Evaluation of Extensive Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Patients With Advanced Epithelial Ovarian Cancer

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Objective: Although standard treatment for advanced epithelial ovarian cancer (EOC) consists of surgical debulking and intravenous platinum- and taxane-based chemotherapy, favorable oncological outcomes have been recently reported with the use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The aim of the study was to analyze feasibility and results of CRS and HIPEC in patients with advanced EOC.

Materials/Methods: This is an open, prospective phase 2 study including patients with primary or recurrent peritoneal carcinomatosis due to EOC. Thirty-nine patients with a mean (SD) age of 57.3 (9.7) years (range, 34–74 years) were included between September 2005 and December 2009. Thirty patients (77%) had recurrent EOC and 9 (23%) had primary EOC.

Results: For HIPEC, cisplatin and paclitaxel were used for 11 patients (28%), cisplatin and doxorubicin for 26 patients (66%), paclitaxel and doxorubicin for 1 patient (3%), and doxorubicin alone for 1 patient (3%). The median intra-abdominal outflow temperature was 41.5°C. The mean peritoneal cancer index (PCI) was 11.1 (range, 1–28); and according to the intraoperative tumor extent, the tumor volume was classified as low (PCI <15) or high (PCI ≥15) in 27 patients (69%) and 12 patients (31%), respectively. Microscopically complete cytoreduction was achieved for 35 patients (90%), macroscopic cytoreduction was achieved for 3 patients (7%), and a gross tumor debulking was performed for 1 patient (3%). Mean hospital stay was 23.8 days. Postoperative complications occurred in 7 patients (18%), and reoperations in 3 patients (8%). There was one postoperative death. Recurrence was seen in 23 patients (59%) with a mean recurrence time of 14.4 months (range, 1–49 months).

Conclusions: Hyperthermic intraperitoneal chemotherapy after extensive CRS for advanced EOC is feasible with acceptable morbidity and mortality. Complete cytoreduction may improve survival in highly selected patients. Additional follow-up and further studies are needed to determine the effects of HIPEC on survival.

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Among gynecological tumors, epithelial ovarian cancer (EOC) is the most common cause of death in the Western world, and most patients with EOC present with disease at an advanced International Federation of Gynecology and Obstetrics (FIGO) stage, that is, III or IV.[1,2] The current standard treatment for these patients consists of cytoreduction (often to residual nodules less than 1 cm in size) and systemic chemotherapy with paclitaxel along with a platinum agent, either carboplatin or cisplatin.[3] The extent of cytoreduction has a direct impact on survival, and maximal cytoreduction was found to be one of the most powerful determinants of survival among patients with stage III or IV EOC in a meta-analysis of almost 7000 patients.[4] Furthermore, phase 3 randomized controlled trials have established the superiority (ie, improved progression-free and overall survival rates) of intraperitoneal cisplatin-based chemotherapy compared to the systemic delivery of the agent for the treatment of small-volume residual advanced EOC.[5–7] Less evidence is available for either medical[8] or surgical[9,10] management of recurrent EOC.

Over the past decade, the treatment strategies have changed, and other options for prolonging survival are now available. Improved long-term results can be achieved in highly selected patients using cytoreductive surgery (CRS), including parietal and visceral peritonectomy procedures, in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC).[11–18] Platinum-based chemotherapeutic regimens have been shown to produce high response rates and to penetrate tumor tissue much more deeply under hyperthermic conditions when administered intraperitoneally.[19–21] Because of the peritoneal-plasma barrier, platinum derivatives remain in the peritoneal cavity longer, permitting prolonged exposure to the drug. The complete removal of large tumor masses requires major surgery in a number of cases, leading to a longer operating time and significant blood loss. Most experience with this aggressive treatment has been gained in selected patients with peritoneal carcinomatosis owing to primary peritoneal neoplasms secondary to gastrointestinal malignancies.[22–24] Despite extended surgery, most patients return to baseline or better levels of function within 3 months after treatment, and long-term survival with good quality of life is possible.[25] Although it would seem from these studies that treating peritoneal carcinomatosis due to EOC with peritonectomy and HIPEC is an attractive option, there are no prospective randomized trials available at present to confirm the superiority of this aggressive treatment concept in EOC.[17]

The aim of this study was to analyze the feasibility of CRS and HIPEC in patients with peritoneal carcinomatosis due to EOC.

