

## Safety considerations for operating room personnel during hyperthermic intraoperative intraperitoneal chemotherapy perfusion

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### Abstract

The new treatment strategy for Peritoneal Surface Malignancy combines a cytoreductive surgery and perioperative intraperitoneal chemotherapy. Cytoreduction removes all macroscopic tumor. Intraperitoneal chemotherapy avoids implantation of microscopic residual tumor cells on intra-abdominal surfaces when it is administered intraoperatively and/or early in the postoperative period. Delivering cytotoxic drugs directly into the peritoneal cavity maximizes dose intensity and minimizes systemic toxicity. Hyperthermia is selectively cytotoxic for malignant cells and potentiates the effect of chemotherapy.

Implementation of this procedure makes the perioperative personnel to face a risk of exposure to cytotoxic agents. Furthermore, peritonectomies and electro-evaporation of tumor nodules are performed with high voltage electrocautery, generating a large amount of surgical smoke during several hours. Inhalation of these fumes may be also a risk for healthcare workers.

In this article, we analyse in depth these new risks of the operating room personnel, we review the literature, and we give guidelines for secure performance of cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy, as well as for early postoperative intraperitoneal chemotherapy administration.

These new procedures are safe techniques for patients and healthcare workers provided adequate policies are adopted to avoid occupational exposure.

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### Introduction

Many patients with Peritoneal Surface Malignancy (PSM) have criteria of loco-regional disease, without systemic dissemination. Consequently, a curative approach based on a dose intensification treatment in the abdominal cavity is rational. This new strategy combines maximal cytoreductive surgery (by peritonectomies, visceral resections and electro-evaporation of small tumor nodules) for the macroscopic disease and regional perioperative chemotherapy (hyperthermic intraoperative intraperitoneal chemotherapy – HIIC, with or without early postoperative

intraperitoneal chemotherapy – EPIC) for the microscopic residual disease. Several phase II and phase III studies on the treatment of PSM using this combined strategy<sup>1–5</sup> have shown a long-term survival in about 25% of the patients.

This innovative treatment strategy introduces cytotoxic drugs at the operating room for performing an intraperitoneal perfusion of hyperthermic chemotherapy during the operation. Cytotoxic agents are not commonly used by the operating room personnel. In addition, the way of administration, directly into the abdominal cavity; the time of applying, during the operation or immediately after; and the use of chemotherapy with hyperthermia (42–43°C), to maximize toxicity on tumor cells, are not the usual form of management of chemotherapy. All these novelties demand a new technology that has to be introduced into the operating room. Similarly, EPIC is administered in the Intensive Care Unit and the surgical ward where chemotherapy is not frequently used.

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Healthcare workers involved in these new procedures have to face new risks of exposure to cytotoxic drugs. They must be fully informed, suitably educated and properly trained in order to perform cytoreduction, HIIC and EPIC safely.

### Education as a safety factor

Operating room personnel is familiar to occupational hazards such as exposure to infectious diseases (HBV, HCV, HIV, TBC, ...), exposure to ethylene oxide remains, inhalation of anesthetic gases, use of X rays, etc. Safety regulations adopted have made safe their work. Similarly, institutions implementing treatments based on cytoreduction and perioperative intraperitoneal chemotherapy must elaborate and write down specific guidelines for safe administration of cytotoxic drugs based on established regulations from acknowledged National Health Work.<sup>6</sup>

Introduction of cytotoxic agents inside the operating room demands complete information to all personnel involved in HIIC: nurses, ancillary staffs, assistants, anesthesiologists, surgeons, residents, etc. The educational program will cover the surgical technique, intraperitoneal chemotherapy perfusion, cytotoxic agents used, effects of hyperthermia on the drugs and on the patient, and indications, rationale and results of the procedure. Particular consideration deserves the routes of exposure and risks of low-dose occupational exposure to cytotoxic agents. Finally, the personnel should be trained on how to avoid these exposure hazards during administration of HIIC, and how to perform a safe procedure. We should not forget that, when we perform EPIC, some other personnel at the Intensive Care Unit and at the surgical ward will be involved in the administration of intraperitoneal chemotherapy. The staff of these units should be included in the educational program.

