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Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Persistent and Recurrent Advanced Ovarian Carcinoma: A Multicenter, Prospective Study of 246 Patients

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ABSTRACT

Background. Epithelial ovarian carcinoma is the main cause of death from gynaecological cancers in the western world. The initial response rate to the frontline therapy is high. However, the prognosis of persistent and recurrent disease remains poor. During the two past decades, a new therapeutic approach to peritoneal carcinomatosis has been developed, combining maximal cytoreductive effort with hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods. A retrospective, multicentric study of 246 patients with recurrent or persistent ovarian cancer, treated by cytoreductive surgery and HIPEC in two French centers between 1991 and 2008, was performed.

Results. An optimal cytoreductive surgery was possible in 92.2 % of patients. Mortality and morbidity rates were 0.37 % and 11.6 %, respectively. The overall median survival was 48.9 months. There was no significant difference in overall survival in patients with persistent or recurrent disease. In multivariate analysis, performance status was a significant prognostic factor in patients with extensive peritoneal carcinomatosis (peritoneal cancer index >10).

Conclusions. Salvage therapy combining optimal cytoreductive surgery and HIPEC is feasible and may achieve long-term survival in highly selected patients with recurrent ovarian carcinoma, including those with platinum resistant disease, with acceptable morbidity.

Epithelial ovarian carcinoma (EOC) is the main cause of death from gynecological cancers in the western world.[1] Often diagnosed at an advanced stage when peritoneal carcinomatosis (PC) has developed, the disease remains confined to the peritoneal cavity for much of its natural history.[2] Standard frontline therapy is comprehensive cytoreductive surgery (CRS) followed by platinum-based systemic chemotherapy.[3] The initial response rate is high; however, approximately 20 % of EOC are naturally resistant to platinum.[4] Of those with platinum-sensitive disease that achieve a frontline complete pathologic response confirmed at a second surgery, 60 % will recur within 5 years.[5] Because of selection pressure over time most tumor recurrences develop resistance to systemic platinum. Options for salvage therapy include alternative systemic chemotherapy and further CRS, but the prognosis remains poor.[6–8]

During the two past decades, a new therapeutic approach to PC has been developed, combining maximal cytoreductive effort with hyperthermic intraperitoneal chemotherapy (HIPEC).[9] Its efficacy in nongynecologic carcinomatosis has been widely demonstrated.[10–12]

The sensitivity of EOC to chemotherapy and retention within the peritoneal cavity make it an ideal target for directed locoregional treatment utilizing intraperitoneal chemotherapy. Although intraperitoneal chemotherapy has been shown to have significant efficacy in frontline EOC in three, large, randomized studies, it has not been fully adopted as standard care, especially in Europe, partly

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because of its toxicity, complexity, and heterogeneity of the delivery.[13–15] HIPEC adds the advantage of hyperthermia effect, and because it is delivered immediately following CRS, this avoids the problem of "cancer cell entrapment" by postoperative adhesions, which limits distribution of chemotherapy agents to all sites. However, it represents a single-shot treatment and cannot easily be repeated every month.

There are multiple reports of the use of HIPEC for EOC in the literature, but the majority are relatively small case-series from single institutions, which are difficult to interpret and compare.[16] In a previous report from one of the participating centers, we analyzed 81 procedures.[17] The aim of this study was to bring together the experience of Centre Hospitalier Universitaire de Nice and Centre Hospitalier Lyon Sud, two centers in France that have incorporated HIPEC into the treatment of EOC over many years using similar management philosophies.