MATERIALS AND METHODS

Patients

This study was an open, prospective, nonrandomized, bicentric phase 2 study including patients with primary or recurrent peritoneal carcinomatosis due to EOC. The study was performed at the Unit of General, Emergency and Transplant Surgery of St. Orsola-Malpighi Hospital, University of Bologna, Italy, and the Unit of Surgery and Advanced Oncologic Therapies of Morgagni-Pierantoni Hospital, Forlì, Italy, between September 2005 and December 2009. The study protocols (CARcinosi PEritoneale trattata con Peritonectomia Associata a ChEMio ipertermia intra peritoneale [CARPEPACEM] and Protocollo di trattamento delle carcinosi peritoneali primitive e secondarie da tumori gastrointestinali ed ovarici plurirecidivi e delle sarcomatosi addominali mediante Citoriduzione chirurgica e ChemioIpertermia Intra-Peritoneale [CIIP]) were approved by the St. Orsola-Malpighi Hospital's Ethical Review Board in March 2007 (no. 038/2007/O/Sper) and by the Morgagni-Pierantoni Hospital's Ethical Review Board in June 2005.

During the study period (September 2005 to December 2009), 39 patients were included and followed prospectively. For primary advanced EOC, the inclusion criteria were patients with stage IIIC disease with up to 2 Eastern Cooperative Oncology Group performance status (any histologic type) who accepted to participate in the study. For recurrent EOC, the inclusion criteria were presence of carcinomatosis with up to 2 Eastern Cooperative Oncology Group performance status (any histologic type) in patients who accepted to participate in the study. Exclusion criterion for both types of patients was presence of systemic metastases. In the same study period in the 2 participating centers were seen 54 patients with primary advanced EOC and 82 patients with recurrent EOC who met the aforementioned inclusion criteria among whom were recruited 9 and 30 patients, respectively, who accepted to participate in the study. The characteristics of these patients are reported in Table 1.

Surgical Procedures

At the time of the exploratory laparotomy before cytoreductive surgery, tumor load measurements were taken according to the peritoneal cancer index (PCI) described by Sugarbaker,[26] which integrates both the peritoneal implant size and the distribution of the peritoneal surface malignancy.

The surgery performed was intended to remove all macroscopically visible tumor nodules from the visceral and parietal peritoneum. To accomplish complete cytoreduction,

TABLE 1. Characteristics of the 39 patients included in the study

Characteristics	Values
Age, mean (SD), (range), yrs	57.3 (9.7), (34–74)
Primary/recurrent EOC, n (%)	9 (23)/30 (77)
Histologic type, serous/mucinous/endometrioid, n (%)	27 (69)/7 (18)/5 (13)
Grading, 1/2/3, n (%)	5 (13)/14 (36)/20 (51)
Patients with prior systemic chemotherapy, n (%)	37 (95)
Regimens of prior systemic chemotherapy, cisplatin or carboplatin alone/in combination with taxanes/in combination with gemcitabine, n (%)	4 (11)/30 (81)/3 (8)
Time since prior systemic chemotherapy, mean (SD), (range), mo	3.4 (1.4), (1–9)
Platinum-responsiveness status, sensible/resistant/unknown, n (%)	13 (33)/24 (62)/2 (5)
ECOG performance status, 0/1/2, n (%)	3 (8)/23 (59)/13 (33)

ECOG, Eastern Cooperative Oncology Group.

a variable number of peritonectomy procedures (up to 6) were required, as previously described by Sugarbaker. These procedures included omentectomy and splenectomy, left subdiaphragmatic peritonectomy, right subdiaphragmatic peritonectomy, pelvic peritonectomy with rectosigmoidectomy, and cholecystectomy with lesser omentectomy.[27,28]

Completeness of cytoreduction was assessed by measuring the size of the residual peritoneal implants after surgery and assigning a completeness of cytoreduction (CC) score, as proposed by Sugarbaker: CC0, no residual disease; CC1, residual nodules measuring less than 2.5 mm; CC2, residual nodules measuring between 2.5 mm and 2.5 cm; or CC3, residual nodules greater than 2.5 cm.[29]

After surgery, HIPEC was performed using a heat exchanger, 2 roller pumps and a heater/cooler unit (Exiper, Medica S.p.A., Medolla, Modena, Italy or Performer LRT, RanD, Medolla, Modena, Italy). Hyperthermic intraperitoneal chemotherapy was performed as an open procedure with the Coliseum technique[26,30,31] using cisplatin (100 mg/m^2) and/or paclitaxel (175 mg/m^2) and/or doxorubicin (35 mg/m^2), depending on the previous systemic chemotherapy undergone by each individual patient. Intraperitoneal chemotherapy was performed for 90 minutes, with a peritoneal and outflow thermal plateau of 41.5°C.

