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Cytoreductive surgery and perioperative intraperitoneal chemotherapy in recurrent ovarian cancer

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ABSTRACT

Background and aims. Cytoreductive surgery with perioperative intraperitoneal chemotherapy is another approach for recurrent ovarian cancer. The purpose of the study was to assess the feasibility and the effect of cytoreduction and perioperative intraperitoneal chemotherapy in recurrent ovarian cancer.

Patients and methods. Twenty-nine women with recurrent ovarian cancer underwent cytoreductive surgery. Clinical variables were correlated to morbidity, hospital mortality, recurrences, and survival.

Results. Complete cytoreduction was possible in 58.6%. Extensive seeding of the small bowel and distant metastases excluded the possibility of performing complete cytoreduction. Perioperative intraperitoneal chemotherapy was given in 75.9%. Morbidity and hospital mortality rates were subsequently 24.1% and 3.4%. Recurrence was recorded in 48.3%. The extent of peritoneal dissemination was an independent variable of recurrence ($P = 0.014$). The 5-year survival rate was 30%. The extent of peritoneal dissemination and the completeness of cytoreduction were related to survival ($P < 0.05$). The completeness of cytoreduction independently influenced survival ($P = 0.013$).

Conclusions. Secondary cytoreduction with intraperitoneal chemotherapy is feasible in most women with recurrent ovarian cancer with acceptable morbidity and mortality. Complete cytoreduction is not possible if distant and unresectable metastases are present or if the small bowel is extensively seeded. Long-term survivors are patients with limited peritoneal dissemination who may undergo complete cytoreduction. **Free full text available at www.tumorionline.it**

Introduction

The role of secondary cytoreduction in recurrent ovarian cancer has been strongly questioned[1-5]. Optimal cytoreductive surgery has been identified as one of the most powerful determinants of survival in the treatment of primary ovarian cancer, provided that the entire macroscopically visible tumor has been removed[6-8].

The treatment strategies for recurrent ovarian cancer have changed over the last decade. Complete cytoreductive surgery with standard peritonectomy procedures and perioperative intraperitoneal chemotherapy is available and seems to improve long-term survival[9-11]. Complete cytoreduction is not always feasible. The feasibility of complete cytoreduction varies widely, ranging from 38-83% in the literature[12,13].

The objectives of the study were: 1) to assess the feasibility of complete cytoreductive surgery and identify the clinical factors that exclude the possibility of complete cytoreduction, 2) to evaluate the impact of complete cytoreduction on long-term survival and identify the clinical variables related to survival, and 3) to assess the clinical factors related to hospital mortality and morbidity in women with recurrent ovarian cancer.

Key words: cytoreductive surgery, intraperitoneal chemotherapy, morbidity-mortality, recurrent ovarian cancer, survival.

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Patients and methods

The records of 29 women with recurrent ovarian cancer treated from 2000-2008 were retrospectively reviewed. Their mean age was 59.9 ± 9.5 years (range, 44-82). All the patients had been heavily treated with systemic combination chemotherapy consisting of carboplatin plus taxanes. The interval between the last dose of systemic chemotherapy and secondary surgery was at least 7 months. The diagnosis and staging was possible by physical examination, hematological-biochemical examinations, tumor markers, abdominal and thoracic computed tomography scan, and bone scan.

Variables such as performance status, age, extent of previous surgery, tumor volume, completeness of cytoreduction, extent of peritoneal dissemination, the presence of ascites and distant metastases, and treatment with systemic or intraperitoneal chemotherapy were evaluated and correlated to survival, morbidity, and hospital mortality.

The presence of metastatic disease in lymph nodes that had no anatomic relation to the primary site was considered as distant metastasis. The extent of peritoneal dissemination was calculated using the peritoneal cancer index (PCI)[14]. The extent of previous surgery was assessed using the prior surgery score, and the completeness of cytoreduction (CC) score[15]. Only CC-0 surgery was considered as complete cytoreduction. The Karnofsky performance scale was used to assess the physical status.