METHODS

Population

Patients treated with CRS and HIPEC for EOC at the two centers between the years 1991 and 2008 were identified from prospective databases at each institution and that included previous reported population.[17] The minimal preoperative investigations included: physical examination, cardiopulmonary investigation with cardiac echography and functional pulmonary exploration, nephrological investigation: creatininemia and clearance of creatinine, biologic evaluation of the hepatic function, evaluation of nutritional state: body mass index, albuminemia and pro-albuminemia; and extent of disease and staging: contrast-enhanced multisliced computed tomography (CT), and if necessary FDG-PET, magnetic resonance imagery or laparoscopic exploration.[18] Inclusion criteria were patients aged 18 to 75 years, considered fit for surgery with platinum-resistant advanced EOC (either persistent disease following optimal standard first-line therapy using combined CRS cytoreductive surgery and systemic chemotherapy with platinum regimen or recurrence after a progression-free interval (PFI) of <6 months) or with platinum-sensitive recurrent disease after a PFI of >6 months. For patients with their second recurrence, the platinum sensitivity was based on the PFI from the most recent course of platinum chemotherapy. The PFI parameters were those normally accepted as differentiating platinum-sensitive from platinum-resistant disease.[19] Patients with no extra-abdominal metastases on pre-inclusion thoracic and cerebral CT scans, with a World Health Organization (WHO) index of <2, with satisfactory cardiorespiratory and renal status, and informed consent. [20]

Exclusion criteria were: patients who underwent abdominal radiotherapy, renal or cardiac failure, extra-abdominal metastases, and unfit for surgical treatment second malignancy of nonovarian origin.

Treatment

All patients were taken to surgery with the intention of performing an optimal cytoreduction to no visible residual disease. On entry to the peritoneal cavity, the extent of PC was assessed and scored using the peritoneal cancer index (PCI).[21,22] Peritonectomy procedures were performed only for peritoneal surfaces involved by tumor. Open HIPEC was performed using "coliseum" procedure and closed HIPEC with the Lyon device.[23,24] Bowel anastomoses were performed before HIPEC in closed procedures to avoid to reopen the patient and after HIPEC in case of open procedure.

The completeness of the cancer resection (CC-score) was evaluated by the surgeon at the end of CRS before HIPEC perfusion and was classified as follows: CC-0 = no macroscopic residual cancer, CC-1 = residual nodule <2.5 mm, CC-2 = residual nodule between 2.5 and 25 mm, CC-3 residual nodules >25 mm.[25,26]

Following CRS, HIPEC perfusion was performed under the same anesthetic and with initial general hypothermia (34 °C), to reduce the risk of core hyperthermia during the procedure. HIPEC was delivered using either an open or closed technique.[17] The perfusate (Travenol, Norfolk, UK, 2 L/m^2 body surface) containing the drugs was circulating for 90 min with inflow temperatures ranging from 44 to 46 °C and aimed outflow temperatures between 41 and 43 °C. Modalities of HIPEC were quite homogenous in the two centers concerning the temperatures, the duration, and the drug concentrations.

Cisplatin was used in 95.5 % of procedures, alone or in combination with doxorubicin or mitomycin C (MMC).

Data

Study data were collected prospectively. This included detail of the patient's status before CRS and HIPEC, including the age, extent of PC, and the previous treatment with systemic chemotherapy.

Information recorded about the combined procedure included the date, the PCI, CCR score, the simultaneous resection of primary tumor or liver metastasis, the number of organ resection, the presence or absence of lymph node metastases, the modalities of HIPEC (duration, drugs, closed or open procedures, temperatures), and treatment with adjuvant systemic chemotherapy. Perioperative mortality was defined as death within 30 days after surgery and morbidity variables during this period were graded 0 to IV

according to the National Cancer Institute's common toxicity criteria.[27]

Follow-up data recorded included the status of the patient (alive with disease, alive without disease, dead with disease, dead without disease), the site and date of initial recurrence, and all other sites of recurrence.

