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## Early and long-term postoperative management following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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### Abstract

Peritoneal surface malignancies have been traditionally regarded as end-stage conditions amenable to merely palliative options. The combination of aggressive cytoreductive surgery (CRS), involving peritonectomy procedures and multivisceral resections, with intra-operative hyperthermic intra-peritoneal chemotherapy (HIPEC) and/or early postoperative intra-peritoneal chemotherapy (EPIC) to treat the microscopic residual tumor is a new concept. In recent years, promising results have been reported for peritoneal mesothelioma and carcinomatosis of gastrointestinal and gynaecologic origin treated by this combined protocol. However, CRS with HIPEC and/or EPIC is a complex procedure associated with high rates of potentially life-threatening complications. Furthermore, disease progression following comprehensive treatment is not uncommon and represents a relevant cause of treatment failure. The present paper reviews the available information on early postoperative management and long-term follow-up in patients treated with CRS and intraperitoneal chemotherapy. The peculiar clinical and biological alterations that can be expected during

an uncomplicated postoperative course, as compared to standard digestive surgery, are discussed. Early recognition and appropriate management of the most common adverse events are addressed, in order to minimize the impact of treatment-related morbidity on survival and quality of life results. Since re-operative surgery with additional HIPEC, has proven to be useful in selected patients with recurrent disease, long-term surveillance aiming at early detection of postoperative disease progression has become a relevant issue. Current results on follow-up investigations are presented.

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**Key words:** Peritoneal surface malignancies; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Hyperthermic intra-peritoneal chemotherapy; Follow-up

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### INTRODUCTION

Peritoneal surface malignancies (PSM), both primary or metastatic, have been traditionally regarded as end-stage conditions managed merely by palliative options. During the last three decades, better knowledge of their natural history, innovative surgical procedures and technical advances in loco-regional delivering of chemotherapy have resulted in a new treatment strategy and in a change

of perspective from simple palliation to possible cure<sup>[1]</sup>.

The first experience with hyperthermic intraperitoneal chemotherapy was reported by Spratt *et al*<sup>[2]</sup> in 1980. Aggressive cytoreductive surgery (CRS), involving peritonectomy procedures and multivisceral resections to remove all the visible peritoneal disease, combined with intra-operative hyperthermic intra-peritoneal chemotherapy (HIPEC) and/or early postoperative intra-peritoneal chemotherapy (EPIC) to treat the microscopic residual tumor is a new concept that was developed and greatly popularized by Sugarbaker<sup>[3]</sup>.

In recent years, the treatment of PSM with CRS and perioperative intra-peritoneal chemotherapy (PIC) has gained great popularity. According to several phase II studies, promising survival results have been reported for peritoneal mesothelioma, pseudomyxoma peritonei and peritoneal carcinomatosis from ovarian cancers<sup>[4-6]</sup>. Although the majority of pseudomyxoma peritonei are minimally aggressive, a long-term survival of only 20%-30% was achieved with conventional treatments, namely serial debulking surgery and palliative chemotherapy. In prospective case-series treated by cytoreductive surgery and PIC, 5-year survival rates vary now from 52% to 96% and median survival from 51 mo to 156 mo<sup>[4]</sup>. Median survival rates for peritoneal mesothelioma have dramatically improved from about 12 mo to 34-92 mo with the advent of the local-regional treatment approach<sup>[6]</sup>. With systemic chemotherapy, median survival is 29 mo for patients with platinum-sensitive recurrent ovarian cancer and 17 mo for those with platinum-resistant disease. In contrast, median survival of up to 54 mo has been reported in trials on cytoreductive surgery and PIC, although most of them included a large proportion of patients with recurrent disease<sup>[7]</sup>.

A phase III study has confirmed the efficacy of CRS and HIPEC in the treatment of carcinomatosis from colorectal cancer<sup>[8]</sup>. Median survival was 23 mo with the combined approach and 12.6 mo with standard treatment; i.e. systemic chemotherapy and palliative surgery ( $P = 0.0032$ ). In a recent retrospective controlled study, median survival was 23.9 mo with systemic chemotherapy and an unprecedented 62.7 mo for patients undergoing optimal cytoreduction and HIPEC ( $P < 0.05$ )<sup>[9]</sup>.