The patients received hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with the Coliseum technique[14,15] after the completion of cytoreduction and before reconstruction of the gastrointestinal tract with the use of a heat exchanger, one roller pump, one reservoir, and a heater/cooler unit (ThermoChem Ht-1000, ThermaSolutions, White Bear Lake, MN, USA). Cisplatin (50 mg/m^2) with doxorubicin (15 mg/m^2) was used during HIPEC for 90 min at a stable mean temperature of 42-42.5 °C. Early postoperative intraperitoneal chemotherapy (EPIC) was performed during the first five postoperative days either with docetaxel (100 mg/m^2) or with 5-fluorouracil (650 mg/kg body weight). The treatment plan for patients who underwent complete cytoreduction was adjuvant HIPEC only. HIPEC and EPIC was planned for patients with CC-1 or CC-2 surgery and EPIC and systemic chemotherapy for those with CC-3 surgery. Additional systemic chemotherapy was planned for patients who had systemic disease (lymph node involvement). Severe hematological toxicity was classified according to the WHO scale.

During the follow-up, patients were assessed with physical examination, hematological-biochemical examinations, tumor markers, and CT scans every 6 months.

The proportions of patients with a given characteristic were compared by chi-square analysis or by Fisher's exact test. Differences in the means of continuous measurement were tested by Student's *t* test. Survival curves were obtained using the Kaplan-Meier method, and the comparison of curves was calculated using the logrank test. Cox's regression model was used for multiple analysis of survival. Logistic regression analysis was used for multiple analysis of recurrence. A two-tailed *P* value <0.05 was considered statistically significant.

Results

The physical status of most of the patients (86.2%) was excellent (90-100%). Extensive cytoreductive surgery (in more than 2-5 abdominopelvic regions) had been performed in nearly half of the patients at initial surgery. Large volume tumors were found in 75.9% of the patients. Ascites and extensive peritoneal dissemination (PCI >13) were present in nearly half of the patients. Distant metastases were found in 5 patients. Three of them had positive nodal disease and 2 had positive pleural effusion (Table 1).

Table 1 - Patient characteristics

Variable	No	%
Performance status (Karnofsky)		
z 90-100%	25	86.2
70-80%	3	10.3
50-60%	1	3.4
PSS		
1	15	51.7
2	7	24.1
3	7	24.1
Tumor volume		
Small	7	24.1
Large	22	75.9
PCI		
<13	15	51.7
>13	14	48.3
Ascites	15	51.7
Metastases	5	17.2
Systemic chemotherapy	22	75.9
Intraperitoneal chemotherapy		
EPIC	11	37.9
HIPEC	9	31
HIPEC + EPIC	2	6.9
CC score		
0	17	58.6
1, 2, 3	12	41.4
Morbidity	7	24.1
Hospital mortality	1	3.4

CC score, completeness of cytoreduction; EPIC, Early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraoperative intraperitoneal chemotherapy; PCI, peritoneal cancer index; PSS, prior surgery score.

Treatments

Midline laparotomy was used for maximal abdominal exposure. The patients underwent cytoreductive surgery with standard peritonectomy procedures (Table 2). Complete cytoreduction was possible in 17 patients (58.6%). Twenty-two patients (75.8%) received intraperitoneal chemotherapy. Eleven of them received EPIC, 9 HIPEC, and 2 HIPEC + EPIC. Six patients received systemic chemotherapy because of incomplete cytoreduction. In addition to perioperative intraperitoneal chemotherapy, systemic chemotherapy was administered in 13 patients for whom histologic examination revealed positive lymph nodes (Table 1). Complete cytoreduction was not feasible in 12 cases (41.4%). Extensive seeding of the small bowel was identified in 10 cases (83.2%) and nodal involvement at distant sites from the primary region which were unresectable in 2 cases (16.7%).

Morbidity and hospital mortality

The hospital mortality rate was 3.4% (one patient). No clinical variable related to mortality was identified. Major morbidity was recorded in 7 patients (24.1%). One patient (3.4%) presented pulmonary failure, 3 patients (10.3%) had anastomotic failure, 2 (6.9%) had wound infection, 2 (6.9%) had grade II neutropenia, and 2 patients (6.9%) had cardiac arrhythmia. Two patients who underwent complete cytoreduction and 5 patients who underwent incomplete cytoreduction had major complications. Although no clinical factor was found to be related to morbidity, the CC score showed a trend to be adversely related to morbidity (P = 0.064). The higher the CC score, the higher the morbidity. Severe hematological toxicity was not recorded. Grade II neutropenia was recorded in 2 patients but did not require any treatment.