The surgical procedure length was calculated from the induction of anesthesia to the closure of the abdominal wall.

Postoperative Treatment, Outcomes, and Follow-Up

To analyze postoperative morbidity, all surgical and nonsurgical complications that occurred during the hospitalization and follow-up period were considered. Severe hematological toxicity and nephrotoxicity were classified according to the World Health Organization (WHO) scale.

Statistical Analysis

Patients' data, including epidemiologic, surgical, pathologic, and survival figures, were compiled into a database (SPSS, version 11.5, 2003). Survival rates were calculated using the Kaplan-Meier method and were compared using the log-rank test ($P < 0.05$ was considered statistically significant).

RESULTS

The mean (SD) operating time was 10.9 (2.3) hours (range, 7.0–16.3 hours).

For intraoperative chemotherapy, a combination of cisplatin and paclitaxel was used for 11 patients (28%), cisplatin and doxorubicin for 26 patients (66%), paclitaxel and doxorubicin for 1 patient (3%). and doxorubicin alone for 1 patient (3%). The median intra-abdominal outflow temperature was 41.5°C.

In the group of patients studied in this report, the mean (SD) PCI was 11.1 (7.6) (range, 1–28), and according to the intraoperative tumor extent, the tumor volume was classified as low (PCI <15) or high (PCI ≥15) in 27 patients (69%) and 12 patients (31%), respectively. Microscopically complete cytoreduction (CC0) was achieved for 35 patients (90%), macroscopic cytoreduction (CC1) was achieved for 3 patients (7%), and a gross tumor debulking (CC3) was performed for 1 patient (3%).

The mean (SD) stay at intensive care unit was 4.97 (4.7) days (range, 2–29 days), and the mean (SD) hospital stay was 23.8 (6.1) days (range, 14–39 days).

Postoperative complications occurred in 7 patients (18%). These complications included pulmonary embolism (1/39), surgical wound dehiscence (1/39), bladder-vaginal fistula (1/39), pelvic abscess (1/39), colonic ischemia (1/39), postoperative intra-abdominal hemorrhage (1/39), and pleural effusion (1/39).

World Health Organization grades 1, 2, and 3 hematological toxicity was seen in 5 patients (13%), 10 patients (26%) and 5 patients (13%), respectively. World Health Organization grade 1 nephrotoxicity was seen in 2 patients (5%).

Reoperation was required for 3 patients (8%) owing to colonic ischemia (1/39 patients), abdominal abscess (1/39 patients), or hemorrhage (1/39 patients). One patient died postoperatively owing to peritonitis and septicemia after colonic ischemia.

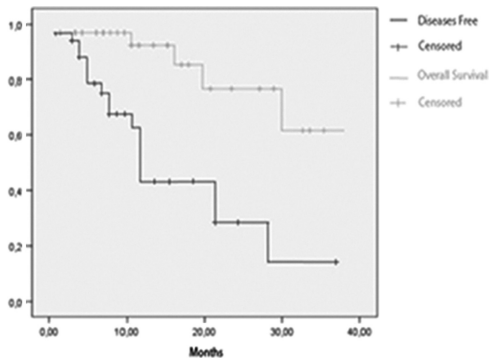

FIGURE 1. Overall and disease-free survival curves after cytoreduction and HIPEC in 39 patients with peritoneal carcinomatosis due to primary or recurrent EOC.

Postoperatively, 27 patients (69%) received further systemic chemotherapy consisting of different drug regimens.

The mean (SD) follow-up period was 19.8 (12.7) months (range, 1–54 months). During this follow-up, recurrence occurred in 23 patients (59%), with a mean (SD) recurrence time of 14.4 (11.7) months (range, 1–49 months). The disease-free and overall survival curves for the 39 patients included in this study are reported in Figure 1. The overall and disease-free survival curves for patients with primary or recurrent disease, with low (PCI <15) or high (PCI ≥15) tumor volume and with a score of CC0 or CC1–CC3 are presented in Figures 2–4, respectively. The difference in survival in the various groups did not reach statistical significance, but there was a significant difference in disease-free survival between the patients with scores of CC0 and CC1–CC3 ($P = 0.02$, log-rank test).