CRS with PIC is a complex procedure involving extensive stripping of the peritoneal surface, multiple visceral resections, up to 4-5 bowel anastomoses and high-dose chemotherapy under hyperthermic conditions. An operative time of 10-14 h is the rule. High rates of potentially life-threatening complications have been reported by all the centres managing these patients<sup>[10-15]</sup>. In this context, an appropriate postoperative management with early recognition and successful resolution of adverse events is needed to minimize treatment-related mortality and to maximize survival and quality of life results.

Furthermore, disease progression following comprehensive treatment is not uncommon and still represents a relevant cause of mortality. Re-operative surgery, possibly with additional HIPEC, has proven to be useful for selected patients with recurrent PSM<sup>[16-18]</sup>. Therefore, careful

follow-up and prompt diagnosis of disease progression may contribute to maximizing the clinical outcome.

The present paper reviews the available literature on early postoperative management and long-term follow-up in patients with PSM treated with CRS and PIC.

## UNCOMPLICATED POSTOPERATIVE COURSE

Following CRS and PIC, a postoperative course can be considered uneventful in a substantial number of patients. In these cases, however, several clinical and biological parameters do not follow the usual pattern as standard digestive surgery and many postoperative disturbances should be considered as physiological rather than pathological.

The “natural history” of uncomplicated CRS followed by PIC was described by Elias *et al*<sup>[19]</sup> in 32 patients having an uneventful postoperative course and leaving hospital within the 15th postoperative day.

Eighteen patients were women and 14 were men with a mean age of 49.3 years (range 24-62). The origin of the peritoneal carcinomatosis was colorectal in 15 cases, appendiceal in 10, peritoneal mesothelioma in 5, and miscellaneous lesions in 2. All the patients underwent complete CRS with no visible remaining peritoneal tumour and open-abdomen HIPEC with various drugs, including cisplatin + mitomycin-C, oxaliplatin ± irinotecan + intravenous 5-fluorouracil (5-FU) and leucovorin. The mean duration of the procedure was 354 min (range 140-720 min) and the mean blood loss was 497 mL (range 0-1460 mL).

The temperature was close to 38°C during the first 10 postoperative days, in absence of sepsis, due to the high-inflammatory syndrome following HIPEC. This was underlined by the evolution of the fibrinogen level in 2 phases: initially low, owing to the immediate postoperative hypocoagulability state, and then, a gradual and marked increase. This inflammatory syndrome, with no documented infection, was associated with digestive hypersecretion.

Pain, evaluated on a visual analogue scale from 1 to 10, was close to 4 from day 1 to day 4, and then decreased notably. Daily diuresis was stable at 2000-2500 mL/d and no sign of renal failure was observed.

The daily amount of fluid collected by drains decreased progressively from 450 to 50 mL/d from the 1st to the 7th postoperative day and drains were removed before day 9. In contrast, the daily fluid output of the nasogastric tube was close to 1000 mL/24 h until day 6. Removing this tube earlier could have resulted in vomiting and inhalation of digestive secretion in the lungs. Resumption of digestive transit occurred between day 4 and day 6 in 20 of 32 (63%) patients. This happened earlier in 5 patients. Accordingly, the authors recommend removal of the nasogastric tube when the flow rate has declined markedly, and the resumption of the digestive transit has occurred. In 63% of the patients, transitory diarrhoea occurred between day 4 and day 6. The median number of stools was 6/d between day 4 and day 14, without positive stool cultures.