Statistical Analysis

To study relationships between variables, standard tests have been used: chi-square with two qualitative variables and Pearson's correlation if quantitative. Survival analysis was performed using the Kaplan-Meier method and comparisons of curves were made with the log-rank test.[28] The cut-off date for survival analysis was fixed to October 2008. Cox model enabled us to realize multiple analyses of survival, and the logistic regression model to estimate complications risk of several factors together. Standard probability cut-off, $p < 0.05$, was chosen as the significance level. SPSSv6® software (2009 Chicago: SPSS Inc.) was used to perform calculations. Disease-free survival was defined as time from HIPEC until recurrence or last follow-up, if free of disease. For patients who died of disease, if the date of recurrence was unknown, the date of death was used for the calculation of disease-free survival. The patients treated with CC-2 or -3 resections with residual tumor nodules >2.5 mm were considered as immediate relapse. Perioperative deaths were not excluded from the survival analysis. Data on preoperative and postoperative systemic chemotherapy were recorded. Adequate description of prior chemotherapy regimens and subsequent chemotherapy regimens to HIPEC was not possible.

RESULTS

A total of 246 patients underwent CRS and HIPEC between 1991 and 2008. Sixty-two were platinum-resistant persistent or recurrent with PFI <6 months and 184 were platinum-sensitive recurrent with PFI >6 months, as defined in "Methods" section. Details of patient characteristics, previous number of chemotherapy regimens and surgeries, and surgical variables are given in Table 1. All patients received at least one regimen of platinum-based chemotherapy before CRS and HIPEC. The mean PCI was 10.6 (standard deviation, 7.3). An optimal surgery with no residual or <2.5 mm residual tumor (CC-0 or CC-1) was achieved in 92.2 % of procedures.

No patient received perioperative bevacizumab during the study period. One patient died postoperatively (0.37 %). A 59-year-old who underwent CRS with small-bowel resection, peritonectomies, and HIPEC for stage III EOC recurring 12 months after completion of frontline therapy. She developed an anastomotic leak resulting in peritonitis, acute renal failure, and death on postoperative day 12.

TABLE 1 Patients characteristics

Characteristics	*N* (%)	Mean	Maximum	Minimum	SD
Age (year)	268	57.5	77.6	28.6	9
BMI	203	23.7	44.5	20	4.5
Prior chemotherapy	248	3.6	18	1	2.6
No. of procedures					
1	246 (91.7)				
2	20 (7.5)				
3	2 (0.7)				
PCI	260	10.8	30	1	7.3
CC score					
0–1	247 (92.2)				
2–3	21 (7.8)				

Grade III or IV complications occurred in 31 of 268 (11.6 %) procedures. Eight patients experienced grade 3 leukopenia (3 %), 6 patients (2.4 %) experienced intra-abdominal hemorrhage, and required blood transfusion and/or surgical treatment. Twelve patients (4.9 %) experienced postoperative anastomotic leakage, requiring surgery or percutaneous drainage. By univariate analysis, four variables were found to be significant risk factors influencing major postoperative complications: PCI, CC-score, the number of organ resections, and the combination of cisplatin and MMC for HIPEC. Morbidity rates were 7.3 % in the subgroup of patients treated with complete CRS versus 18.4 % in the subgroup of patients who underwent an incomplete CRS ($p < 0.05$).

Survival analysis was performed in 246 patients. Overall median survival was 48.9 months: 48 months for patients with platinum-resistant persistent and recurrent disease and 52 months for patients with platinum-sensitive recurrent disease. The overall survival rates at 1, 3, and 5 years were 86, 60, and 35 % respectively (Fig. 1).

By univariate analysis performance status, PCI and CC-score were found to be significant prognostic factors (Figs. 2, 3). There was no significant difference in survival between patients with platinum-resistant persistent and recurrent disease and patients with platinum-sensitive recurrence ($p = 0.568$; Fig. 4).

In multivariate analysis, Cox model was stratified by PCI level. In the group of PCI 0-10 patients, CC-score had a strong prognostic influence, whereas its influence was not significant when PCI was >10. For this group of patients, the performance status (PS) was the only significant prognostic factor (Table 2).