The cumulative effects of long-term, low-dose exposure to cytotoxic agents are unknown, but institutional policies must protect patients and their healthcare workers from occupational exposures adopting conservative policies.

*Cytotoxic agents:* Clinical research protocols are designed to study toxicities of therapeutic dosages. Long-term effects of prolonged, repeated occupational exposure to low doses are not known.

The drugs usually used in HIIC are mytomicin C, cisplatin and doxorubicin; lately new drugs like, oxaliplatin<sup>1</sup> and irinotecan<sup>7</sup> have been introduced with good results. They are drugs cell-cycle independent that show a pharmacokinetic advantageous profile when directly delivered in peritoneal cavity as compared with their intravenous administration, and whose effects are amplified by heat.

*Routes of exposure* to chemotherapy during HIIC may be direct contact, inhalation of aerosols or vapors, accidental injection and ingestion.<sup>8,9</sup> Direct contact of cytotoxic agent with skin or mucous membranes produces irritation or dermatitis. Inhalations of aerosols happen mainly during dose preparation at the Pharmacy Department. Particulate material, solid or liquid, remains in the air, and it could be

inhaled. Other possibility should be vaporization of cytotoxic drugs because of hyperthermia. Studies in vitro by Connor et al.<sup>10</sup> on mytomicin C, doxorubicin, cisplatin and 5FU concluded that they were not detected as vapors with temperatures of 23–37°C. Stuart et al.<sup>21</sup> did not find environmental contamination during HIIC administration using open technique with mytomicin C at 43°C. The use of the smoke evacuator under the plastic sheet during the perfusion minimizes this route of exposure. Accidental injection of drug during HIIC is not common, and it should be by puncture or cut with a contaminated needle or knife. The chance of oral route exposure is even more remote but could possibly happen by ingestion of contaminated food or drinks from operating room waste.

*The perfusion circuit:* A roller pump for the inflow line and another roller pump for the outflow line are used. The inflow line goes through a heat exchanger in order to heat the chemotherapy solution for an infusion temperature of about 45°C (Fig. 1). The outflow line goes to a reservoir, where the chemotherapy solution is initially poured or can be collected, should a problem during the perfusion occur in the abdomen. The circuit has three or four outflow ports exiting the abdomen which meet at the outflow line, and the inflow line uses only one through a Tenckhoff catheter. The surgeon will build the circuit and the perfusionist (or an ad hoc trained nurse, or surgical resident) will handle the heater and pumps to obtain the desired flow, temperature and perfusate level into the abdomen. Another new machine at the operating room is the smoke evacuator that holds an important role in this procedure by suctioning



Fig. 1. Operating room during HIIC.

the smoke generated from electrosurgical cytoreduction and minimizing risk of aerosol exposure during HIIC.

*Hyperthermia* increases cytotoxicity<sup>11</sup> of chemotherapy in several ways: increases drug penetration, increases cell membrane permeability, and improves cell membrane transport<sup>12</sup>; it also alters cellular metabolism, changes drug pharmacokinetic and excretion, inhibits repair mechanisms, increases drug action and overcomes drug resistance.<sup>13</sup> There is experimental and clinical evidence to indicate that malignant cells are selectively destroyed by hyperthermia in the range of 41–43°C.<sup>14</sup>

### Electrocautery and surgical smoke

Cytoreductive surgery is achieved by peritonectomies of the parietal peritoneum, multiple visceral resections and electro-evaporation of tumor nodules on peritoneal surface (mesentery, Glisson capsule, small bowel wall, ...).<sup>15</sup> This surgical procedure is performed with electrocautery on pure cut, high voltage, with an extended insulated shaft of 10–15 cm, and a 3 mm ball tip,<sup>16</sup> producing a large amount of surgical smoke. The procedure may take from 8 to 12 h, making prolonged exposure to surgical smoke.

