

Safety and Potential Benefit of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Peritoneal Carcinomatosis From Primary or Recurrent Ovarian Cancer

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Objectives: To analyze the outcomes of cytoreductive surgery and HIPEC in patients with peritoneal carcinomatosis from ovarian cancer.

Methods: Fifty-three patients with peritoneal carcinomatosis from primary (45 cases) and recurrent (8 cases) ovarian cancer were previously treated by systemic chemotherapy with platinum and taxanes and then submitted to surgical cytoreduction and HIPEC (cisplatin and mitomycin-C) with a closed abdomen technique. The median follow-up period was 27 months (range: 3–107).

Results: At the end of operation a complete cytoreduction (CCR-0) was obtained in 37 patients (70%). Major morbidity occurred in 12 patients (23%); reoperation was necessary in 2 patients (4%), and no postoperative mortality was observed. Overall 5-year survival probability was 55%; it was 71% in CCR-0, 44% in CCR-1, and none in patients with CCR-2 or CCR-3 residual tumor (log-rank test: $P = 0.017$). The cumulative risk of recurrence in 37 CCR-0 cases was 54% at 5 years from operation.

Conclusions: The results of our study indicate the feasibility and the potential benefit of a protocol including systemic chemotherapy, surgical cytoreduction and HIPEC in patients with peritoneal carcinomatosis from ovarian cancer. A phase III trial to compare this approach with conventional treatment is needed.

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KEY WORDS: primary ovarian cancer; cytoreductive surgery; HIPEC; intraperitoneal chemotherapy; neoadjuvant chemotherapy

INTRODUCTION

Ovarian cancer is the sixth most common neoplasm in women, and age-standardized incidence and mortality rates reach the highest values in Northern-Western Europe and Northern America [1]. Due to the lack of specific symptoms and early tendency to peritoneal dissemination, in most cases diagnosis is made in advanced stages; this accounts for the poor prognosis recently reported by EUROCARE Working Group, with 5-year survival probabilities ranging between 30% and 40% [2].

The standard treatment of primary ovarian cancer with peritoneal dissemination involves optimal surgical cytoreduction followed by platinum/taxane based chemotherapy [3,4]. However, despite the notable chemosensitivity of this neoplasm, tumor recurrence occurs in most cases, particularly when extra-pelvic peritoneal dissemination is present, resulting in very low long-term survival probability [5–8]. In order to improve these results, perioperative normothermic intraperitoneal chemotherapy (IP) has been proposed, with the aim to increase the intraperitoneal concentration of chemotherapy agents and improve the contact with cancer cells. Phase III studies demonstrated a survival benefit of IP compared with systemic therapy [9,10]. However, these trials considered only patients submitted to optimal cytoreduction, and several complaints mainly related to the management of the catheter for IP and patient compliance were reported, so that less than half of patients finally complete the treatment [11].

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a locoregional treatment which involves the washing of peritoneal cavity with heated solution and high drug concentrations [12–15]. The rationale for HIPEC is based on direct cytotoxicity of hyperthermia against

malignant cells, combined with heat-related enhanced cytotoxic effects and pharmacokinetic advantages of the intraperitoneal route of anticancer drugs. Intraperitoneal administration is associated with a significantly greater drug concentration in the abdominal cavity compared with systemic concentration. The “peritoneal plasma barrier” mechanism provides locally dose-intensive therapy, in addition to the synergistic effect of hyperthermia. Moreover, hyperthermia provides a greater depth of tissue penetration of antitumor agents with respect to normothermic administration. In the treatment of peritoneal carcinomatosis, HIPEC is generally associated with surgical debulking and peritonectomy, with the aim to remove macroscopic tumor [16]. This advanced multimodality treatment is indicated in patients with pseudomyxoma peritonei, peritoneal mesothelioma and peritoneal carcinomatosis of colorectal origin, with significant

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy; ICU, intensive care unit; IP, intraperitoneal chemotherapy; NAC, neoadjuvant chemotherapy; PCI, peritoneal cancer index; SD, standard deviation; SE, standard error.

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improvement in long-term results with respect to the conventional treatment [12–14]. It has also been proposed in the adjuvant setting for the prevention of peritoneal recurrence from gastric cancer [12]. To date, several experiences have been reported on HIPEC as treatment of advanced ovarian cancer. Among these, the vast majority analyzed patients with recurrent disease or platinum-resistant and only a minority enrolled patients with primary ovarian cancer [15].

