital Center, Washington, DC (USA)
	Mitomycin C,10 mg/mL perfusate/60 min	No	No	Centre hospitalo-universitaire Lyon-sud, Lyon (France)
Peritoneal mesothelioma	Cisplatin, 50 mg/m^2 doxorubicin, 15 mg/m^2/90 min	5-FU, 400 mg/m^2; LV, 20 mg/m^2	Taxol 4 days	Washington Hospital Center, Washington, DC (USA)
	Cisplatin, 43 mg/L doxorubicin ,15.25 mg/mL/90 min	No	No	National Cancer Institute, Milan (Italy)
	Mitomycin C, 0.5 mg/kg cisplatin 0.7 mg/kg/60 min	No	No	Centre hospitalo-universitaire Lyon-sud, Lyon (France)

(*cont.*) →

Table 10.1 (*continued*)

Indication	HIPEC: dose/perfusion time	Concomitant IV therapy	EPIC	Center
	Cisplatin, 250 mg/m^2/90 min	No	5-FU Taxol 1 days	National Cancer Institute, Bethesda, MD (USA)
Adverse ovarian cancer	Cisplatin, 50 mg/m^2 doxorubicin, 15 mg/m^2/90 min	5-FU, 400 mg/m^2; LV, 20 mg/m^2	Taxol 4 days	Washington Hospital Center, Washington, DC (USA)
	Cisplatin, 43 mg/L doxorubicin,15.25 mg/mL/90 min	No	No	National Cancer Institute, Milan (Italy)
	Cisplatin, 20 mg/m^2/L/90 min	No	No	Centre hospitalo-universitaire Lyon-sud, Lyon (France)

HIPEC, hyperthermic intraperitoneal chemotherapy; *IV,* intravenous; *5-FU,* 5-fluorouracil; *LV*, leucovorin

authors agree that the desirable range at which to maintain intra-abdominal temperature is 41.5–43°C, which necessitates maintaining an inflow temperature of 46–48°C [26].

To establish the optimal temperature during perfusion, it is useful to consider several aspects, such as the interaction between heat and chemotherapeutic agents, method of temperature control, and risk of side effects. Usually, drug type does not constitute a problem, as all agents typically used for HIPEC are chemically stable at temperatures as high as 50.8°C.

Synergism between various cytotoxic drugs and hyperthermia starts at 39.8°C but is stronger at higher temperatures; according to in vitro studies on culture cells at 45.8°C, agent cytotoxicity is far more intense than at 41°C or 42.8°C; thus it is intuitively reasonable to use the highest level of hyperthermia, restricted only by clinical tolerance. The limiting factor of temperatures as high as 45.8°C is the tolerance level of the small bowel. Only one study addresses thermotolerance, and that study was performed using an animal model (rat). The authors concluded that 44.8°C for 30 min was the maximal, well-tolerated temperature [27].

10.7 Choosing HIPEC Delivery Mode

Each HIPEC perfusion technique has its advantages and disadvantages (Table 10.2). No formal prospective controlled comparison of delivery methods has been performed, and there is no evidence to establish the superiority of one method over the others regarding patient outcomes, morbidity, or safety to surgical staff. Thus, the following factors must be taken into account: (1) the perceived risk of environmental chemotherapy exposure (the real risk is negligible if proper safety measures are followed); (2) concerns regarding possible differences in uniform distribution of the chemotherapeutic agent or heat throughout the peritoneal cavity, which may result in visceral thermal injury; and (3) possible differences in dosage and perfusate volume inherent to the closed method.

Table 10.2 Choosing the hyperthermic intraperitoneal chemotherapy (HIPEC) procedure

Feature	Open	Closed	Semiopen
Uniform heat and chemotherapy distribution	√		√
Minor heat dissipation		√	
No direct contact of surgeon with chemotherapeutic agent		√	
Minimize risk of chemotherapeutic agent exposure to operating-room staff		√	√
Minimize risk of thermal injury	√		√
User friendliness		√	

10.8 Environmental/Surgical-staff Exposure

During HIPEC, a so-called major spill of chemotherapeutic agents (defined by the US Occupational Safety Health Administration as <5 g or 5 mL of undiluted cytotoxic agent) is impossible to imagine, as chemotherapeutic drugs are always diluted, and their doses are in micrograms. Nevertheless, the effects of prolonged, repeated occupational exposure to low doses of chemotherapeutic agents remain unknown. For this reason, all precautions and guidelines for chemotherapy handling should be observed (Box 10.1) [28].