DISCUSSION

In the 1980s, a new therapeutic approach for the treatment of peritoneal carcinomatosis was described by Dr. Sugarbaker,[32] namely, combining CRS with HIPEC. This procedure has already been used with a variety of different devices and techniques to treat disseminated peritoneal appendiceal and colorectal cancer, peritoneal mesothelioma, and pseudomyxoma peritonei by many teams all over the world.[33] Because more than two thirds of all patients with EOC are at an advanced stage (IIIC or IV) at the time of diagnosis with peritoneal involvement, a similar approach has been attempted even for these patients. In a select group of patients, particularly those with low tumor volumes, parietal and visceral peritonectomy with the aim of complete macroscopic cytoreduction and HIPEC can improve the prognosis.[12,13,17,34] Despite a general acceptance of cytoreduction during primary treatment,[4] the role of secondary cytoreductive surgery for recurrence has yet to be defined.[35] Preliminary data suggest, however, that survival may be improved in certain patients.[36] It had already been clearly defined since the 1990s that during primary surgery for advanced EOC, all attempts should be made to achieve complete cytoreduction because this is directly associated with the improved survival in these groups of women.[4,37–40] This concept has become so solid in recent years that now, in primary EOC, the only cytoreduction-defined optimal is the complete one.[41] On the contrary, with regard to recurrent EOC, there is no full evidence yet from randomized controlled trials (RCTs) that secondary surgical cytoreduction and chemotherapy show clinical advantages compared to chemotherapy alone,[42] but much evidence, although not of level 1, has accumulated that even in recurrent EOC survival time seems directly associated to the completeness of cytoreductive surgery.[10,43–45] These considerations are consistent with our results, where both survival curves (overall survival and disease-free survival, Fig. 2) revealed no significant differences when comparing the group of patients with primary and recurrent EOC, whereas DFS (Fig. 4) was significantly longer in patients with complete cytoreduction. This confirms the importance of cytoreduction either in primary or in recurrent EOC.

Of our 39 patients, 30 (77%) had recurrent EOC; thus, even in our series, there was a mix of primary and recurrent EOC, as in most experiences reported in the literature in the 19 studies enclosed in the review of Chua et al[17] up to May 2009 and in the further 15 published studies we later found

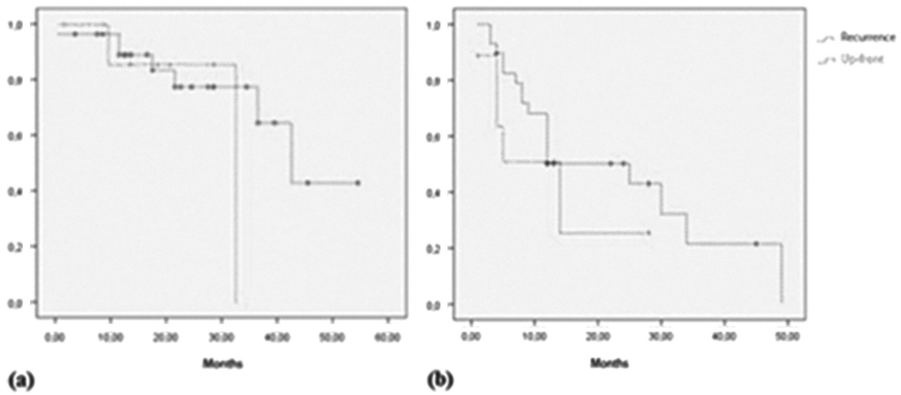

FIGURE 2. Kaplan-Meier estimate of overall survival (A) and disease-free survival (B) in the primary and recurrent groups.