The aim of the present study is to evaluate the early and late results of HIPEC in patients with peritoneal carcinomatosis of ovarian origin; the peculiarity of our approach is the use of preoperative chemotherapy with platinum and taxanes before submitting patients to surgical cytoreduction and HIPEC in patients with advanced primary ovarian cancer.

MATERIALS AND METHODS

Patients

Between January 2000 and April 2009, 53 patients with peritoneal carcinomatosis of ovarian origin were treated by surgical cytoreduction and HIPEC at the Department of Human Pathology and Oncology, Section of Surgical Oncology, University of Siena, Italy.

General preoperative indications to treatment with HIPEC were histological or cytological diagnosis of ovarian cancer, evidence of peritoneal involvement, age lower than 73 years, good general conditions with adequate renal, hepatic and cardiovascular functions, performance status 0–2 (according to Eastern Cooperative Oncology Group, ECOG), and absence of haematogenous or extra-abdominal spread of disease. Preoperative staging included thoraco/abdominal CT scan, upper digestive endoscopy and complete colonoscopy. Of the 53 patients included in this study, 45 had a primary ovarian cancer and 8 a recurrent tumor. The main clinicopathological characteristics of the entire cohort, including associated co-morbidities, are listed in Table I.

In patients with primary ovarian cancer, extra-pelvic peritoneal dissemination of the disease was present in all cases at the time of primary diagnosis; most patients (40 cases, 89%) were classified in stage IIIc, and the remaining five patients (11%) in stages IIIa or IIIb according to the TNM-FIGO classification [5]. Our policy was to downstage the peritoneal disease before surgical cytoreduction; as such, all patients were treated by systemic chemotherapy with platinum and taxanes (generally six cycles) before being submitted to surgery and HIPEC. In particular, 14 out of 45 patients with primary ovarian cancer were submitted to primary debulking (including radical hysterectomy and adnexectomy) followed by systemic chemotherapy and final treatment with HIPEC, whereas 31 patients were treated by neo-adjuvant chemotherapy (NAC) followed by surgical cytoreduction and HIPEC. In this latter subgroup, explorative laparotomy or staging laparoscopy were always performed, with ovarian and/or peritoneal biopsies, before starting NAC.

As such, we could identify three potential groups of study: group A (NAC), group B (primary debulking), group C (recurrent tumor).

The applied treatment protocol was approved by the local ethical committee and informed consent was obtained from all patients.

Surgical Cytoreduction and HIPEC

After laparotomy, an accurate intraoperative re-staging of the disease, was performed, with complete examination of parietal and visceral peritoneum and multiple biopsies when necessary. Complete pelvic peritonectomy, peritonectomy of other abdominal quadrants, and visceral resections were performed, when necessary, in order to obtain a complete resection of the tumor [16,17]. Extensive involvement of the small bowel was the main contraindication to this aggressive approach. In patients with primary ovarian cancer, standard surgical debulking involved the en bloc pelvic peritonectomy with

TABLE I. Clinical and Pathological Characteristics of 53 Patients With Peritoneal Carcinomatosis From Primary or Recurrent Ovarian Cancer at the Time of Enrolment in the Study

Characteristics	n (%)
Age (years)	
Median	56
Range	28–72
≤50	16 (30)
>50	37 (70)
Body mass index	
Median	25
Range	19–41
<25	25 (47)
25–29	19 (36)
≥30	9 (17)
Type of pathology	
Primary ovarian cancer	45 (85)
Recurrent ovarian cancer	8 (15)
FIGO stage (primary ovarian cancer)	
IIIa	1 (2)
IIIb	4 (9)
IIIc	40 (89)
Co-morbidities	
Hypertension	8 (15)
Atherosclerosis	4 (8)
Thyroid dysfunction	3 (6)
Diabetes	2 (4)
Cardiac arrhythmia	2 (4)
Pleuropulmonary diseases	2 (4)
Epilepsy	1 (2)
Previous abdominal surgery	
Yes	7 (13)
No	46 (87)
ECOG performance status	
0–1	39 (74)
2	14 (26)

radical hysterectomy and adnexectomy, omentectomy, appendicectomy, para-aortic, and pelvic lymphadenectomy. This approach was also performed in the few cases with complete peritoneal response to NAC.

The type of surgical procedure performed is described in Table II. In most cases, extended or total peritonectomy was performed; however, in only a minority of cases visceral resections were necessary. Peritonectomy in the right diaphragm was commonly performed in our experience (25 cases).