**Table 1** Morbidity and mortality rates after cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy

Authors, yr	Patients (n)	PSM	Death (%)	Overall morbid (%)	Major morbid	Most common complications		
						1st	2nd	3rd
Jacquet <i>et al</i> <sup>[21]</sup> , 1996	60		5	-	35			
Stephens <i>et al</i> <sup>[10]</sup> , 1999	200	Mixed	1.5	-	27	Peripancreatic	Bowel perf/anast leak	Bleeding
Glehen <i>et al</i> <sup>[11]</sup> , 2003	216	Mixed	3.2	30.5	23.6	Bowel perf/anast leak	Haematol	Prolonged ileus
Kusamura <i>et al</i> <sup>[14]</sup> , 2006	209	Mixed	0.9	-	12	Bowel perf/anast leak	Bleeding	Sepsis
Smeenck <i>et al</i> <sup>[12]</sup> , 2006	103	PMP	11	54	54	Infection	Bowel perf/anast leak	Cardiopulm
Gusani <i>et al</i> <sup>[15]</sup> , 2008	124	Mixed	1.6	56.5	29.8	Reoperation	Bowel perf/anast leak	Sepsis
Sugarbaker <i>et al</i> <sup>[23]</sup> , 2006	356	PMP	2.0	74.2	40.2	Haematol	Gastroint	Cardiovasc
Yan <i>et al</i> <sup>[24]</sup> , 2007	70	PM	3.0	41	14	Bleeding	Resp failure	Bowel perf/anast leak
Elias <i>et al</i> <sup>[13]</sup> , 2007	106	Mixed	4	-	66	Bowel perf/anast leak	Lung infection	Haematol
Levine <i>et al</i> <sup>[26]</sup> , 2007	501	Mixed	4.3	43.1	-	-	-	-
Verwaal <i>et al</i> <sup>[22]</sup> , 2004	102	CRC	7.8	65	35	Bowel perf/anast leak	Infection	Haematol
Feldman <i>et al</i> <sup>[27]</sup> , 2003	49	PM	0	38	-	Hepatic	Renal	Haematol
Stewart <i>et al</i> <sup>[28]</sup> , 2006	110	PMP	6	38	-	Wound infection	Haematol	Resp failure

PSM: Peritoneal surface malignancy; PMP: Pseudomyxoma peritonei; PM: Peritoneal mesothelioma; CRC: Colorectal cancer carcinomatosis; perf: Perforation; anast: Anastomoses.

At days 2 and 3, transient severe hypo-phosphoremia was observed, which was impossible to normalise despite a daily administration of phosphorus (4 g/24 h). Early hypo-phosphoremia was due to renal tubulopathy related to hyperthermia. It induces decreased diaphragm motility leading to lung atelectasis and increased insulin requirements.

Concerning blood counts, haemoglobin remained stable and above 10 g/L in uncomplicated cases. Leukocyte counts progressively decreased until the 12th postoperative day, from 12000/mm<sup>3</sup> to 5000/mm<sup>3</sup>. Platelet counts decreased from 200000 at day 1 to 120000/mm<sup>3</sup>-150000/mm<sup>3</sup> at days 3 and 4 before progressively increasing until day 15, even though 50% of the patients underwent a splenectomy. Haematopoietic growth factors were not used.

Hepatic tests showed early but moderate cytolysis without cholestasis. Transaminases increased 2- to 3-fold during the first 4 postoperative days, probably due to extensive electrocoagulation of the liver capsule.

## POSTOPERATIVE COMPLICATIONS

A large number of studies on adverse events following CRS and PIC are included in the literature. The main studies on postoperative complications are summarized in Table 1. They can be categorized as follows: (1) series focusing on complications regarding a specific PSM; (2) series focusing on complications in all-type PSM; (3) series reporting both long-term survival and perioperative outcomes; and (4) series addressing specific adverse events<sup>[10-15,20-28]</sup>. It is also important to note that these reports come from tertiary referral centers with extensive experience in local-regional therapies and there appears to be a significant learning curve with performing these complex procedures<sup>[20]</sup>.

Morbidity after comprehensive treatment can be broadly divided into surgical complications, generally considered to be related to the operative component of the procedure, and systemic toxicity, presumably related to the absorption of the intraperitoneally administered drugs into systemic circulation. Nevertheless, this categorization

has to be considered cautiously since, in a series of 209 patients treated at our institution, intraperitoneal cisplatin dosage > 240 mg correlated with the occurrence of post-operative complications in multivariate analysis<sup>[14]</sup>.

