Abstract. Cytoreductive surgery followed by platinum based systemic chemotherapy is an effective treatment for advanced ovarian epithelial carcinoma, resulting in up to 80% complete response (CR) rate; however only 30% of patients reaches 5-year survival. The low extra-abdominal relapse attitude leads to consider the opportunity of treatment intensification combining aggressive cytoreductive surgery with locoregional chemotherapy for FIGO stage III/IV ovarian carcinoma recurrent after the first-line chemotherapy, having still a curative intent. Patients and Methods: An "open" intra-abdominal hyperthermic perfusion with 25 mg/m²/l cisplatin of perfusate or 50 mg/m² cisplatin plus 15 mg/m² doxorubicin was carried out throughout the abdomino-pelvic cavity on 42 patients affected by peritoneal carcinomatosis from ovarian primary, soon after tumor removal en bloc with regional involved peritoneum. Clinical and oncologic data have been prospectively recorded on a dedicated database. Results: Forty-two patients, submitted to peritonectomy, achieved no residual macroscopic disease in 83% of the cases. Hyperthermic chemoperfusion was performed in 95% of the patients. Major complications were observed in 21.4%, being directly correlated to the duration of the surgical procedure (p=0.03). The operative mortality was 4.7%. At a mean follow up of 22 months, the overall 3-year survival was 61.4%, with a median survival of 41 months. Conclusion: Complete cytoreduction is possible for the majority of patients, allowing encouraging survival to be reached. Careful selection of patients could reduce surgical risk and further improve survival.

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Approximately 25,000 woman are diagnosed each year with epithelial ovarian carcinoma in the USA. Because of the absence of specific symptoms in the early stage of the disease, two-thirds of patient are initially diagnosed with advanced disease (1).

Standard treatment for advanced ovarian cancer consists in debulking surgery followed by platix and taxol-containing systemic chemotherapy: an objective response can be achieved in 70-80% of the patients with a high rate of complete response. However, up to 47% of complete responders relapse within 5 years and only 30% reach 5 year overall survival (2); moreover second-line chemotherapy fails to induce cure.

Surgical debulking has been one of the mainstays in the treatment of advanced ovarian cancer since Griffith showed an inverse relationship between residual tumor diameter and survival (3). Recently Bristow evaluated, by a meta-analysis, the impact on survival of surgical cytoreduction in 6,885 stage III/IV ovarian carcinoma patients treated with platinum-based chemotherapy (4). The results showed a statistically significant positive correlation between the percentage maximal cytoreduction and the log of the median survival time: each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time. This can be explained by the log-kill hypothesis: chemotherapeutic agents kill a constant fraction of cells, rather than a specific number of cells, increasing the likelihood that repeated cycles of chemotherapy will reduce the number of viable tumor cells toward zero, after the initial surgical reduction of tumor volume (5). In recent years, peritonectomy procedures have been proposed by Sugarbaker in order to increase the rate of optimal cytoreduction and to enhance the survival benefit (6).

Further therapy intensification has been proposed by modifying the chemotherapeutic approach. The NIH sponsored Gynecology Oncology Group (8) carried out a phase III study among 415 patients with advanced ovarian carcinoma and no
residual mass greater than 1 cm after debulking surgery. Patients were randomized to receive intravenous cisplatin and paclitaxel vs. intraperitoneal cisplatin and paclitaxel plus intravenous paclitaxel every three weeks for six cycles. Despite the fact that less than half of the patients in the experimental arm completed all these six cycles, their group still had a significantly longer median duration of disease-free survival ($p=0.05$) and overall survival ($p=0.03$).

The hyperthermic intraperitoneal chemotherapy, performed immediately after peritonectomy, takes advantage of the synergism between hyperthermia and employed antiblastic drugs, providing a better distribution on peritoneal layers and a better penetration in the residual tumor than does delayed intraperitoneal infusion chemotherapy, and can be easily integrated with peritonectomy.

On the basis of this rationale, we employed the association of peritonectomy and regional perfusion chemotherapy in advanced peritoneal carcinomatosis from epithelial ovarian primary. The present study concerns our experience on 42 consecutive patients treated in two Institutions.