After surgical resection, five silicon drains were inserted in the abdomen, temperature probes were positioned above the mesocolon and in the pelvis, and the abdominal wall was then closed. HIPEC was performed using a specific device (RAND Performer, Modena, Italy), with two pumps (inflow and outflow), a thermal exchanger, and a

TABLE II. Procedures Performed at the Time of HIPEC in 31 Patients in Group A (Neo-Adjuvant Chemotherapy), 14 Patients in Group B (Primary Debulking) and 8 Patients in Group C (Recurrent Ovarian Cancer)

Procedure	Group A (n = 31)	Group B (n = 14)	Group C (n = 8)
Hysterectomy ± adnexectomy	31	0	0
Peritonectomy			
Partial (1–3 regions)	4	5	2
Extended (4–6 regions)	17	5	4
Total (>6 regions)	10	4	2
Large bowel resection	3	2	2
Small bowel resection	1	0	0
Splenectomy	1	0	0

sterile closed circuit, as described elsewhere [18]. After reaching an intra-abdominal temperature of at least 41°C, chemotherapy agents (mitomycin C 25 mg/mq and cisplatin 100 mg/mq) were injected in 5 L of perfusate, and circulated with a flow rate of 700–800 ml/min for 60 min. The mean amount of perfusate injected into the abdomen was 3.1 L. Intra-abdominal temperature during circulation was kept between 41 and 43°C. A cooling and washing phase was performed in the initial phase of our experience (first 10 cases) and omitted afterwards. Anastomoses were performed at the end of HIPEC, after abdominal relaparotomy. At the end of operation, patients were generally admitted to the intensive care unit (ICU) and returned to the surgical ward when cardiovascular and pulmonary functions became stable. Antibiotic and thromboembolic prophylaxes were administered to all patients.

Classifications

The extent of peritoneal dissemination at the time of surgery and HIPEC was scored according to the peritoneal cancer index (PCI), which is commonly used for the classification of peritoneal carcinomatosis from different diseases [12]. The extent of peritonectomy was classified according to the number of removed regions in partial (1–3 regions), extended (4–6 regions), or total (>6 regions).

Residual tumor was classified according to standardized criteria in: CCR-0 (no residual tumor), CCR-1 (no residual nodule greater than 2.5 mm in diameter), CCR-2 (no residual nodules greater than 25 mm), and CCR-3 (residual nodules greater than 25 mm) [12]. Due to the low number of cases in CCR-2 and CCR-3 categories, these were included in the same group for statistical analysis.

Morbidity and mortality rates were calculated considering postoperative complaints occurring during the hospital stay or within 30 days from operation [19,20]. Pleural effusion was considered as a complication when postoperative drainage was required. In cases with multiple surgical or medical complications, the most severe was considered for quantitative analysis in each category. Complications and toxicity were graded from 1 to 5, according to the Common Terminology Criteria for Adverse Events (CTCAE) classification, version 3.0 [20,21].

Postoperative Treatments and Follow-Up

Postoperative consolidation chemotherapy with platinum and taxanes (three cycles) was generally administered to patients included in this study. After discharge, all patients were submitted to periodical follow-up examinations. These involved quarterly tumor marker assay (CA 125, CEA, CA 15-3), and thoraco-abdominal CT scan every 6 months for the first 3 years. From the fourth year after operation, marker assay was performed every 6 months and CT scan yearly.

Follow-up was closed on November 2009 and no patient was lost. The median follow-up period was 27 months (range: 3–107).

Statistical Analysis

For statistical analysis, a preliminary data exploration was performed. Numerical variables were expressed as median and range, and were compared by non-parametric tests (Mann–Whitney *U*-test). Qualitative data were expressed as frequencies and organized into contingency tables; the association between categorical variables and morbidity was investigated by means of the Fisher's exact test or Person's Chi-square.

Long-term survival was calculated according to Kaplan–Meier method, considering the interval between the date of operation and the date of death, and expressed as percent probability \pm standard error (SE); for surviving patients, the date of the last contact was considered as the end-date. Statistical difference between survival curves was

performed using the log-rank test. The risk of recurrence was calculated by Kaplan–Meier method and plotted as one minus survival, considering the interval between the date of operation and the date of the clinical diagnosis of the recurrence, as described elsewhere [22].