Morbidity rates after CRS and PIC varied from 30% to 74%. Mortality ranged from 0% to 19% in the literature and from 0% to 8% in the main series, which may be considered acceptable for a major surgical procedure<sup>[10-15,21-28]</sup>. However, clinical results are difficult to compare, due to the broad variability among centres in terms of therapeutic indication, patient selection, surgical technique, as well as timing, modality, duration, degree of hyperthermia, and type and dose of drugs for local-regional chemotherapy. Furthermore, different classification systems have been used when reporting complications. The most commonly used rating systems are the Clavien classification<sup>[29]</sup>, the Elias classification<sup>[29]</sup> and the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCICTCAE v.3; <http://ctep.cancer.gov/forms/CTCAEv3.pdf>). Such systems are different in terms of the total number of classes (4 vs 5) and of correspondence between the grades, in that a given grade in a scoring system may not refer to the same clinical severity according to another classification<sup>[29]</sup>. Despite such limitations, if we consider only severe complications requiring re-intervention, ICU recovery or invasive procedures for their management, major morbidity rates range from 12% to 54%<sup>[10-15,21-28]</sup>.

## DIGESTIVE COMPLICATIONS

The prevalent complications in most series are digestive fistulae, either in the form of anastomotic leak or bowel perforation away from anastomotic lines. Fistulae have been reported to occur in 3.9% to 34% of patients (Table 2)<sup>[10,11,20,21,30-35]</sup>. Such figures are somewhat higher than the 5% rate reported for common elective surgery<sup>[36]</sup>.

It has been demonstrated that the influence of chemotherapy on anastomotic suture healing depends on the type of drug used. In animal studies, anastomotic healing

**Table 2** Bowel complications associated with cytoreductive surgery and perioperative intra-peritoneal chemotherapy

Authors, yr	Patients (n)	Ratio anast/patient	Protective ostomy (%)	BC/A ratio (%)	Bowel complications rate (%)	Risk factors for bowel complications
Jacquet <i>et al</i> <sup>[21]</sup> , 1996	60	1.8	None	9.3	17	Duration, No. of peritonectomy procedures <sup>1</sup> Intraoperative blood loss <sup>1</sup>
Stephens <i>et al</i> <sup>[10]</sup> , 1999	200	NA	NA	NA	7.5	
Witkamp <i>et al</i> <sup>[30]</sup> , 2001	46	2	39	17.4	34	
Elias <i>et al</i> <sup>[31]</sup> , 2001	64	2.6	NA	8	18.8	
Elias <i>et al</i> <sup>[32]</sup> , 2003	36	2.8	NA	7.2	22.2	
Parvaiz <i>et al</i> <sup>[33]</sup> , 2002	43	NA	NA	NA	5	Carcinomatosis extent, duration, No. of anastomoses <sup>1</sup>
Glehen <i>et al</i> <sup>[11]</sup> , 2003	56	0.6				
Glehen <i>et al</i> <sup>[34]</sup> , 2003	73		NA	NA	10.7	
Verwaal <i>et al</i> <sup>[22]</sup> , 2004	102	> 2	42	NA	17.6	
Shen <i>et al</i> <sup>[35]</sup> , 2004	77	NA	13	NA	NA	

<sup>1</sup>On univariate analysis. anast: Anastomoses; BC/A: Bowel complications/Anastomoses ratio; NA: Not available.

can be impaired by intra-peritoneal MMC, but not by 5-FU at a normal temperature or by paclitaxel<sup>[37,38]</sup>. Local hyperthermia alone has no adverse effect on rat anastomotic healing<sup>[39]</sup>.

These observations may have an impact on the definition of the optimal timing for bowel anastomoses when performing CRS and HIPEC: anastomoses can be performed either after or before HIPEC. Proponents of the first alternative argue that delaying the anastomosis permits a better distribution of heat and drugs inside the peritoneal cavity. In addition, they state that the risk of postoperative bowel complications can be diminished, due to the less potential adverse effect of heat and chemotherapy on suture lines.