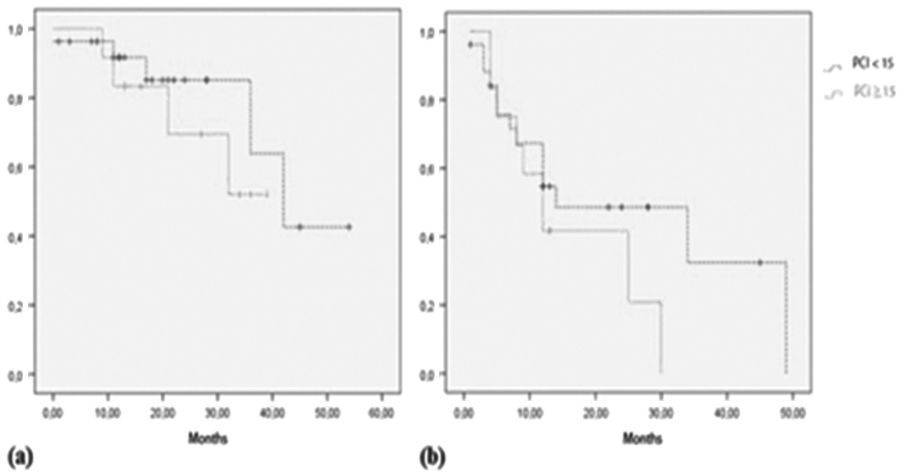

FIGURE 3. Kaplan-Meier estimate of overall survival (A) and disease-free survival (B) in the PCI less than 15 and PCI 15 groups or more.

up to December 2011.[18,46–59] This limitation must always be taken into account when considering the results of our study.

Complete reduction (CC0) or CC1 was performed successfully in all but one of our patients, which is considerably better than other data from unselected patients (30%–50% complete or acceptable cytoreduction)[60] and most probably reflects the high selection rate in our patients.

Following CRS, HIPEC was performed in our patients; the main cytostatic agent used was cisplatin. The duration of the procedure and the length of hospital stay were comparable to those in other studies.[17]

Different HIPEC techniques have been developed, either with the abdomen completely open or opened with the use of peritoneal expanders or with the abdomen temporarily closed before completion of gastrointestinal anastomoses and other reconstructive procedures. In the past decade, closed-abdomen HIPEC procedures after the completion of surgical anastomoses have been described with acceptable results and an acceptable level of adverse effects.[61,62] In this study, in which we used the open technique, an acceptable major morbidity rate was recorded. The overall morbidity was similar to that found in established centers, where CRS and HIPEC are performed to treat peritoneal surface malignancies.[17,63,64] Morbidity related to chemotherapy is determined by the type of substance used and particularly by the dosage and regimen of administration. In most of our patients, we used cisplatin at rather high doses (100 mg/m^2) and observed a relatively high rate of renal and bone marrow toxicity. However, serious complications such as grade 3 or 4 toxicity only occurred rarely in our patients. Prolonged serious postoperative ileum and anastomotic leakage were not observed for any patient. The higher rate of such complications seen in other studies of the use of HIPEC to treat gastrointestinal cancer is likely to be related to the intraperitoneal drug infused, such as mitomycin C or 5-fluorouracil, as observed by van der Vange et al.[65] Moreover, peritonectomy procedures in cases of carcinomatosis due to EOC are generally less complicated because, in this case, peritoneal implants tend to be

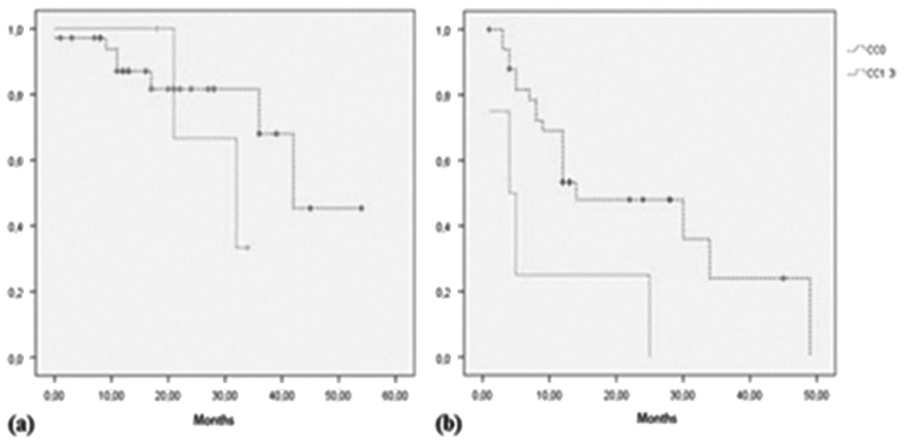

FIGURE 4. Kaplan-Meier estimate of overall survival (A) and disease-free survival (B) in the CC0 and CC1–CC3 groups.

less penetrating than those used in cases of gastrointestinal cancer.