Inhalation of these fumes may be a risk for healthcare workers.<sup>17</sup> Surgical smoke is composed of a 95% of water steam and a 5% of organic and inorganic compounds, particulate material and microorganisms.<sup>18</sup> Organic compounds in the surgical smoke include benzene, toluene, formaldehyde, cyanine hydroxide and aromatic hydrocarbons. Inorganic compounds are those of combustion (CO, CO<sub>2</sub>, NO<sub>2</sub> and SO<sub>2</sub>). The particles of the surgical smoke are of 0.01–200 microns in size. The microorganisms can be bacteria, mycobacteria, fungus and virus. Surgical smoke may produce headache, eye irritation and respiratory tract irritation, but there is no evidence of mutagenicity. Moreover, it may cause problems for visualization of the surgical field for the surgeon and bad smell.

Investigations done by the Safety Work Agencies in Europe and the United States have shown that it is possible to control air contamination from the electrocautery by good ventilation of the operating room and by using all the time a laser smoke evacuator.<sup>19</sup>

*To maintain a good quality of air at the operating room* air conditioning should be working all the time during the surgical procedure, producing a slightly higher pressure in relation to the surrounding area. Air inflow volume should be 15% higher than the outflow, with 15–20 air renewals per hour; air speed must be lesser than 0.3 m/s. Filters of the air conditioned should be high efficiency particulate air (HEPA filters) and should be verified once a month for contamination. Doors should be closed during the operation with hermetic closures. Temperature should be 18–26°C and air humidity 45–60%.<sup>18</sup>

*The smoke evacuator* device must have a suction unit, a filter which should be an absorbent HEPA filter, and a tube for smoke conduction with a rigid end. Recommended

suction speed is 100–150 feet per minute at the beginning of the tube. The tip of the smoke evacuator should be kept about 5 cm from the origin of the smoke to catch all contaminating vapors. Suction must work always while the smoke is being produced. Filters have an indicator of fullness, and they should be changed frequently. At the end of the procedure, filter, tube and absorption system must be disposed as biological hazardous material.<sup>20</sup>

*High power filtration mask* with a good fit to nose and mouth should be worn by personnel at the operating room during cytoreduction and HIIC. These “health care respirators” offer high filtration of sub-micron particles and protect against concentrations of solid and non-volatile liquid particles. They do not protect against gases or vapors.

*Eye protection* should be worn as a mechanical barrier for the smoke, cytostatic agents and bodily fluid exposure, as part of a universal precaution protocol.

### Perioperative intraperitoneal chemotherapy

*Handling the cytotoxic solutions:* The chemotherapy solution is prepared in the Pharmacy Department, and is sent to the operating room in a closed light-protected bag which is handled with gloves checking integrity of the bag. Any leak detected makes the bag to be returned to the Pharmacy Department. If the bag is approved, there is no risk of direct exposure, and it is given to the person responsible for the perfusion.

*Risk during HIIC administration:* There are three methods for intraperitoneal administration of hyperthermic chemotherapy: open abdomen technique, closed abdomen technique and use of peritoneal expander devices, each of which poses risks to the operating team.

*The Open method:* Once cytoreduction has been completed, an inflow catheter and closed suction drains are placed through the abdominal wall and made watertight with a purse string suture at the skin. Temperature probes are secured to the skin edge. The skin of the abdominal incision is suspended to a self-retaining retractor by a running suture to create an open space in the abdominal cavity.

The open technique may increase exposure of operating room personnel to chemotherapy by route of direct contact and inhalation. Stuart et al.<sup>21</sup> evaluated the safety of operating room personnel during the open technique. All assessments of potential exposures (urine from members of the operating team, air in the operating room and permeability of sterile gloves used during the procedure) were found to be negative.