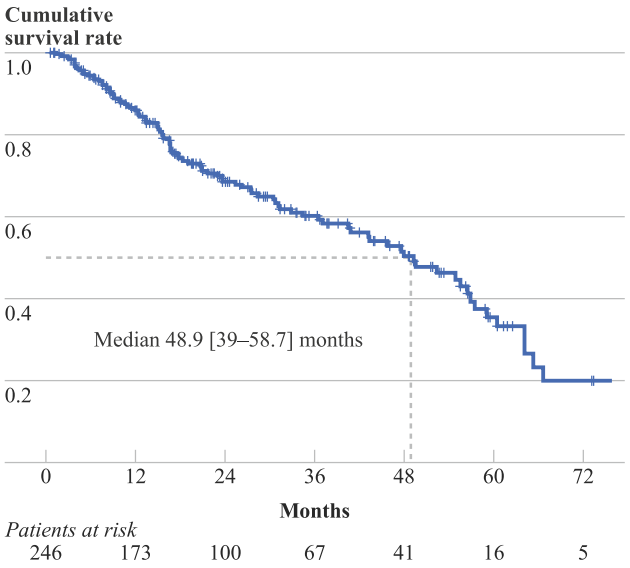

FIG. 1 Overall survival

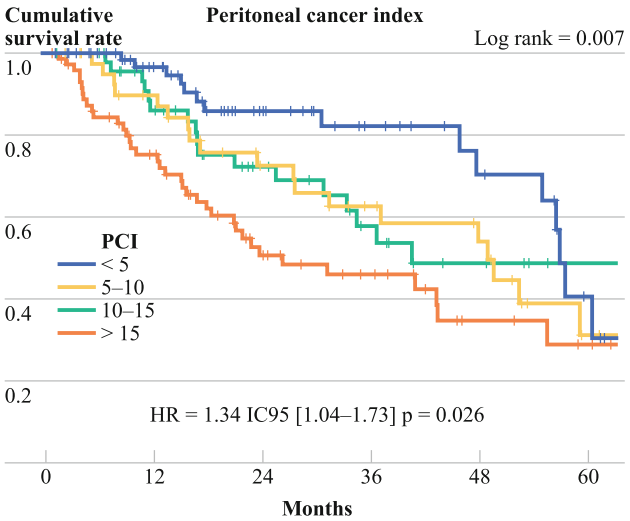

FIG. 2 Overall survival by PCI

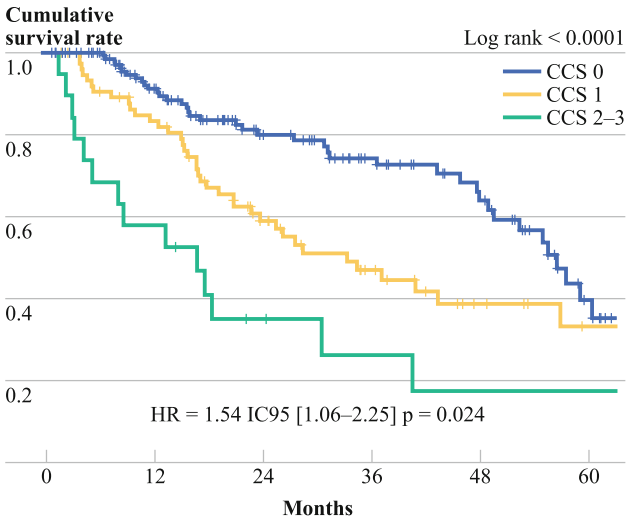

FIG. 3 Overall survival by CCS

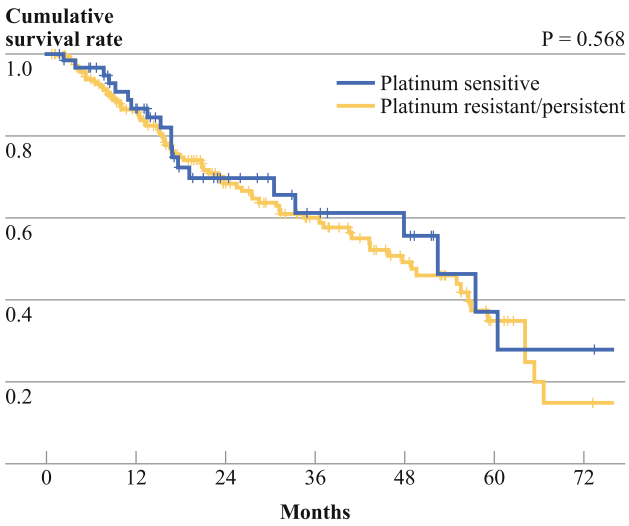

FIG. 4 Overall survival of platinum-resistant/persistent group versus platinum-sensitive group