Patients and Methods

Patients affected by peritoneal carcinomatosis from ovarian epithelial primary have been considered for combined surgical treatment in two Institutions, with the same protocol, the only exception concerning the perfused drugs: cisplatin and doxorubicin at the San Camillo Hospital vs. cisplatin alone at the Regina Elena Cancer Institute. Inclusion criteria were the following: histological diagnosis of stage III/IV epithelial invasive ovarian carcinoma; age less than 75 years; recurrences after surgery and first line chemotherapy; partial response to first line chemotherapy with persistent disease; leukocyte count >3500/mm$^3$, neutrophyl count >1500/mm$^3$, and platelet count >100,000/mm$^3$; adequate renal function with serum creatinine level <1.5 mg/dl; performance status (ECOG) 0, 1; informed consent from the patients; cytoreducible disease evaluated by abdominopelvic CT scan or laparoscopy.

Patients with abdominal non resectable disease or extra-abdominal disease were excluded from the study.

Combined aggressive treatment consisted of surgical cytoreduction (peritonectomy) and hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin and doxorubicin in 19 patients and cisplatin alone in 23 patients.

Total peritonectomy is the completion of several surgical procedures well standardized by Sugarbaker (6) deriving from the division of the peritoneum into different surgical areas. Soon after the fascia incision, the dissection should remain extraperitoneal until most of the subdiaphragmatic and parietocolic peritoneum is removed clean. The peritoneum is then opened and the abdomen carefully explored in order to confirm the pre-operatorary videolaparoscopic report. All visceral disease is removed en bloc with the peritoneum, most frequently the cecum and the right colon where the tumor implants usually develop a large neoplastic plate; gastric antrum resection due to the presence of tumor deposits may often be necessary.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is carried out throughout the abdominal-pelvic cavity at the completion of peritonectomy; the temperature has to be maintained at 41.5°C - 42.5°C, which, according to our studies (9), is the optimal temperature to obtain a true synergism with the employed antiblastic drugs, maintaining regional toxicity at acceptable levels. At the abdominal temperature of 41.5°C cisplatinum, 25 mg/m$^2$l of perfusate (23 patients), or cisplatin at 50 mg/m$^2$l plus doxorubicin at 15 mg/m$^2$ (19 patients), are introduced into the circuit, perfusion lasting for 60-90 minutes.

The first postoperative recovery takes place in the Intensive Care Unit.

Clinical data have been recorded in a standard database form and evaluated by the same author. Toxicity was defined according to the WHO criteria. Survival analysis was performed with Kaplan-Meier’s method and comparison of curves with the Log-rank test. Standard probability cut-off, $p<0.05$, was chosen as significance level.

Results

Forty-two patients, mean age 52 years, with peritoneal carcinomatosis from ovarian epithelial primary underwent peritonectomy in two Institutions. A member of the surgical staff participated in most of the integrated treatments at both Centres. Informed consent was obtained in all cases.

The primary tumor at the presentation was FIGO stage IIIB in 5 patients, IIIC in 24 and stage IV in 11; the stage of the primary in 2 cases was not available. The disease was persistent in 22 patients (52.4% ) and recurrent in 20 patients (47.6% ) after at least one chemotherapy regimen (median 1.6, range 1-4). Some surgery, not including laparotomic or laparoscopic abdomino-pelvic exploration and biopsies, had been previously performed in 45% of the patients, with a median number of surgical procedures of 1 (range 1-4).

Many carcinomatoses were advanced, the median Sugarbaker peritoneal cancer index (PCI) being 16 (range 6-29). Preoperatively, 38.1% of the patients showed initial symptoms of intestinal occlusion and one was completely occluded; 29 patients had ascites at their presentation.

As far as the extent of cytoreduction is concerned, total peritonectomy was carried out in 31% of the patients and subtotal peritonectomy was performed in 59.9%; only 9.5% had fewer than 3 abdominal regions resected. Peritonectomy was completed with no evidence of macroscopic disease in 83.3% of the cases, while completeness of cytoreduction (CC) scored 1 in 9.5% and 2 in 7.1% of the patients.

The average duration of the procedure was 9 hours (range 6-12 hours). Intraoperative complications (cardiovascular failures) in 2 patients forced the peritonectomy to be halted before the cytoreduction was completed. Another patient encountered intraoperative bleeding that evolved into disseminated intravascular coagulopathy and to death on the second postoperative day.