For the entire statistical analysis the significance levels was established at $P < 0.05$. All tests were two-sided. Statistical analysis was conducted by using SPSS statistical package (version 16.0) (SPSS™, Chicago, IL).

RESULTS

Surgical Data

In group A, after preoperative chemotherapy no macroscopic peritoneal dissemination of the tumor (PCI=0) was found in 9 out of 31 cases (29%); PCI was 1–6 in 12 cases (39%), 7–14 in 5 cases (16%), and ≥ 15 in 5 cases (16%). In group B, PCI was 0 in 3 cases (21%), 1–6 in 8 cases (57%), 7–14 in 2 cases (14%), and ≥ 15 in one patient (7%). In group C, PCI ranged between 1 and 6 in seven patients, and in the other patient it was ≥ 15 (Pearson's Chi-square: $P = 0.289$).

The median duration of operation was 7 h (range: 4–12). In group A, at the end of operation a complete cytoreduction (CCR-0) was obtained in 20 patients (64%); residual tumor was classified as CCR-1 in four patients (13%) and CCR-2 or CCR-3 in seven patients (23%). In group B, CCR-0 was obtained in 11 cases (79%), CCR-1 in one patient (7%), and CCR-2 or CCR-3 in two patients (14%). In group C, six cases (75%) were classified as CCR-0, and the other two cases (25%) as CCR-1 (Pearson's Chi-square: $P = 0.473$).

Postoperative Period and Analysis of Safety

The median stay in ICU was 24 h (range: 0–96). Postoperative surgical complications were observed in 11 patients (21%). Pleural effusion requiring drainage was the most common surgical complaint (Table III). Medical complications and toxicity were classified according to the CTCAE criteria, and were present in 22 patients (42%). Most complications were graded as mild or moderate, whereas 12 patients (23%) had grades 3 or 4 complications or toxicity (major morbidity). Most complications were treated conservatively or by interventional radiology, and reoperation was necessary in only two cases (4%). No postoperative mortality was observed.

The median postoperative hospital stay was 10 days (range: 7–49); it was 13 days (range: 9–49) in patients with major morbidity, and 9 days (range: 7–15) in patients without major complications (Mann–Whitney *U*-test: $P < 0.001$).

In order to evaluate clinical or surgical factors potentially predictive of major morbidity, a statistical analysis has been conducted (Table IV). Of the different factors under study, duration of operation and residual tumor after surgical resection resulted to be significantly associated with higher incidence of major complications. In particular, very low rates were observed in patients submitted to complete cytoreduction (CCR-0) or with minimal residual tumor (CCR-1); the highest rate (67%) was found in the CCR-2/CCR-3 subgroup. Other factors, such as the extent of peritonectomy, visceral resections and the study group, did not result as statistically significant predictors of major morbidity.

Late Results

At the end of follow-up period, 22 patients were alive and disease-free, 16 patients were alive with disease (including living patients with macroscopic residual tumor after surgical resection), and 15 patients died from ovarian cancer. Overall 5-year survival probability of the entire cohort was $55 \pm 10\%$ (Fig. 1). It was $58 \pm 12\%$ in group A,

TABLE III. Postoperative Complications and Treatment Performed in Patients Under Study (Multiple Complications Are Included)

Postoperative complications	No. cases (%) ^a	Grade of morbidity and treatment (CTCAE classification version 3.0)
Surgical complications		
Pleural effusion	5 (9)	Grade 3; percutaneous drainage
Wound infection	2 (4)	Grade 2; drainage
Intestinal fistula	1 (2)	Grade 4; reoperation
Intra-abdominal bleeding	1 (2)	Grade 4; reoperation
Abdominal abscess	1 (2)	Grade 3; US-guided drainage
Bleeding gastric ulcer	1 (2)	Grade 3; endoscopic haemostasis
Medical complications and toxicity		
Hematological	17 (32)	Grade 2; medical treatment
Hepatobiliary/pancreatic	7 (13)	Grade 2; medical treatment
Renal/genitourinary	3 (6)	Grade 2; medical treatment
Cardiac arrhythmia	2 (4)	Grade 3; medical treatment
Cardiac (hearth failure)	1 (2)	Grade 4; medical treatment, ICU Grade 2; medical treatment
Dermatology (rush)	1 (2)	
Major morbidity	12 (23)	
Reoperation rate	2 (4)	
Mortality rate	0	

CTCAE, Common Terminology Criteria for Adverse Events; US, ultrasound; ICU, intensive care unit.