TABLE 2 Mortality risk factors and disease-free risk factors, multivariate analysis

PCI	Variable	Hazard ratio	95 % CI		*p*
			Minimum	Maximum	
Mortality risk factor					
PCI <10	CC-score (CC-0 or 1 vs. CC-2 or 3)	2.26	1.3	3.91	0.004
PCI >10	Performance status	4.3	1.23	14.39	0.017
Disease-free risk factor					
PCI <10	Performance status	2.2	1.2	4.11	0.004
	No. of regions from PCI involved	1.2	1.5	9.8	0.021
PCI >10	None				

PCI peritoneal cancer index

Median disease-free survival was 12.8 months, and the disease-free survival rates at 1, 3, and 5 years were 50, 20, and 9 %, respectively. In univariate analysis, PS ($p = 0.032$), PCI ($p = 0.006$), the number of abdominal regions from PCI involved ($p < 0.001$), and the CC score ($p < 0.001$) were found to be significant factors. In multivariate analysis, Cox model also was stratified by PCI level. In the group of PCI <10, the PS and the number of abdominal regions from PCI involved had strong prognostic influence, whereas its influence was not significant when PCI was >10 (Table 2).

DISCUSSION

This paper includes the largest number of cases of EOC treated with CRS and HIPEC to date. The size of the dataset coming from only two centers with similar treatment philosophies gives substantial weight to the analysis. The overall median survival of 48.9 months in patients traditionally thought to have a poor prognosis and with median survival of 48 and 52 months in the platinum-resistant persistent and recurrent and platinum-sensitive recurrent disease groups are very encouraging.

Chemotherapy alone for the treatment of recurrent disease rarely results in median overall survival of greater than 30 months and in specifically platinum-resistant disease it is just greater than 12 months.[7,29] Surgery with or without chemotherapy for recurrent disease has traditionally been reserved for patients with localized, resectable disease that has recurred after a relatively long time interval. Two meta-analyses have analyzed results in this setting; one reporting that survival of 41–60 months is possible in highly selected patients and another reporting a mean weighted median post-recurrence survival time of 30.3 months.[7,30] In a report of patients undergoing CRS for recurrence (DESKTOP 1), the overall median survival was 29.5 months for 250 patients.[31] However, for the 125 with PC the median survival was only 19.9 months.

In a recent report of the HYPER-O registry, the median overall survival time for 83 patients with recurrent disease of all types was 23.5 months where 85 % had widespread PC and 28.6 % were platinum-resistant.[32] In other reports of HIPEC for EOC, median overall survival varied from of 28 to 57 months, and mean overall survivals were 57 and 41.4 months.[17,33–36] These studies were based on heterogeneous groups and included patients with persistent and recurrent within which it is difficult to determine the platinum response category. Our study helps to clarify outcomes within two clearly separate group's platinum-sensitive recurrent and platinum-resistant persistent and recurrent.

The fact that there was no difference in survival in the two subgroups suggests that the same therapeutic strategy (CRS and HIPEC) may be used in both situations irrespective of prior platinum response. It may suggest an effect from the addition of hyperthermia and the intraperitoneal administration of the drug. Intraperitoneal administration of anticancer drugs has many pharmacokinetic advantages and provides high response rates in the abdomen because the "peritoneal plasma barrier" provides dose-intensive therapy. High concentrations of anticancer drugs may be directly in contact with the tumor cells. The direct cytotoxicity of heat has been demonstrated in vitro at 42.5 °C.[37] Hyperthermia has been shown to increase the beneficial effects of some anticancer agents by augmenting cytotoxicity and/or increasing the penetration of drugs into tissue, such as cisplatin, and may explain the potential effect of intraperitoneal cisplatin in platinum-resistant patients.[38] However, the marginal benefit of hyperthermia with intraperitoneal chemotherapy has never been demonstrated in clinical trials. Interestingly, the HYPERO registry, which included 141 patients with EOC treated with CRS and HIPEC at different natural history time points reported that patients with platinum-resistant disease did have a significantly worse OS and PFS than those that were platinum-sensitive. The reason for this is not clear.