As in similar studies,[17] an acceptable (1/39 [3%]) perioperative mortality rate for patients who underwent extensive surgery and HIPEC for massive diffuse peritoneal carcinomatosis was observed. The cause of death was peritonitis and septicemia after colonic ischemia. As for other major interventions, morbidity and mortality are increased during the learning curve and decrease with cumulative experience.[17,63,64]

The significant advantage in disease-free survival shown in our study in patients with complete surgical cytoreduction (CC0) confirms that the best results for EOC treatment can be achieved in cases with variable-volume peritoneal carcinomatosis in which aggressive CRS lessens the tumor volume to a minimum. Indeed, it is well known that smaller residual tumor size after CRS is the most important favorable predictive factor in patients with EOC. A survival advantage has been established even with traditional CRS in patients with residual tumor diameters less than 1 to 2 cm, especially if the remaining tumor mass does not exceed 5 mm.[66] The best results with HIPEC are also achieved if the treatment is combined with maximal CRS.[17] Indeed, CRS is able to eliminate macroscopic tumor load and can be combined with HIPEC to treat residual microscopic disease. The intraperitoneal administration of chemotherapy can also be combined with hyperthermia, in theory, synergistically increasing the activity against cancer cells. It is known that a temperature of 42°C is cytotoxic in and of itself, increasing membrane permeability, inhibiting DNA repair, and promoting macrophagic lysosomal exocytosis with subsequent apoptosis.[67,68] Tumor cells are more vulnerable to heat because of their chronic hypoxia, which causes a lower intracellular pH and abnormal metabolism. Moreover, raising the temperature to 42°C or 43°C sensitizes tumor cells to some antineoplastic agents, increasing vascular permeability and intracellular drug concentrations. Antineoplastic drugs used for HIPEC in the treatment of EOC (cisplatin, doxorubicin, and paclitaxel) have very high molecular weights. These drugs can only penetrate through the peritoneal-plasma barrier to a small extent, with the resulting intra-abdominal drug concentration being higher than in the rest of the body.[69–71] The cytotoxicity of cisplatin in vivo and in vitro is synergistically increased by the simultaneous use of hyperthermia, which increases cellular cisplatin uptake and cisplatin-DNA adduct formation at 41°C with no obvious enhancement of toxicity at 43°C.[72] Pharmacokinetic studies of HIPEC have revealed that the quantity of cisplatin reaching systemic circulation is only approximately 20%, with great individual variability.[73] Even for doxorubicin, tissue penetration was significantly enhanced with hyperthermia when the drug was administered intraperitoneally, and in addition, hyperthermia did not affect the pharmacokinetic advantages of intraperitoneal administration of doxorubicin.[74] In contrast to cisplatin and doxorubicin, other drugs presently used in the treatment of EOC have demonstrated either no synergism with heat, as with carboplatin,[75] or greater activity but also enhanced toxicity, as with docetaxel.[76] Regarding paclitaxel, recent studies indicate that there is no effect of temperature on the permeation of paclitaxel through the peritoneum and show no influence of hyperthermia on the cytotoxic activity of paclitaxel.[77,78]

The relative importance of CRS and HIPEC in prolonging survival of patients with carcinomatosis of different origin remains somewhat undefined. For pseudomyxoma peritonei[79] and peritoneal mesothelioma,[80] CRS combined with HIPEC has become the standard of care without the need for RCTs. Only one RCT has been conducted that has demonstrated the significant increase in survival time to patients affected by peritoneal carcinomatosis of colorectal origin when treated with CRS associated to HIPEC but comparing it with only palliative surgery.[81] In patients with carcinomatosis from gastric cancer, especially synchronous, the results of a recent RCT showed that the CRS associated to HIPEC significantly improves survival compared to the only CRS.[82] Instead, with regard to ovarian carcinomatosis in the literature, there are no reported RCTs in which has been studied up the eventual improvement in survival when HIPEC is added to CRS. The only nonrandomized comparative study where HIPEC was the only variable studied is that of Kim et al who showed that HIPEC with paclitaxel during second-look laparotomy in carcinomatosis from chemosensitive EOC has a good effect on survival.[58]

There are 2 major limitations of our study. First, it included heterogeneous groups of patients with primary and recurrent EOC with a mix of patients who were chemosensitive and chemoresistant. Second, it was an observational study with prospective enrolment of patients and no control group.