Follow-up

The median follow-up was 34 months. Recurrence was recorded in 14 patients (48.3%). Distant metastases were recorded in 4 patients (13.8%) and local-regional recurrence in 10 patients (34.5%). The extent of peritoneal dissemination was found to be related to recurrence (P = 0. HR 016). By multivariate analysis, it was shown that the PCI was an independent factor of recurrence (P = 0.014; = 6.875; 95% CI, 1.348-35.059). In patients with complete cytoreduction, the recurrence rate was restricted to 29.4% (5 patients). Distant metastases were recorded in 2 of them and local-regional relapse in 3. In patients with a PCI <13, the recurrence rate was 26.7% (4 patients). Two patients were recorded with local-regional recurrence and 2 others with distant metastases.

Survival

The overall 5-year survival rate was 30%. The median survival was 34 months (95% CI, 14-54) (Figure 1). The extent of peritoneal dissemination (P = 0.0356) and the completeness of cytoreduction (P = 0.0007) were the clinical variables found to be related to survival. Physical status, the presence of metastasis, prior surgery score, the presence of ascites, treatment with systemic chemotherapy, and tumor volume were not related to survival (P>0.05). The five-year survival rate for patients

Table 2 - Peritonectomy procedures

Procedure	No	%
Epigastric peritonectomy	29	100
Pelvic peritonectomy	19	65.5
Subdiaphragmatic peritonectomy		
Right	4	13.8
Bilateral	3	10.3
Cholecystectomy + resection of omental bursa	13	44.8
Greater omentectomy		
+ splenectomy	5	17.2
– splenectomy	10	34.4
Lesser omentectomy	2	6.9
Lateral peritonectomy		
Right	1	3.5
Left	2	6.9
Bilateral	12	41.4
Visceral peritonectomy		
Segmental small bowel resection	14	48.3
Subtotal colectomy	6	20.7
Antrectomy	1	3.5
Right colectomy	2	6.9

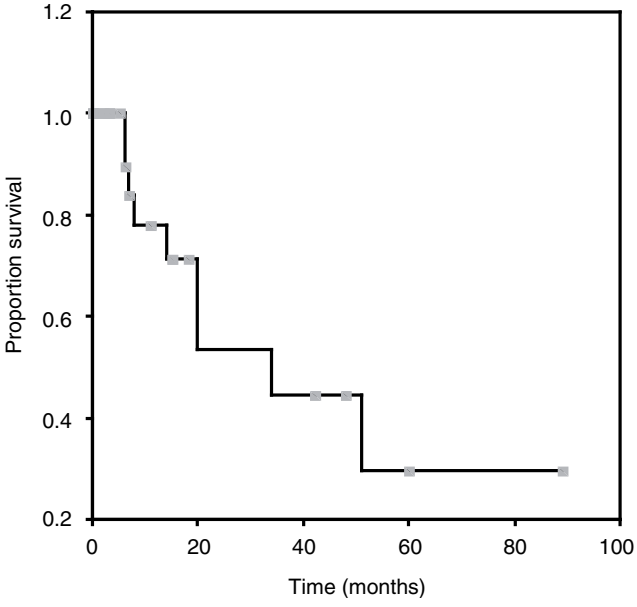

Figure 1 - Overall 5-year survival rate in patients with recurrent ovarian cancer.

with limited peritoneal spread was 68% and mean survival 66 ± 15 months (range, 37-95) (Figure 2). For patients with complete cytoreduction, the 5-year survival rate was 58% and mean survival 67 ± 12 months (range, 43-91) (Figure 3). The 5-year survival rate for patients with extensive peritoneal spread was 0% and mean survival 24 ± 7 months (range, 11-37) (Figure 2). For patients with incomplete cytoreduction, the 5-year survival rate was 0% and mean survival 16 ± 4 months (range, 7-24) (Figure 3). By multivariate analysis, the completeness of cytoreduction was identified as the single independent factor of survival (P = 0.013; HR = 3.409: 95% CI, 1.302-8.928). At this writing, 11 (37.9%) patients were alive without evidence of disease, 4 (13.8) were alive with stable disease, 1 (3.4%) patient had disease progression, 9 (31%) patients had died for extensive disease, and 4 (13.8%) had died for reasons unrelated to the disease or treatment (including one hospital death).