There are two major routes of exposure to chemotherapeutic agents: direct contact, and inhalation of aerosolized or vaporized agent particles. Dermatitis or mucositis are the consequences of direct contact with skin or mucous membranes. Theoretically, systemic effects (bone marrow toxicity, gastrointestinal toxicity, hair loss, and so forth) may be produced by frequent exposure and absorption of low dose of such drugs, but such data are lacking in the literature [29].

Inhalation could occur if cytotoxic drugs vaporize due to the hyperthermia. Using a smoke evacuator under the plastic sheet during HIPEC administration with the coliseum technique, or using acrylic covers in semiopen methods, minimizes this risk. Studies by Stuart et al. and Schmid et al. [30, 31] evaluated personal safety during open HIPEC using the coliseum technique. The studies assessed the level of mitomycin C in urine of members of the operating team and in the air below and above the plastic sheet, and the permeability of sterile gloves commonly used in the operating room. No potential risk of

Box 10.1 Rules for safe administration of hyperthermic intraperitoneal chemotherapy (HIPEC). (Modified from [29])

- Use impervious, disposable drapes; no textile cloth in surgical fields
- Accurate lap-pad count should be obtained before HIPEC initiation
- Operating-room doors closed during HIPEC; signs placed outside the operating room advising that HIPEC is in progress
- Restrict personnel circulation
- Place absorbent towels on the floor around the surgical table in the event of spills
- Use disposable, impervious gown (closed front, long sleeves, closed cuffs)and shoe covers; eye protection (goggles); high-power filtration mask (FFP-3); double, powderless, latex gloving, outer ones elbow length; change of outer gloves should be made every 30 min
- Adequately ventilate the environment
- Use smoke evacuator continuously over surgical field (under plastic drape in coliseum technique)
- Use rigid, leak-proof containers labeled “cytotoxic agents” for every material or bodily fluid discarded during or after HIPEC and during the following 48 h

exposure was found, and all assessments were in compliance with safety standards [30, 31]. A Swedish study detected no platinum in urine or blood of the surgeon or perfusionist during HIPEC with oxaliplatin using the coliseum technique. These studies confirm that, even in the method with a higher chance of chemotherapy exposure for surgical staff, HIPEC is a safe procedure from the occupational risk standpoint when standard protective measures are observed [32].