*In the closed technique* catheters and temperature probes are placed in the same fashion, but the skin edges are sutured watertight, so that perfusion is done in a closed circuit. The closed technique offers minimal contact or inhalation exposure of the operating room staff to the chemotherapy. The only way for exposure should be leakage

through the surgical wound or catheter wounds. HIIC by closed technique can be performed safely as it has been reported in several articles.<sup>22,23</sup> Heterogeneous distribution inside the closed abdomen may increase the rate of intra-abdominal complications.

*Peritoneal cavity expander technique (PCE):* 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 intestine, allowing it to float freely and be manually manipulated in the solution.<sup>24</sup> After HIIC is completed, the solution is drained, and the PCE is removed. The PCE technique presents the same risks of exposure to chemotherapy of the operating room personnel as in the open technique.<sup>25</sup> Fujimura et al. reported about PCE-HIIC use in carcinoma-tosis from various malignancies with good results. Yonemura et al. reported the use of the PCE-HIIC technique for prophylaxis against recurrence of gastric cancer following resection with 5-year survival of 55%, but only a 30% in surgery-only controls.<sup>26</sup> Although there are no studies directly comparing PCE to the open technique, the reported results appear to be similar.

*Risk during EPIC administration:* At the end of HIIC, catheters are left in place as regular surgical drains if postoperative intraperitoneal chemotherapy is planned. Immediate postoperative abdominal lavage is indicated, to avoid fibrin deposits that can modify the uniform distribution of chemotherapy. In the first postoperative day, intraperitoneal perfusion of chemotherapy is infused by the Tenckhoff catheter with drains closed, leaving the cytotoxic agent inside the abdomen for 23 h; the hour 24th is for drainage of chemotherapy solution. This is repeated for 5 consecutive days.

It is a closed abdomen normothermic perfusion, which has only an exposure way by leakage from the surgical wound or drains.

### **Personnel selection for cytoreduction and perioperative chemotherapy**

Implementation of a Program of Treatment of Peritoneal Surface Malignancy makes the perioperative personnel to face a risk of exposure to cytotoxic agents and surgical smoke. Though cumulative effects of long-term, low-dose occupational exposure to cytotoxic agents have not been reported, institutional policies must be elaborated to protect patients and healthcare workers.

Participation in this procedure requires a personnel selection to avoid association with developing health problems in the future. Limiting criteria to participate would include pregnant or nursing women, history of abortions, congenital malformations or teratogenic disease; individuals actively pursuing pregnancy (women or men), hematological or malignant disease history, previous chemotherapy or radiotherapy treatments, usual work

with X rays or radiation therapy, known immunosuppression, allergy to cytotoxic drugs or latex or severe dermatologic disease.

A routine medical surveillance should be established for strengthening the safety of the procedure. A health check up every 6 months collecting the information on exposure frequency to the procedure, incidents (spillage, skin contact, ...) during HIIC or EPIC; symptoms in skin, mucous, gastrointestinals or hair loss; complete blood cell counts and follow up. Analysis of records of healthcare workers participating in HIIC and EPIC will be useful for evaluating the safety of the Program.

### **Guidelines for safe administration of HIIC**

At the beginning of the operation, *the surgical field* should be arranged with impervious, disposable sheets and drapes, avoiding the use of any non-disposable fabric cloth.

*Restriction of personnel inside the operating room:* All personnel not actually involved in the administration of HIIC should leave the operating theater during the administration of chemotherapy.

*Doors of the operating room should be closed* and signs advising that HIIC is in progress must be placed at the entrance of the dedicated surgical area.

*Absorbent towels* with impervious back are placed on the floor, all around the surgical table, for possible spills.

*Rigid containers*, leakproof for biologically hazardous material labeled properly with "cytotoxic agent" labels are placed in the operating room. They should not be full more than a half. Chemotherapy contaminated material should be handled as little as possible and with minimal agitation to prevent dissemination into the environment.