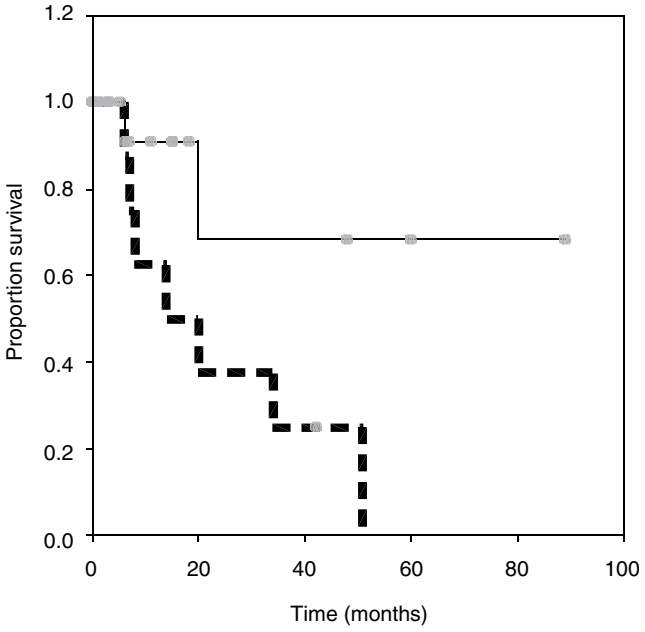

Figure 2 - Five-year survival rate and extent of peritoneal spread. Continuous line, patients with a PCI <13. Dotted line, patients with a PCI >13 (P = 0.0356).

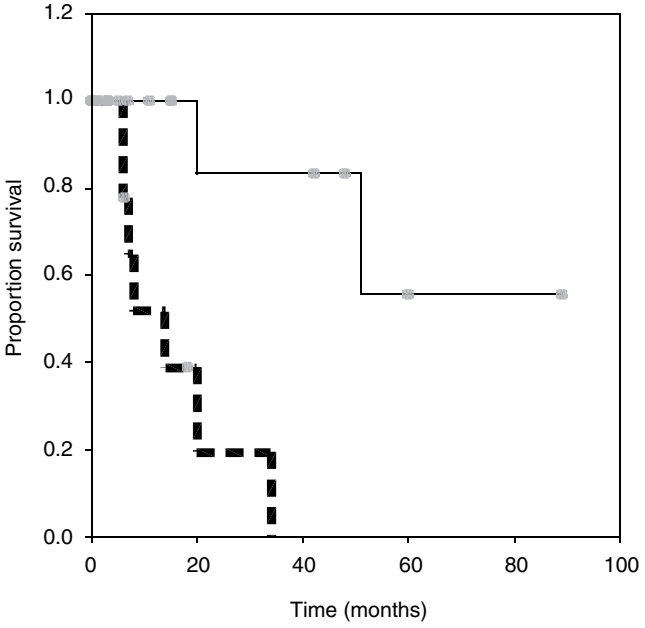

Figure 3 - Five-year survival rate and completeness of cytoreduction. Continuous line, CC-0 surgery. Dotted line, incomplete cytoreduction (P = 0.0007).

Discussion

Cytoreductive surgery followed by systemic chemotherapy is the standard therapeutic approach in the management of epithelial ovarian cancer[16]. More than 80% of ovarian carcinomas are chemoresponsive and achieve complete remission[17]. Despite advances with consecutive lines of systemic aggressive chemotherapy, the recurrence rate is still high (80%)[18] and 5-year survival rate is limited to 25-30%[19]. Systemic chemotherapy without cytoreductive surgery has a limited effect on overall survival because median survival is restricted to 11-15 months[20, 21]. Moreover, secondary cytoreduction alone offers a median survival of 5 to 43 months, depending on the completeness of the performed cytoreduction, and a 5-year survival rate of 28%[8,12,13].

Maximal cytoreductive surgery with standard peritonectomy procedures, as originally described by Sugarbaker[22], is likely to improve long-term survival from ovarian cancer[6,7,10]. Recently, the initially described peritonectomy procedures have been modified to: 1) epigastric peritonectomy, 2) subdiaphragmatic peritonectomy (right, left, bilateral), 3) pelvic peritonectomy, 4) cholecystectomy + resection of the omental bursa, 5) greater omentectomy (± splenectomy), 6) lesser omentectomy, 7) lateral peritonectomy (right, left, bilateral), and 8) visceral peritonectomy requiring resection of other organs (segmental resection of the small bowel, subtotal colectomy, right colectomy, gastrectomy etc)[14].