References

1. Verwaal VJ, van Ruth S, de Bree E et al (2003) 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 21:3737–3743
2. Gonzalez-Moreno S (2006) Peritoneal surface oncology: A progress report. Eur J Surg Oncol 32:593–596
3. Szafnicki K, Narce C (2006) Towards a crippled-mode operation of an industrial wastewater treatment plant. Water Res 40:579–587
4. Elias DM, Ouellet JF (2000) Intraperitoneal chemohyperthermia: Rationale, technique, indications, and results. Surg Oncol Clin N Am 10:915–933
5. Glehen OMF, Gilly FN (2004) Peritoneal carcinomatosis from digestive tract cancer: New management by cytoreductive surgery and intraperitoneal chemohyperthermia. Lancet Oncol 5:219– 228
6. Sugarbaker PH (2005) Technical handbook for the integration of cytoreductive surgery and perioperative intraperitoneal chemotherapy into the surgical management of gastrointestinal and gynecologic malignancy, 4th ed. Grand Rapids, Michigan, Ludann Company
7. Elias D, Antoun S, Goharin A et al (2000) Research on the best chemohyperthermia technique of treatment of peritoneal carcinomatosis after complete resection. Int J Surg Investig 1:431–439
8. Jacquet P, Averbach A, Stephens AD et al (1998) Heated intraoperative intraperitoneal mitomycin C and early postoperative intraperitoneal 5-fluorouracil: Pharmacokinetic studies. Oncology 55:130–138
9. Stephens AD, Alderman R, Chang D et al (1999) Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. Ann Surg Oncol 16:790–796
10. Glehen O, Cotte E, Kusamura S et al (2008) Hyperthermic intraperitoneal chemotherapy: nomenclature and modalities of perfusion. J Surg Oncol 98:242-246
11. Fujimura T, Yonemura Y, Fushida S et al (1990) Continuous hyperthermic peritoneal perfusion for the treatment of peritoneal dissemination in gastric cancers and subsequent second-look operation. Cancer 65:65–71
12. Rat P, Benoit L, Cheynel N et al (2001) Intraperitoneal chemohyperthermia with overflow open abdomen. Ann Chir 126:669–671
13. Sugarbaker PH (2005) An instrument to provide containment of intraoperative intraperitoneal chemotherapy with optimized distribution. J Surg Oncol 92:142–146
14. Esquivel J, Vidal-Jove J, Steves MA et al (1993) Morbidity and mortality of cytoreductive surgery and intraperitoneal chemotherapy. Surgery 113:631–636
15. Glehen OKF, Sugarbaker PH, Elias D et al (2004) Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: A multi-institutional study. J Clin Oncol 22:3284–3292
16. Crile G Jr (1963) The effects of heat and radiation on cancers implanted on the feet of mice. Cancer Res 23:372–380

17. Elias D, Ouellet JF (2000) Intraperitoneal chemohyperthermia: Rationale, technique, indications, and results. Surg Oncol Clin N Am 10:915–933
18. Glehen OMF, Gilly FN (2004) Peritoneal carcinomatosis from digestive tract cancer: New management by cytoreductive surgery and intraperitoneal chemohyperthermia. Lancet Oncol 5:219–228
19. Sugarbaker PH (1998) Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis. Semin Surg Oncol 14:254–261
20. Elias D, Benizri E, Di Pietrantonio D et al (2007) Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. Ann Surg Oncol 14:509–514
21. de Bree E, Tsiftsis DD (2007) Principles of perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis. Recent Results Cancer Res 169:39-51
22. Elias DM, Bonnay M, Puizillou et al (2002) Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol 13:267-272
23. Van der Speeten K, Stuart OA, Sugarbaker PH (2009) Pharmacokinetics and pharmacodynamics of perioperative cancer chemotherapy in peritoneal surface malignancy. Cancer J 15:216-224
24. Mohamed F, Sugarbaker PH (2003) Carrier solutions for intraperitoneal chemotherapy. Surg Oncol Clin N Am 12:813-824
25. Mohamed F, Sugarbaker PH (2003) Intraperitoneal taxanes. Surg Oncol Clin N Am 12:825-833
26. Kusamura S, Elias DM, Baratti D et al (2008) Drugs, Carrier Solutions and Temperature in Hyperthermic Intraperitoneal Chemotherapy. J Surg Oncol 98:247–252
27. Shimizu T, Maeta M, Koga S (1991) Influence of local hyperthermia on the healing of small intestinal anastomoses in the rat. Br J Surg 78:57–59
28. Yodaiken RE, Bennett D (1986) OSHA work practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. Occupational Safety and Health Administration. Am J Hosp Pharm 43:1193–1204
29. González-Moreno S, González-Bayón L, Ortega-Pérez G (2012), Hyperthermic Intraperitoneal Chemotherapy Methodology and Safety Considerations. Surg Oncol Clin N Am 21:543–557
30. Stuart OA, Stephens AD, Welch L et al (2002) Safety monitoring of the coliseum technique for heated intraoperative intraperitoneal chemotherapy with mitomycin C. Ann Surg Oncol 9:186–191
31. Schmid K, Boettcher MI, Pelz JO et al(2006) Investigations on safety of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with mitomycin C. Eur J Surg Oncol 32:1222–1225
32. Na¨slund Andre´asson S, Anundi H, Tho´ren SB et al (2010) Is platinum present in the blood and urine from treatment givers during hyperthermic intraperitoneal chemotherapy? J Oncol 2010:649–719