^aPercentage was calculated on 53 patients under study.

55 ± 24% in group B, and 44 ± 22% in group C (log-rank test: $P = 0.720$).

Survival function according to the PCI at the time of surgical resection is reported in Figure 2. Five-year survival probability was 100% in patients with PCI 0, 48 ± 13% in patients with PCI 1–6, and none in patients with PCI > 6 (log-rank test: $P = 0.003$). A significant correlation between residual tumor and long-term outcome was also observed (Fig. 3). Five-year survival was 71 ± 10% in CCR-0,

44 ± 22% in CCR-1, and none in patients with residual tumor > 2.5 mm (CCR-2/CCR-3) (log-rank test: $P = 0.017$).

The cumulative risk of tumor recurrence was calculated in 37 patients without macroscopic residual tumor (CCR-0) after cytoreductive surgery. Of these 37 patients, 15 recurred with a median interval of 14 months (range: 4–69). The first site of recurrence was peritoneal in 11 cases, lymphnodal in 3 cases and haematogenous in one patient. At 5 years, the estimated cumulative risk of recurrence was 54 ± 12% (Fig. 4).

TABLE IV. Risk Factors for Major Morbidity (Grade 3 or 4 Complication/ Toxicity)

Variable	With major morbidity (n = 12)	Without major morbidity (n = 41)	P
Age (median and range)	56, 30–66	56, 28–72	0.924 ^a
Body mass index (median and range)	26, 10–37	25, 19–41	0.052 ^a
Peritoneal cancer index (PCI)			0.177 ^b
0	1 (8)	11 (92)	
1–6	5 (19)	22 (81)	
7–14	3 (43)	4 (57)	
≥15	3 (43)	4 (57)	
Study group			0.687 ^b
Group A	7 (23)	24 (77)	
Group B	4 (29)	10 (71)	
Group C	1 (12)	7 (88)	
Extent of peritonectomy			0.137 ^b
Partial	3 (27)	8 (73)	
Extended	3 (12)	23 (88)	
Total	6 (37)	10 (64)	
Visceral anastomosis			1.000 ^c
Not performed	10 (22)	35 (78)	
Performed	2 (25)	6 (75)	
Duration of operation (h) (median and range)	8, 6–12	7, 4–12	0.006 ^a
Residual tumor			0.002 ^b
CCR-0	6 (16)	31 (84)	
CCR-1	0 (0)	7 (100)	
CCR-2/CCR-3	6 (67)	3 (33)	

Numbers in parentheses are percentage. SD, standard deviation.

^aMann–Whitney *U*-test.

^bPearson's Chi-square.

^cFisher's exact test.

DISCUSSION

Despite the high sensitivity of ovarian cancer to cisplatin/taxane based chemotherapy, patients with peritoneal dissemination treated by cytoreductive surgery and systemic chemotherapy often experience peritoneal recurrence after clinically complete response to treatment. This may be due to the microscopic persistence of tumor in the peritoneal cavity even in absence of clinically assessed macroscopic residual tumor [17,23].

The application of HIPEC in patients with advanced ovarian cancer has a well established rationale. Most studies reported in literature applied cytoreductive surgery and HIPEC in recurrent ovarian cancer, and the largest series was published by the Lyon group [24–27]. In patients with recurrent ovarian cancer, the probability of long-term survival largely depends on the presence of residual tumor after cytoreductive surgery. In cases with residual tumor less than 2.5 mm in diameter, 5-year survival rates range between 20% and 40%; however, optimal cytoreduction is precluded in a significant proportion of patients with recurrent disease [24,26]. Furthermore, in platinum-resistant patients intraperitoneal chemotherapy may result in limited response to treatment. In our experience we tended to treat only few patients with recurrent ovarian cancer, and advanced recurrent cases were treated with HIPEC only if a clinical response to systemic chemotherapy was observed. The high rates of CCR-0 in group C and good long-term results achieved are indicative of this patient selection.