A possible explanation for digestive non-anastomotic perforation could be partial-thickness mechanical damage to intestinal surfaces, focal heat injury at the tip of the inflow catheter, the suctioning effect of the outflow catheter, or postoperative shrinking of infiltrating metastatic nodules on the intestinal wall because of the antiproliferative effect of HIPEC. The risk for such complications should be minimized by careful lyses of adhesions and dissection, with a judicious use of the ball-tip electrocautery on the serosal surfaces of the intestine.

A study to assess the bowel complication rate and the risk-factors for their occurrence in patients undergoing CRS and closed-abdomen HIPEC was conducted at the National Cancer Institute of Milan<sup>[40]</sup>. One hundred ninety-eight consecutive patients undergoing 203 combined procedures from 1995 to 2004 constituted the study population. Mean organ resections were 2.4 per patient overall. A total of 194 anastomoses were performed, with a mean of 0.96 anastomoses per patient (range, 0-4). Ninety-four patients (46%) had none performed. Conversely, 26% of patients had one anastomosis performed, 17% had two performed, 8% had three performed, and 3% had four performed.

During the entire study period, anastomoses were carried out before HIPEC and no protecting stoma was routinely performed, except in one female patient who had a terminal ileostomy after a total colectomy with small-bowel resection, because the ileorectal anastomoses could not be fashioned because of undue tension.

Interesting information on the management of bowel

complications was provided by the study. Twenty-two patients (10.8%) had bowel complications occurring at a mean of 11.5 d after the operation (range 3-28 d). Overall, two patients (1%) died. Complications occurred at an anastomotic suture line in 17 patients and away from anastomoses in 6 patients. An ileocolic anastomosis was the most common site of a bowel complication. Five patients with ileocolic anastomotic leaks underwent re-operation and bowel resection with re-anastomosis, two patients had a protective ileostomy and two patients were conservatively treated with total parenteral nutrition until recovery. One small-bowel anastomotic leak was surgically treated, and another was conservatively managed. Three small-bowel perforations occurred at sites unrelated to suture lines and all were surgically treated. One patient with a colorectal anastomotic dehiscence was surgically treated and given a colostomy, whereas the other was conservatively treated with drainage and parenteral nutrition. Overall, six patients (27%) received a stoma as part of their final management, including one performed to gain access to a major presacral bleed.

## RESPIRATORY COMPLICATIONS

Following the gastrointestinal tract, the respiratory tract is probably the second most affected system by postoperative complications. Pulmonary morbidity was found in 15 cases in our series. Fortunately, most of them were of Grade 1/2, with the exception of one case of pulmonary embolism and one of respiratory failure<sup>[14]</sup>.

Thoracic complications were studied in a series of 42 patients with various PSM treated with CRS and HIPEC at Wake Forest University<sup>[41]</sup>. Chest X-rays were obtained in all patients preoperatively, within 3 d postoperatively and thereafter as necessary. A control group of 14 patients who had prolonged abdominal surgery without HIPEC was collected. Thoracic complications occurred in 36 patients (86%), including atelectasis in 32 (76%) patients, pleural effusions in 27 (64%) patients, pulmonary oedema in 10 (24%) patients, pneumonia in 2 (5%) patients, and pneumothorax in 2 (5%) patients. Most effusions (74%) occurred 1-3 d after CRS and HIPEC and lasted < 4 d. The incidence of thoracic complications in the HIPEC group was significantly higher than in the