The epigastric peritonectomy procedure includes the en bloc resection of the old scar, the round and the falciform ligament of the liver and sometimes the xiphoid process. The procedure is necessary in those cases in which midline laparotomy had been used at initial surgery because a 60% recurrence rate has been reported at this site[23].

The intensification of treatment during surgery using instillation of cytostatic drugs in the abdominal cavity is a challenge for ovarian cancer. Intraperitoneal chemotherapy has been proved to be another powerful tool for the eradication of microscopic tumor in pseudomyxoma peritonei[24, 25], colorectal[26], and gastric

cancer with peritoneal spread[27], peritoneal mesothelioma and sarcomatosis[28], but has been sporadically used in recurrent ovarian cancer[9-11]. EPIC has been successfully used in gastric cancer[27] but has been rarely used in ovarian cancer.

The feasibility of secondary cytoreduction in recurrent ovarian cancer varies widely from 38-83%[12,13], probably because different clinical criteria are used. Extensive dissemination of the tumor at the peritoneal surfaces of the small bowel is the most important clinical factor excluding the possibility of complete cytoreduction. In addition, the presence of metastatic disease at lymph nodes that have no anatomic relation to the primary source and that cannot be resected or metastatic lesions at distant sites that are also unresectable makes complete cytoreduction impossible[7]. Thus, complete cytoreduction was possible in only 58.6% of the cases.

Numerous clinical factors influencing long-term survival have been identified and consistently reproduced. The most important is the completeness of cytoreduction[3,5-8]. The CC score has been identified by both univariate and multivariate analysis to be related to survival. The survival of patients who underwent incomplete cytoreduction did not exceed 2 years despite further systemic chemotherapy. Various studies have reported that 5-year survival does not exceed 16% when treatment consists only of cytoreductive surgery and HIPEC[11,30]. Although the ideal treatment of recurrent ovarian cancer has not yet been defined, it appears reasonable to use cytoreductive surgery and HIPEC only in patients undergoing CC-0 surgery. Even after CC-1 surgery, further treatment seems to be required[11]. Once patients with recurrent ovarian cancer have been heavily treated with several lines of systemic chemotherapy, the ideal cytostatic drug or a chemotherapy regimen and their proper dose have not yet been standardized for use in the perioperative period.

The extent of peritoneal spread seems to play the same role in prognosis as in primary ovarian cancer[29]. The survival of patients with extensive peritoneal dissemination did not exceed 3 years. PCI was identified as the most important factor of recurrence. It is interesting that most recurrences develop in patients who undergo incomplete cytoreduction or in those who have extensive peritoneal spread. Consequently, it is meaningful that 29.4% of patients with CC-0 surgery and 26.7% of those with a PCI <13 developed a recurrence. Ovarian cancer is a malignancy with predominantly intracelomic spread. Therefore, most recurrences were local-regional (10 patients, 34.5%) with only 4 (13.8%) distant metastases recorded.

As reported in similar studies, hospital mortality and morbidity rates were within an acceptable range, although the morbidity rate was relatively high (24.1%)[10,11,30]. The most frequent postoperative complication was anastomotic leak after low anterior resection. Anastomotic failure in addition to wound infection was attributed to perioperative chemotherapy, although it could not be statistically proved. It has been well established that cytostatic drugs exert an adverse effect on wound healing[31]. In contrast, no severe hematological or nephrological toxicity was recorded in patients who received perioperative chemotherapy. It is also well known that severe systemic toxicity is very infrequent when cytostatic drugs are administered intraperitoneally[32]. Therefore, only 2 patients had mild and transient hematological toxicity.

Conclusions

Secondary cytoreduction and perioperative intraperitoneal chemotherapy is a safe and feasible method for the treatment of recurrent ovarian cancer. Significant survival benefit may be obtained in patients undergoing complete cytoreduction. Complete cytoreduction is feasible in patients with limited peritoneal dissemination at the surfaces of the small bowel who have no distant metastases. Extensive peritoneal spread is a significant caveat for the performance of complete cytoreduction.

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