The main series regarding treatment with HIPEC in primary ovarian cancer are limited to few patients or have a short follow-up time [28–32]. In the largest experience reported by a Korean group HIPEC was performed after primary debulking surgery and systemic chemotherapy, and results were compared with patients treated with conventional protocol (primary debulking and systemic chemotherapy) [33,34]. A

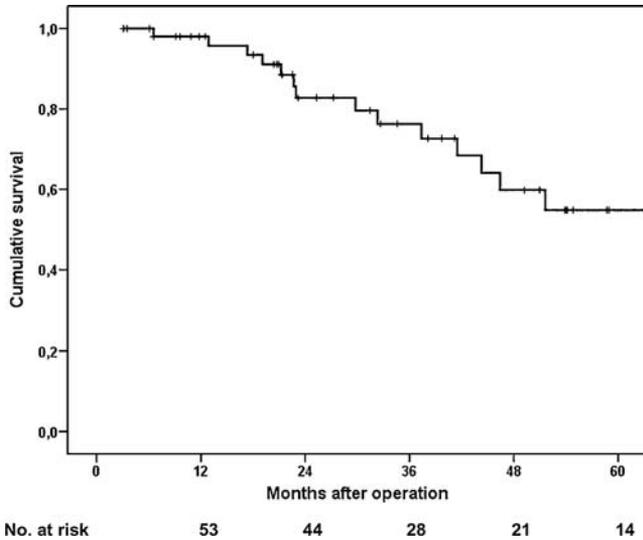


Fig. 1. Kaplan–Meier overall survival curves in 53 patients with peritoneal carcinomatosis from ovarian cancer treated by systemic chemotherapy, cytoreductive surgery, and HIPEC. Five-year survival probability is $55 \pm 10\%$ with a median follow-up period of 27 months.

significant improvement in overall survival was observed in the HIPEC group, above all in stage III tumors.

With respect to indications and preoperative treatment, the therapeutic approach developed at our Department focused on to patients with primary advanced ovarian cancer, and the main aim was to downstage the peritoneal disease by systemic chemotherapy before performing cytoreductive surgery and HIPEC. In the initial period of the study, patients were generally submitted to primary debulking followed by systemic chemotherapy and final treatment with HIPEC (group B); more recently, we tended to treat most of our patients with NAC, followed by surgical cytoreduction and HIPEC (group A). Even

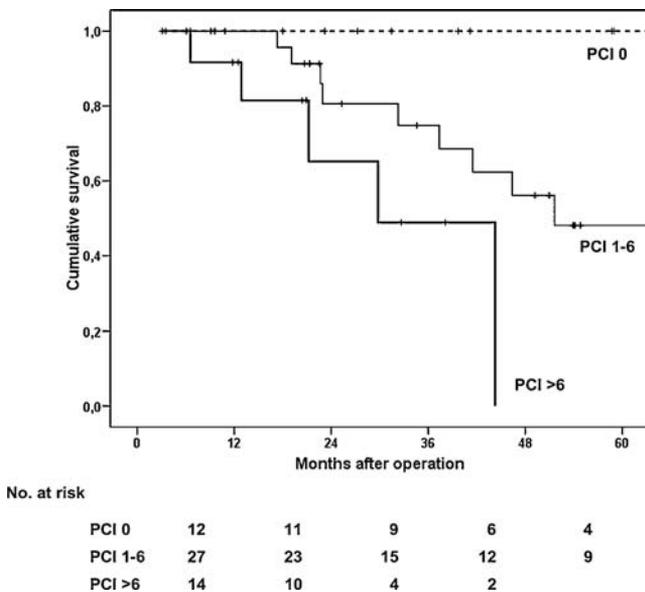


Fig. 2. Kaplan–Meier survival curves according to the peritoneal cancer index (PCI) at the time of surgery. The difference between the three groups is statistically significant (log-rank test: $P=0.003$, Chi-square: 11.72, df: 2).

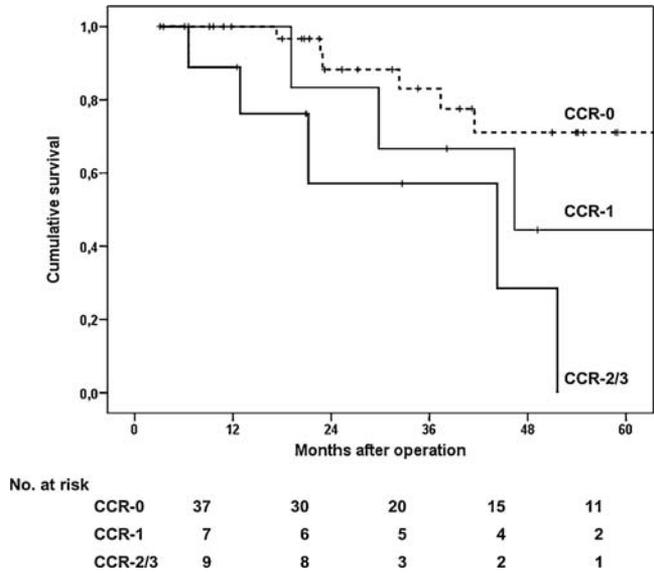


Fig. 3. Kaplan–Meier survival curves according to the residual tumor after cytoreductive surgery (CCR-0: no macroscopic residual tumor; CCR-1: residual nodules not greater than 2.5 mm; CCR-2/3: residual nodules greater than 2.5 mm). The difference between the three groups is statistically significant (log-rank test: $P=0.017$, Chi-square: 8.19, df: 2).