**Table 3** Systemic toxicity after cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy

Authors, yr	Patients (n)	HIPEC drug schedule	EPIC	Severe hematological toxicity (%)	Renal toxicity (%)	Mortality (%)	Risk factor for systemic toxicity
Jacquet <i>et al</i> <sup>[21]</sup> , 1996	60	MMC	60	7	-	5	Not identified
Schnake <i>et al</i> <sup>[44]</sup> , 1999	242	MMC/CDDP	Yes	2.5	-	4	Not identified
Stephens <i>et al</i> <sup>[10]</sup> , 1999	200	MMC	145	4	-	1.5	Not identified
Glehen <i>et al</i> <sup>[11]</sup> , 2003	216	MMC or CDDP or CDDP + MMC	-	4.6	1.3	3.2	NA
Verwaal <i>et al</i> <sup>[22]</sup> , 2004	102	MMC	-	18.6	4.9	8	NA
Shen <i>et al</i> <sup>[35]</sup> , 2004	77	MMC	-	19	-	4	NA
Smeenk <i>et al</i> <sup>[12]</sup> , 2006	103	MMC	-	10.6	-	11	NA
Elias <i>et al</i> <sup>[43]</sup> , 2005	83	Ox + CPT11 + ev 5-FU + AF	-	48	-	4.8	Duration of proc; PCI
Kusamura <i>et al</i> <sup>[42]</sup> , 2007	247	CDDP + MMC or CDDP + Dx	-	5.3	5.7	1.2	CDDP dose > 240 mg; CDDP + Dx schedule for HIPEC

CHT: Chemotherapy; HIPEC: Hyperthermic intraperitoneal chemotherapy; EPIC: Early postoperative intraperitoneal chemotherapy; MMC: Mitomycin-C; Ox: Oxaliplatin; CDDP: Cisplatin; CPT11: Irinotecan; 5-FU: 5-fluorouracil; Dx: Doxorubicin; PCI: Peritoneal Cancer Index.

control group ( $P < 0.05$ ). Pleural effusions affected the left side in 8 patients and both sides in 19.

Bibasilar atelectasis and pleural effusions are common findings after IPHC with MMC, but most of them do not necessarily warrant intervention. The stripping of the diaphragmatic peritoneum elicits a mechanical and thermal injury, leading to occult communications between the abdominal and pleural cavities and passage of perfusate to the thorax during HIPEC. Moreover, inflammatory reactions could be responsible for postoperative production of abundant exudates in the pleural space. The possibly impaired contractive function of the diaphragmatic muscle due to surgical trauma, along with general causes related to any major surgery (prolonged anaesthesia time, inappropriate postoperative analgesia) are further potential factors for the emergence of pulmonary morbidities. The prevention and management of such complications include careful inspection of the integrity of the diaphragmatic muscle after the stripping of its peritoneum, the prompt repair of eventual macroscopic holes, the prophylactic insertion of thoracic drains after cytoreduction, a careful control of postoperative pain, a judicious management of respiratory rehabilitation and administration of antibiotics.

## SYSTEMIC TOXICITY

Only a few authors have conducted comprehensive studies on systemic toxicity associated with CRS and PIC outside the context of a dose-finding study. Systemic toxicity was investigated in a series of 247 combined procedures performed in our institution. HIPEC was administered according to the closed-abdomen technique with either cisplatin + doxorubicin (time = 90 min) or cisplatin + mitomycin-C (time = 60 min), depending on tumour histology. The intracavitary perfusate temperature was 42°C–43°C. Drug dosage was reduced by 30% in patients > 70 years of age or who had undergone previous chemotherapy<sup>[42]</sup>.

In 29 patients, 34 G3–5 systemic toxicity events occurred (NCI CTCAE v3), accounting for a toxicity rate of 11.7%. Nephrotoxicity occurred in 14 patients, bone marrow suppression in 13 patients, febrile neutropenia

in 2 patients; gastrointestinal events in 4 patients and pulmonary toxicity in 1 patient.

There were 6 cases of leukopenia; the nadir was reached at a mean of 12.7 d postoperatively (range 1–26 d) and the mean duration was 4.7 d (range 2–10 d). Severe neutropenia was observed in 9 cases; the nadir was reached at a mean of 13.4 d postoperatively (1–30 d) and the mean duration was 2.9 d (1–6 d). Only one patient received granulocyte-colony stimulating factor for 3 d at a dose of 300 µg/d. One patient with G4 neutropenia and concomitant sepsis died on postoperative day 26. There were 4 cases of thrombocytopenia; the mean day of nadir was 3.3 d (1–6 d) and mean duration was 4 d (1–6 d). Only one patient required platelet transfusion.