Loco-regional chemotherapy was performed in 95.2% of the patients. When locoregional perfusion chemotherapy could not be given, systemic chemotherapy was then administered.
Major morbidity was 21.4%, anastomotic leakage was observed in only one patient. The mortality rate was 4.7%: one patient, as previously outlined, died as a consequence of disseminated intravascular coagulopathy and another one died on 18th postoperative day for adult respiratory distress syndrome. As far as toxicity is concerned, in one patient renal grade 1 toxicity was observed.

The duration of the surgical procedure was directly correlated to the clinical outcome ($p=0.03$).

At a median follow-up of 22 months (range 1-94) the overall 3-year survival was 61.4%, with a median survival of 41 months (95% CI 33-48 months). Disease-free survival at 2, 3 and 5 years was 61.9%, 37.5% and 32.1% respectively (Figure 1).

Stage at presentation correlated to a difference in 3-year survival, being 61.3% for stage III and 37.5% for stage IV.

Three-year disease-free survival was 43.2% and 31.9% respectively for peritoneal cancer index (PCI) lower and higher than the cut-off of 12 (Figure 2). Complete cytoreduction led to 3-year survival of 72% vs. 22.2% following incomplete cytoreduction (Figure 3).

Discussion

Ovarian cancer remains the most lethal of all gynecological malignancies, being responsible for approximate 50% of all deaths from female genital tract cancer (10).

Over the past decades it has become established, through meta-analysis (4), that optimal resection of metastatic epithelial ovarian cancer followed by platinum-based chemotherapy has a favourable impact on the survival of patients with advanced stage disease. Recent studies (11-13) showed a survival advantage in patients affected by peritoneal carcinomatosis from several primaries, when aggressively treated by locoregional integrated therapies, the goal being to remove all the macroscopic disease with peritonectomy procedures and to eradicate microscopic residual disease using hyperthermic intraperitoneal chemotherapy (HIPEC) or early postoperative intraperitoneal infusion chemotherapy (EPIC).

Peritonectomy and hyperthermic intraperitoneal chemotherapy have been the object of numerous phase I and II studies and proved to be effective on carcinomatosis from appendicular, colorectal and even gastric primary adenocarcinoma (14-17). A phase III (11) study on colorectal carcinomatosis treated by palliative surgery, 5-fluorouracil
and leucovorin vs. peritoneectomy and hyperthermic chemoperfusion plus adjuvant systemic chemotherapy found the survival in the experimental arm to be double that in the control arm. Such a treatment promises similar results on ovarian carcinomatosis setting because:

ovarian carcinoma has a low extraregional dissemination, surgical cytoreduction has proven to strongly affect survival of patients affected by advanced ovarian carcinoma, and intraperitoneal chemotherapy demonstrated a survival advantages vs. systemic chemotherapy in several phase III studies on surgically debulked ovarian carcinomatosis.

In spite of this strong specific rationale that overlaps the rationale of locoregional integrated treatment and put together selected carcinomatosis from several primaries, only few studies have been conducted on dealing with ovarian carcinomatosis by peritoneectomy and HIPEC.

Van der Vange et al. (18) issued a feasibility pilot study on 5 patients treated with extensive cytoreductive surgery associated with intraoperative hyperthermic chemoperfusion with cisplatin at the dose of 50-70 mg/m². They found few major complications and a low toxicity rate, with a median period of hospitalization of 25 days. The disease-free interval was short and the Authors concluded that the effectiveness of such a treatment is likely to be dependent on the effectiveness of postoperative adjuvant chemotherapy.

Three years later, Chatzigeorgiou et al. (19) published their experience on 20 heavily pre-treated patients with recurrent ovarian cancer. Cytoreductive surgery consisted of debulking, with remaining disease less than 1.5 cm in greatest diameter in 12 patients and greater than 1.5 cm in 8. Perfusion was performed at a temperature of 39-40°C with cisplatin 50-70 mg/m². The median ascites-free period was 21 months. Median survival was 29 and 7 months respectively in patients with residual disease smaller and larger than 1.5 cm.

In 2004 Plaisant et al. (20) reported a study on 13 patients who received intraperitoneal paclitaxel therapy (175 mg/m²) after secondary cytoreductive surgery or surgery for recurrent disease. Hematological toxicity grade III-IV was reported by 12 patients. Operative mortality was 7.7%. The median overall and disease-free survival were 25.5 and 8.5 months respectively, allowing the Authors to conclude that the locoregional control for recurrent disease was very poor.