if a clear advantage of NAC versus upfront surgery in patients with advanced ovarian cancer has not been demonstrated in literature, above all when survival results are considered, several studies suggested that it could reduce the risk of postoperative complications and increase the rate of curative resections [35–37]. In particular, the odds ratio of suboptimal cytoreduction after NAC has been recently estimated to be 0.50 with respect to primary debulking [35]. Generally, a median of three/four cycles of NAC are provided in literature. In our protocol we planned six cycles of NAC, as advised by some authors, in order to maximize these effects, and reduce as much as possible the extent of peritoneal disease before surgical approach [38]. Indeed, in about one third of patients in group A no peritoneal nodules were found, and the

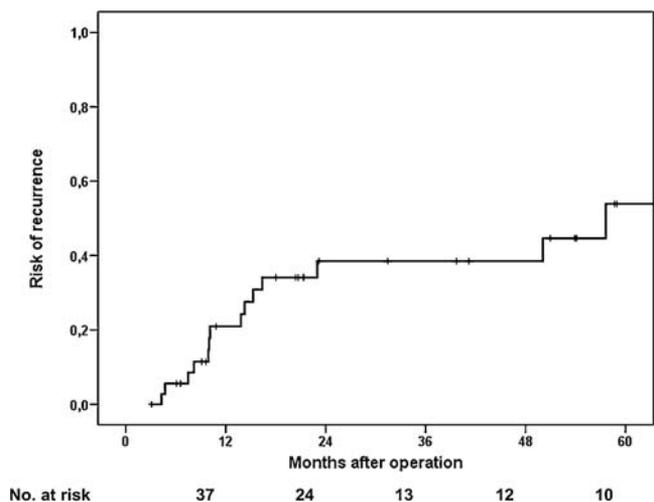


Fig. 4. Cumulative risk of recurrence in 37 patients without macroscopic residual tumor (CCR-0) after cytoreductive surgery. The estimated risk of recurrence is $54 \pm 12\%$ at 5 years from operation.

overall PCI score observed was lower than other recent experiences [30,32]. The higher number of cycles performed may be associated with a better response rate.

In our opinion, performing systemic chemotherapy before cytoreductive surgery and HIPEC may involve several clinical advantages with respect to upfront surgery: (1) the downstaging of peritoneal carcinomatosis reduces the extent of surgery necessary to obtain an optimal cytoreduction [4,35,36,38]. Only few visceral resections and total peritomectomies were necessary in our series and consequently the risk of complications may have been reduced [30,32]. (2) The downstaging of peritoneal disease allowed the inclusion in the protocol of those patients in which a primary "optimal cytoreduction" cannot be obtained (in particular when extensive tumor spread to visceral peritoneum is present) [10,11]. (3) NAC may allow the early identification of patients responders to platinum. The prognosis of platinum-resistant patients is generally poor, and they could benefit by second-line chemotherapy before face up an aggressive and high-risk procedure as HIPEC. Even if in our experience we did not observe significant improvement in PCI and in the rate of CCR-0 resection, as well as long-term survival, between group A and group B, we emphasize that few patients were included in the latter, and the non-randomized design of the study does not allow reliable comparison between groups. However, the notable downstaging of peritoneal disease observed in both groups supports the potential utility of preoperative chemotherapy before approaching peritoneal carcinomatosis with surgical debulking and HIPEC.