Regarding nephrotoxicity, there were 10 cases of G3 and 4 cases of G4 serum creatinine alteration. After a mean period of 16 d (range 7–42 d) from surgery, 5 patients had normal renal function, 5 patients had G1–2 serum creatinine alteration, and 4 patients still presented G3–5 alteration. Three patients required hemodialysis during the immediate postoperative period and evolved with chronic renal failure; two of these patients are currently on chronic hemodialysis.

Risk-factors for overall systemic, renal and hematologic toxicity were assessed. Patients receiving cisplatin and doxorubicin showed a 15.3% rate of combined G3–5 systemic toxicity as compared to 9.4% of those receiving cisplatin and mitomycin-C. When adjusted for other variables, the former group presented a 2.36 times higher risk than the cisplatin and mitomycin-C group. Analogously, a cisplatin dose for HIPEC > 240 mg presented a 2.78 times higher risk. No independent risk factor for renal failure was identified. Only a cisplatin dose > 240 mg presented an univariate correlation with postoperative serum creatinine G3–5 alteration. Finally, only male sex presented a threefold higher risk of developing myelotoxicity.

The main studies reporting systemic toxicity of CRS and HIPEC are summarized in Table 3. Verwaal observed renal failure in 4.9% of cases<sup>[22]</sup>. Glehen observed a postoperative renal failure rate of 1.3%<sup>[11]</sup>. Hematological toxicity rates, according to most authors, range from 2.5 to 19%<sup>[10–12,21,22,35,42–44]</sup>. Only one study presented an outlier value of 48%<sup>[13]</sup>. Elias conducted a study of 83 patients who

were treated with intraperitoneal oxaliplatin (360 mg/m<sup>2</sup>) and irinotecan (360 mg/m<sup>2</sup>) and intravenous leucovorin (20 mg/m<sup>2</sup>) and 5-fluorouracil (400 mg/m<sup>2</sup>). The incidence of severe bone marrow aplasia was 48% and was associated with the duration of surgery and extent of the peritoneal disease<sup>[43]</sup>.

## OTHER COMPLICATIONS

Central line sepsis is reported in 6% to 9.2%<sup>[3,23]</sup>. Sugarbaker noted a high incidence of infection and an unexpectedly high incidence of subclavian vein thrombosis with the subclavian route. Accordingly, he recommended that intraoperative central venous monitoring be performed through an intrajugular line to minimize venous thrombosis and this line should be removed at 7 d and replaced by a peripheral central line<sup>[24]</sup>. Urinary tract infection accounted for 7% to 9.2% of complications. A Foley catheter in patients having extensive pelvic peritonectomy is required for up to 10 d, leading to a high incidence of urinary tract infections, especially in women. More adequate emptying of the Foley catheter tubing may reduce urine stasis in the bladder<sup>[23,24]</sup>.

Pulmonary thromboembolism has been reported in 0.5% to 10% of cases<sup>[11,12,15,23,24]</sup>. In our center and other centres, patients receive a prophylactic treatment with fractionated or low molecular weight heparin. At the Washington Cancer Institute, no heparin is given, but sequential compression devices applied to the patient's legs are used<sup>[23,24]</sup>.

Yan reports a low haemoglobin level of 6.5-7.9 in 26% of patients (grade 3 according to NCI CTCAE). This is often due to hemo-dilution, since patients are given a large volume of intravenous fluid during the administration of intraperitoneal chemotherapy in order to avoid renal toxicities. In addition, absorption of intraperitoneal chemotherapy carrier solution will contribute to complications. More timely blood transfusion and less intraoperative fluid will decrease this grade III morbidity<sup>[24]</sup>.