In the same year Piso et al. (21) published the results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy at 41.5°C with cisplatin or mitoxantrone in 19 patients affected by peritoneal carcinomatosis from primary or recurrent epithelial ovarian carcinoma. Macroscopically complete cytoreduction was achieved in 9 patients. Complications occurred in seven patients and one died postoperatively. The mean overall survival time was 33 months, with a 5-year survival rate of 15%. Survival was found to be influenced by the completeness of cytoreduction (44 vs. 25 months, \(p=0.40\)) and tumor volume (54 vs. 16, \(p=0.002\)). Absence of involved lymph node had a positive influence on prognosis (20 vs. 38 months with lymph node metastases, \(p=0.2\)). Patients with liver metastases had poor prognosis (51 vs. 21 months without liver metastases, \(p=0.1\)). They concluded that integrated treatment may improve survival in a selected group of patients with low tumor volume and no organ metastases, when a complete cytoreduction is feasible.

Again in 2004, Ryu et al. (22) retroactively reviewed 117 stage Ic-III ovarian cancer patients. Fifty-seven patients underwent cytoreductive surgery with HIPEC (carboplatin 350 mg/m² plus interferon-alpha 5,000,000 IU/m² at 43-44°C) and 60 patients underwent cytoreductive surgery only. Considering stage III ovarian cancer patients only, the survival rate was 53.8% in the HIPEC group (n=35) and 33.3% in the control group (n=39) (\(p=0.0015\)). Multivariate analysis showed HIPEC as an independent prognostic factor that was not affected by surgical staging or tumor size after second surgery.

In 2006, Rufián et al. (23) evaluated a series of 33 stage III ovarian cancer patients submitted to peritoneectomy and HIPEC with paclitaxel. Patients with optimal cytoreduction obtained survival rates of 63% at 5 years in recurrent ovarian carcinoma and 60% in primary ovarian carcinoma and they found that optimal cytoreduction (\(p=0.018\)) and negative lymph nodes (\(p=0.005\)) were covariates for major prognostic survival.

The results of a prospective single center study on 81 patients with recurrent or chemoresistant peritoneal carcinomatosis from ovarian cancer were published in 2007 (24). Complete macroscopic resection (CCR-0) was achieved in 45 patients. Mortality and morbidity rates were 2.5% and 13.6%, respectively. With a median follow-up of 47.1 months, the overall median survival was 28.4 months, rising to 54.9 months when considering only patients that had complete macroscopic resection. Extent of carcinomatosis and
completeness of cytoreduction ($p=0.02$ and $p<0.001$, respectively) were identified as independent prognostic factors.

Recently a systematic review (25) of cytoreductive surgery combined with HIPEC for treatment of carcinomatosis in primary and recurrent ovarian cancer found this treatment an option that is worthy of further investigation, but that selection criteria for patients most likely to benefit need to be defined.

In the present study many patients had been heavily pretreated with surgery (45% of the patients had had up to 4 surgical procedures) and systemic chemotherapy (all the patients had had up to 4 chemotherapy regimens). The median PCI was 16, initial signs of intestinal occlusion were present in 38% of patients and carcinoma was associated with ascites in 69%. Despite the advanced disease, complete cytoreduction (no evidence of macroscopic disease) was obtained in 83% of the cases at the cost of 21% major morbidity and 4.7% mortality. Oncological outcome was impressive, the median survival being 41 months and the overall 3-year survival being 61.4%, which rose to 74% when the cytoreduction was complete.

PCI was not significantly correlated to survival. This is in disagreement with other Authors who found a direct correlation between extent of carcinoma and oncological outcome. We believe that PCI is an important factor to consider in patient selection, but basically remains a preoperative index and its impact on survival can be modified during the course of the treatment. Although several Authors (20-23,26) concluded that PCI is a strong prognostic indicator of survival in ovarian carcinomatosis, it must be underlined that in most series, the complete cytoreduction rate was low and HIPEC was not performed in all the studies. A high chemosensitivity after a complete cytoreduction may perhaps modify the adverse prognosis of a high PCI.

Conclusion

The combination of peritonectomy and IHCP is associated with reasonable morbidity and mortality rates. It leads to impressive survival rates in patients with peritoneal carcinomatosis from ovarian epithelial cancer provided that the cytoreduction is complete. Careful patient selection is mandatory and the PCI should be integrated with other prognostic factors.

References