The overall rate of grade III and IV morbidity (11.5 %) was lower than the 30–40 % in series that included non-gynecologic cancers and was one of the lower reported rate of morbidity in series of ovarian PC treated by HIPEC.[33,35,36,39–49] This low rate may associated with the relatively low extent of disease (reflected in the mean PCI before CRS of 10.7), the less extensive involvement of abdominal organs in EOC compared with other, nongynecologic malignancies, and the extensive experience of the surgeons and centers involved in this report.

In frontline treatment, the extent of CRS correlates with survival.[7] In patients treated for an abdominal-confined recurrence, a comprehensive surgery is a prerequisite to improve survival. In this study, more than 90 % of the patients underwent an optimal surgery (CC-0 and CC-1). Our selection criteria meant that the extent of disease to be resected at the time of CRS and HIPEC was relatively low as shown by the mean PCI of 10.7, resulting in less CRS being required. These factors almost certainly contributed to the low morbidity and mortality.

Pharmacokinetic studies found the ratio of the cisplatin AUC for intraperitoneal cavity and plasma being between 1 and 20. Cotte et al. recently demonstrated that this ratio was 6 in the closed abdominal technique used in Lyon.[50] Cisplatin entering the plasma is almost certainly responsible for the hematological toxicity with eight patients (3 %) experiencing aplasia. Many of the patients in this series received multiple courses of platinum-based chemotherapy before HIPEC, which would have contributed to reduced bone marrow reserve. Ongoing studies aim to optimize cisplatin dose delivered to minimize systemic toxicity.

As previously reported CC-score was a significant prognostic factor for survival confirming the need for a comprehensive CRS to achieve this.[7] However, using multivariate analysis, CC-score had no significant impact on DFS and OS in the group of patients with extensive PC (PCI >10). The PS was the only significant prognostic factor. Considering this data, we should pay particular attention to the general health of patients with a resectable but extended carcinomatosis. For patients with PCI >10 and poor general status, CRS and HIPEC should be avoided. A thorough preoperative assessment of the extent of carcinomatosis is essential, but it should be borne in mind that current imaging methods may underestimate this. Studies conducted in PC from peritoneal mesothelioma, colorectal, and appendiceal origin show that it was possible to estimate the probability of complete cytoreduction with preoperative CT; however, it was impossible to detect all of the contraindications for cytoreductive surgery, notably small nodules <5 mm on small bowel serosal surfaces.[51,52]

This paper may present the deficiencies peculiar to nonrandomized studies; subtle differences in patient's selection and treatment methods between the two centers may make the studied population not so homogeneous and introduce some bias. Nevertheless, this large population is from only two centers with conforming treatment philosophies. The weakness of this study is the long period during which patients were enrolled. The development of new technologies and drugs that have been introduced during this period constitute confounding variables that might influence outcomes, leading to cautious interpretation of our results.

A prospective, controlled trial has recently opened in France. CHIPOR will study the role of HIPEC in the first late (>6 months) relapse of EOC. The hypothesis is based on the ICON4 results and aims to improve overall survival of 12 months. Later, we should identify the best time point in the natural history of ovarian carcinoma at which CRS + HIPEC would be relevant.

CRS and HIPEC is an aggressive combined therapy that achieved encouraging survival rates in patients with platinum-resistant persistent or recurrent and platinum-sensitive recurrent EOC. Morbidity and mortality rates are not negligible but stay within the range of acceptable risk.

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