## LONG TERM FOLLOW-UP

Since evidence is growing that CRS and HIPEC is of benefit to patients with PSM, long-term follow-up to deal with treatment-related problems (including recurrent disease) has become a relevant issue. Although early relapse detection may result in long-term survival for selected patients, the cost-effectiveness of follow-up in tumour patients has been often questioned. Most follow-up regimens are empirical and it is still controversial that a survival benefit is found.

Few studies have been published on follow-up after cytoreduction and HIPEC. Verwaal has addressed this issue in a series of 107 patients undergoing comprehensive treatment for carcinomatosis of colorectal origin<sup>[45]</sup>. The follow-up protocol required visits at the outpatient clinic every three months for two years and every six months thereafter. Patient history, physical examination, serum CEA and CA 19.9 were performed at each visit,

and a CT-scan of the abdomen six-monthly. If symptoms arose, a CT-scan or endoscopy was performed, as required. PET scans were obtained in cases of a tumour marker rise and inconclusive CT-scans. In the case of rising tumour markers above normal values, attempts were made to confirm the presence of a recurrence. If the tumour marker value kept rising, the patient was considered to have recurrent disease even if this could not be demonstrated despite an extensive search.

After a median follow-up time of 51 mo, 74 patients developed recurrent disease, which was classified as intra-abdominal relapse in 47 patients, hepatic metastases in 13 patients, thoracic metastases in 2 patients, both intra-abdominal and systemic involvement in 8 patients and unknown in 4 patients.

The results of routine investigations at the moment of a recurrence were assessed in 63 patients with disease progression after optimal cytoreduction and HIPEC. History and physical examination were positive in 38 (61%) patients. Bowel obstruction (33%), pain (10%), blood loss (8%) and mass (6%) were the most common signs or symptoms of recurrence. CEA was raised above normal levels in 20 patients, CA19.9 in 7 patients and both in 12 patients. CT-scan findings were positive in 37 patients (39%). Nineteen patients underwent endoscopy, seven of them because of a rise in tumour markers without clinical symptoms or abnormal CT-scan findings. Only one of these endoscopies, indeed, revealed a recurrence. Disease progression occurred in 11 of 15 patients who had grossly incomplete cytoreduction and was found in all cases by either physical examination or tumour markers.

In a further analysis, the least invasive investigation that could have led to the diagnosis of 63 recurrences after optimal cytoreduction and HIPEC was determined. History and physical examination in 39 (61%) patients, tumour markers in 21 (34%) patients and CT-scans in 3 (4.8%) patients were the initial diagnostic studies that triggered further investigations leading to recurrence diagnosis. Overall, positive clinical or laboratory findings could have identified 95% of all recurrences.

This study demonstrates that most recurrences can be found after relatively simple and inexpensive initial diagnostic tests. A reasonable follow-up schedule could be: baseline CT-scan with CEA and CA 19.9 testing, followed by standard physical examination and tumour marker testing at regular intervals. Abnormal physical examination or elevated tumour markers are the only indications for more invasive and costly tests.

Poor information on follow-up is available for the other PSM. However, the role of serum tumour markers has been underlined. In patients with peritoneal mesothelioma, we reported a sensitivity rate of 100% (12/12) for CA125 in assessing disease progression after complete CRS and HIPEC<sup>[46]</sup>. In patients with pseudomyxoma peritonei with positive baseline values, marker concentrations at progression were elevated in 24 of 29 (82.7%) patients for CEA, in 18 of 22 (81.8%) patients for CA19.9, in 12 of 19 (63.1%) patients for CA125, and in 4 of 6 (66.7%) patients for CA15.3<sup>[47]</sup>. Van Ruth reported that CEA

normalized in 73% patients and CA19.9 in 57% patients with preoperative increased levels, and that CA19.9 was positive in 14 of 14 cases of relapsing PMP with elevated preoperative levels<sup>[48]</sup>. Carmignani reported a sensitivity of 35.2% for CEA and of 62.9% for CA19.9 among 110 patients reoperated on for recurrent PMP, but baseline marker status was not detailed<sup>[49]</sup>.

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