*Protective barrier garments* should be worn for all procedures involving preparation, use and disposal of cytotoxic drugs. At the operating room, during HIIC, all personnel should wear protective disposable impervious gown and shoe covers, eye wear for possible droplet protection (Fig. 2). At the surgical field, staff should wear non-permeable powder less latex gloves as double gloves. Potentially contaminated garments must not be worn outside the work area.

*The protective disposable, impervious gown* should have a closed front, long sleeves and closed cuffs, which must be tucked under the gloves. *Eye wear* is recommended for possible droplet protection. *Latex gloves* are recommended for all procedures involving cytotoxic drugs. They should be used non-permeable, powder less and worn as double gloves for direct contact with chemotherapy.<sup>21</sup> Surgeons in direct contact with chemotherapy should wear the outer glove up to the elbow. Gloves should be routinely changed approximately every 30 min when working steadily with cytotoxic agents and immediately changed after overt contamination. Double gloving is recommended for cleaning up of spills.



Fig. 2. Barrier garments.

*High power filtration mask* (high filtration of sub-micron particles) tight fits to the face is recommended.

*Universal Precautions* for handling biological hazardous materials are implemented and monitored continuously. They include protective barrier garments described related with the route of exposure. Any body fluid, blood sample, tissue specimen, laparotomy pads, drapes, gowns, plastic tubing, must be handled as biological hazardous material. Body fluids are considered contaminated for 48 h after last administration of chemotherapy. *Labels* reading “cytotoxic agent” should be used to mark every sample, specimen, or contaminated trash.

*Smoke evacuator* should be working continuously under the plastic sheet during the perfusion.

*Spills:* Every effort should be done to avoid any spill, but if it happens, the circulating nurse should contain and clean it up immediately. If direct contact with cytotoxic agent occurs, contaminated clothing should be removed immediately and discard it in hazardous waste container. Affected skin should be washed immediately with mild, additive-free soap without dyes or perfumes that may interact with the cytotoxic agent. If the affected area is the eye, it should be flooded immediately with water or isotonic saline for 5 min. The staff member should then report the incident to the occupational health office.

Following OSHA definitions,<sup>8</sup> a *small spill* is a spill lesser than 5 g or 5 ml of undiluted cytotoxic agent. It should be blot dry using absorbent pads and wiped. The area should be washed three times with water and neutral soap. Then, the area can be cleaned in the routine manner. To clean up a small spill, the personnel should wear the whole protective barrier garments already described. A *large spill* is defined as a drop of more than 5 g or 5 ml of pure drug. Personnel containing the spill should wear respirator mask and standard protective clothing. They should take care to avoid creating aerosols when cleaning large spills.

During HIIC and EPIC, chemotherapy is always diluted, never pure, and doses of drugs are in micrograms, so that it is not possible to have major spills.

*Cleaning up the operating room after HIIC:* Personnel should wear the standard protective clothing described. Bactericidal cleaning solutions should not be used to wash contaminated area because they may react with the cytotoxic agents and do not inactivate them. Water with neutral soap is adequate to make the cleaning up of the operating room after HIIC, three consecutive times. Seventy percent isopropilic alcohol is also safe and effective. *Instrument trays* are labeled with “cytotoxic agent” markers. They should be washed three times with water and pure soap before leaving the working area.

### Guidelines for safe administration of EPIC

Drains and inflow catheter are left in place once the procedure is finished. Immediate postoperative abdominal lavage is indicated. If the patient progress satisfactorily on the day after the operation, EPIC is administered at the UVI or at the surgical ward. Patient should be located in a single room with advising signs on the door about chemotherapy administration. The route of exposure is direct contact to the skin or mucous membranes. Use of standard protective universal precautions (eye protection, gown, gloves, ...) should be adequate to avoid any risk. Personnel should wear latex gloves for handling chemotherapy for infusion and drainage. Any spill by the surgical wound or catheter ports should be immediately contained, cleaned up and resolved with a watertight reinforcement suture.

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