About the feasibility and safety of this approach, the results of some experiences warned against postoperative complications of HIPEC in patients with advanced ovarian cancer, with mortality rates ranging between 0 and 10% [15,24–32]. The overall rate of surgical complications and toxicity of our series locates in the range of values reported in the literature [15]; in particular, the incidence of major morbidity (grade 3: 17%, grade 4: 6%) was acceptable, and no postoperative mortality was observed. In our study, we used CTCAE classification to grade the severity of complications, as suggested by an international panel of experts, in order to better compare results with other series [20,21]. Our data confirm the feasibility and safety of this complex multimodality approach. We emphasize that the risk of complications is not negligible, but with an adequate management and an early recognition and treatment most complications may solve favorably [18,39]. Age of patients (younger than 73 years), good performance status, and the low rates of co-morbidities are indicative of an adequate patient's selection and were probably involved in the favorable outcome of complicated patients.

Particular attention should be paid to the potential occurrence of intestinal fistula, which is the main cause of mortality; it was observed in only one patient in our series [26,33,40]. Intestinal fistula may occur not only in the site of visceral anastomosis, but even as a consequence of adhesiolysis. Patients submitted to NAC generally do not require adhesiolysis, and this may be considered another advantage with respect to secondary surgery and HIPEC.

In most of our patients we obtained an optimal cytoreduction without macroscopic tumor residual (CCR-0) after surgical debulking. Five-year survival probability of our series is very high, and resulted significantly related to the CCR status, with 71% 5-year survival probability in the CCR-0 group. This confirms that the therapeutic role of HIPEC should be directed towards the microscopic peritoneal dissemination of the tumor [18]. An intermediate survival rate (44%) was recorded in CCR-1 subgroup, whereas no probability of 5-year survival was observed in patients with residual nodules greater than 2.5 mm, as also reported by other authors [24,26,30]. These findings, and the high rates of complications observed, do not indicate in our opinion this procedure in patients with large residual tumor.

Randomized studies obtained a survival benefit, compared with systemic chemotherapy, using normothermic IP in patients submitted

to optimal cytoreduction [9–11]. However, in these studies less than half of enrolled patients completed IP, mainly because of catheter-related complications. So, few patients could finally benefit from this treatment, and this is a disadvantage with respect to HIPEC, that we performed in all CCR-0 cases. The synergistic effect of heat and chemotherapy, and an increased penetration of chemotherapeutic agents in the peritoneal surface are other potential advantages of HIPEC with respect to IP [15].

The estimated cumulative risk of recurrence in the group of CCR-0 patients was 54% at 5 years. In several cases recurrence occurred in the peritoneum. Three patients were treated again with surgical cytoreduction and HIPEC, but finally died of peritoneal carcinomatosis. The disease-free survival observed in our patients is very high with respect to the rates reported in patients with stage III ovarian cancer who obtained a clinically complete response after conventional treatment [10,34].

However, some limitations of this study should be outlined. First of all, as the residual tumor in our patients was assessed intraoperatively, an indirect comparison with other studies which considered a "clinically assessed complete response" after primary debulking and systemic chemotherapy may be misleading. Another limitation regards the extent of cytoreduction, which is associated with improved survival in ovarian cancer with peritoneal dissemination [3,15]. In protocols including extended debulking and HIPEC the exact role of intraperitoneal chemohyperthermia in improving survival in addition to surgical cytoreduction remains unclear.

The third limitation is the potential selection of patients according to the response to NAC. In this study we could not assess the exact rate and clinical outcome of non-responders, which were excluded from treatment protocol. A prospective phase II trial in collaboration with medical oncologists and gynaecologists of our University Hospital started in 2007 and is ongoing (HIPEC_ovaio, EudraCT number 2007-005674-31); the aim of this trial is to evaluate the rate of response to NAC and the early and late results in a consecutive population of patients with peritoneal carcinomatosis from primary ovarian cancer in an intention-to-treat setting.

Finally, we emphasize that the real survival benefit of HIPEC in ovarian cancer could only be assessed by prospective phase III trials which are under study [41,42]. However, several doubts are raising about the feasibility and safety of multicenter studies involving extensive cytoreductive surgery. In our opinion, the use of NAC as designed in our protocol could facilitate the feasibility of a multicenter trial and reduce the risk of complications associated with extended procedures.

CONCLUSIONS

The results of our study indicate the feasibility and safety of a protocol including systemic chemotherapy, surgical cytoreduction and HIPEC in patients with peritoneal carcinomatosis from ovarian cancer. In many patients this approach results in a complete cytoreduction. The risk of morbidity is acceptable, and an adequate patient selection and perioperative management are able to minimize the risk of mortality. Excellent long-term results in terms of overall and disease-free survival can be achieved in patients with absent or minimal residual tumor. A phase III trial is needed to assess the potential benefit of this approach with respect to conventional treatment.

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