Regarding the heterogeneity of patients with primary and recurrent EOC with variable chemosensitivity, it should be pointed out that platinum-based chemotherapy remains the standard of care for women with advanced EOC. Although most patients will accomplish complete clinical remission after CRS and systemic platinum-based chemotherapy, approximately 25% to 40% of patients with EOC do not have a complete response to frontline platinum-based treatment.[83–88] Moreover, of the patients who respond initially, most will relapse within 14 to 18 months and eventually die from neoplasm progression. Therefore, treatment of recurrent EOC is based on a number of chemotherapeutic options, including topotecan, gemcitabine, pegylated liposomal doxorubicin, platinum analogs, the taxanes docetaxel and paclitaxel, and combinations of these agents. The treatment for women with early recurrent disease or progression with platinum-based chemotherapy shows a disappointing response rate ranging from 5% to 20%, with limited overall and progression-free survival rates.[89–92] Taking all these considerations into account, HIPEC with cisplatin and paclitaxel in cases of primary EOC theoretically acts on a high percentage of chemosensitive neoplasms owing to the aforementioned high rate of chemosensitivity of primary EOC to platinum-based regimens. Thus, it is reasonable to think that aggressive surgical debulking combined with HIPEC involving cisplatin-based regimens is feasible and rational, with acceptable toxicity in patients with primary EOC, but this combination suits only a select group of patients in cases of recurrent EOC. In fact, not every patient can take advantage of the more favorable pharmacokinetics and the

increased cisplatin-DNA adduct formation resulting from HIPEC administration because platinum adduct formation not only decreases with distance from the surface of the tumor nodule, but the chemosensitivity of the tumor is unknown.[93] Therefore, the critical point of this approach is not only cytoreduction to nodules of less than few millimeters, thus allowing HIPEC to be effective but also to take into account that the chemoresistance to platinum-based regimens can be very high, primarily in patients with recurrent EOC. For these reasons, the true effectiveness of HIPEC in addition to extensive CRS is difficult to assess in such a heterogeneous group of patients like those presented in our study.

Furthermore, our study, like most published series,[17] involves a rather small sample and lacks an appropriate control group to test the efficacy of HIPEC beyond CRS in the treatment of EOC. Thus, prospective RCTs are necessary to investigate the role of this aggressive treatment concept. Such a trial should not only be well designed with regard to an appropriate sample size; the time point in the natural course of EOC for treatment with CRS and HIPEC should be chosen wisely. We suggest that CRS and HIPEC should be tested in women after a response to neoadjuvant platinum-based chemotherapy, in an attempt to enhance the probability of optimal cytoreduction and to use the response to neoadjuvant chemotherapy as an in vivo chemosensitivity test.

Particular attention must be given in our study to the morbidity and mortality and to the large use of resources related to a treatment in which a huge surgical cytoreductive effort is associated to the HIPEC. The risks of this complex procedure and the possible gain in survival should be weighed carefully by further phase 2 studies in different but homogeneous subgroup of patients with EOC, and only in some of these, probably HIPEC can be subjected to a randomized controlled trial. Taking into account these limitations, our study shows that this technique is safe enough to deserve further evaluation in a subset of patients with minimal residual disease after CRS. These patients would most likely benefit from the advantage of localized chemotherapy such as HIPEC. Selection criteria (good overall status, acceptable renal and myocardial function, and no extra-abdominal metastasis or unresectable tumors) may have introduced a selection bias in our study; however, our results are similar to those obtained in other recent studies.[17,18] Our data indicate that CRS combined with HIPEC is feasible and is associated with reasonable morbidity and mortality rates in patients with peritoneal carcinomatosis due to EOC. Complete cytoreduction may improve survival in highly selected patients (those with low tumor volume and no organ metastases). We conclude that although an advantage in overall survival seems possible from the combination of aggressive CRS and HIPEC in selected patients affected with primary or relapsed advanced EOC, this approach should not yet replace conventional intravenous therapy as a common therapy for EOC. Instead, the use of the HIPEC technique for the treatment of peritoneal carcinomatosis due to EOC will require some standardization efforts in light of patient indications and selection criteria, and further studies are needed.

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