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ORIGINAL REPORT

Peritoneal Colorectal Carcinomatosis Treated With Surgery and Perioperative Intraperitoneal Chemotherapy: Retrospective Analysis of 523 Patients From a Multicentric French Study

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ABSTRACT

Purpose
Peritoneal carcinomatosis (PC) from colorectal cancer traditionally is considered a terminal condition. Approaches that combine cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC) have been developed recently. The purpose of this study was to assess early and long-term survival in patients treated with that strategy.

Patients and Methods
A retrospective-cohort, multicentric study from French-speaking countries was performed. All consecutive patients with PC from colorectal cancer who were treated with CRS and PIC (with or without hyperthermia) were included. Patients with PC of appendiceal origin were excluded.

Results
The study included 523 patients from 23 centers in four French-speaking countries who underwent operation between 1990 and 2007. The median follow-up was 45 months. Mortality and grades 3 to 4 morbidity at 30 days were 3% and 31%, respectively. Overall median survival was 30.1 months. Five-year overall survival was 27%, and five-year disease-free survival was 10%. Complete CRS was performed in 84% of the patients, and median survival was 33 months. Positive independent prognostic factors identified in the multivariate analysis were complete CRS, PC that was limited in extent, no invaded lymph nodes, and the use of adjuvant chemotherapy. Neither the grade of disease nor the presence of liver metastases had a significant prognostic impact.

Conclusion
This combined treatment approach against PC achieved low postoperative morbidity and mortality, and it provided good long-term survival in patients with peritoneal scores lower than 20. These results should improve in the future, because the different teams involved will gain experience. This approach, when feasible, is now considered the gold standard in the French guidelines.

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INTRODUCTION

Peritoneal dissemination or carcinomatosis from colorectal carcinoma is a form of disease progression that affects 30% to 40% of patients.[1,2] Natural history studies show that peritoneal carcinomatosis (PC) is uniformly fatal, with median survival (not exceeding) attaining 6 months.[3] For more than a decade, a handful of centers have pursued aggressive cytoreductive surgery (CRS) combined with intraperitoneal chemotherapy (PIC), initially without and then with hyperthermia, as an alternative approach to overcome this disease. The aim of surgery is to resect visible disease as much as possible, and the aim of PIC is to treat any residual occult disease. Results from a single center cannot be extrapolated to other centers because of the vagueness of selection criteria, of what CRS represents, and of PIC techniques. This has led to a reasonable degree of skepticism among some oncologists. This is why any multicentric study that collects a large number of patients from many centers is particularly useful. The experience and the techniques are considerably different from one center to another.

In this paper, we present a collaborative effort of 23 French-speaking centers to evaluate the efficiency of this combined approach and to identify the main prognostic factors on the basis of a population of 523 treated patients.

PATIENTS AND METHODS

Patient Population

This multicentric, retrospective study was conducted in French (n = 20), Belgian (n = 2), Canadian (Quebec, n = 2) and Swiss (n = 1) centers. Patients were treated between January 1990 and December 2007. Inclusion criteria were histologically confirmed PC of colorectal origin treated with CRS plus hyperthermic intraperitoneal chemotherapy (HIPEC) or early postoperative intraperitoneal chemotherapy (EPIC). Exclusion criteria were appendiceal malignancies and extra-abdominal metastases.

Data Forms

A standard data form was created to retrieve information on the primary colorectal tumor, on the status of the patient before the combined procedure, and on previous treatment with systemic chemotherapy. The extent of PC was assessed through intraoperative exploration by using the Peritoneal Cancer Index (PCI),[4-5] which has scores from 0 to 3 for each of the 13 defined areas of the abdominal cavity; therefore, the index ranges from 1 to 39. Four PCI subgroups were defined for the analysis: one to 6, 7 to 12, 13 to 19, and greater than 19. Information recorded about the combined procedure included the completeness of CRS, any simultaneous resection of the primary tumor and liver metastases, the presence or absence of lymph node metastases, the type of perioperative intraperitoneal chemotherapy (ie, HIPEC or EPIC) and its modalities, and treatment with adjuvant systemic chemotherapy. Assessment of the completeness of the cancer resection (CCR) with CRS was done by the surgeon at the end of the procedure and was classified into three categories[4]: CCR-0 signified no macroscopic residual cancer; CCR-1, no residual nodules greater than 2.5 mm; and CCR-2, that the diameter of the residual nodules exceeded 2.5 mm. The centers were classified arbitrarily as experienced (> 7 years of practice) and as inexperienced (< 7 years of practice). Major complications (ie, grades 3 and 4 complications according to the National Cancer Institute Common Toxicity Criteria) were considered, and the reasons for reoperation were detailed.

Statistical Analysis

Categoric variables were described in terms of frequency and percentages. The distributions of continuous variables were described with mean, standard error, median, and first and third quartiles. Influence of patient, disease, and treatment characteristics were related to the risk of postoperative morbidity and mortality events by using univariate and multivariate logistic regression models, which were adjusted by centers.

The analysis of long-term mortality censored information after the cutoff date of December 31, 2006, because an active inquiry was performed in all centers to collect the status (ie, dead or alive) of the patients at that date. The analysis of total mortality considered the delay from the first procedure to the date of death, the date of last news, or the cutoff date, whichever came first. The analysis of recurrence or death was based on the delay from the first procedure to the date of first recurrence, the date of death, the date of last news, or the cutoff date, whichever came first. Postoperative deaths were not excluded from the survival analysis. Patients who underwent CCR-2 resections with residual tumor nodules exceeding 2.5 mm were considered to have experienced immediate relapses. When the date of recurrence was unknown in patients who died, the date of death was used instead. For this analysis, 12 patients were lost to follow-up. Kaplan-Meier survival estimates were calculated and were compared between strata with the log-rank test. Influence of baseline risk factors on the hazard of death was assessed by using a multiple proportional hazard regression model stratified by centers. Stratification was justified by a large heterogeneity of hazards between centers and by a strong potential confounding effect on other risk factors. In all multivariate analyses, age and PCI were entered as continuous variables (after their linear relationship with the risk of event was checked). CCR also was entered as continuous when justified by a linear trend across categories. An indicator variable for the HIPEC procedure (ie, yes or no) was forced in the model when an associated covariate (ie, temperature, heating duration, open/close abdomen) was significant. Risk factors with a significance degree $\leq .10$ were retained in the final model. The SAS statistical software (version 9.1; SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Five hundred twenty-three patients who had undergone 543 procedures that combined CRS and PIC for treatment of colorectal PC between May 1990 and December 2007 constituted the study population. The 2008 annual report of the Association Française de Chirurgie was devoted to this particular approach.

Twenty-five institutions were entered into a central database. One institution recorded 152 patients, one recorded 87 patients, five recorded between 20 and 50 patients, and the others recorded fewer than 20 patients.

Patient Characteristics

Patient characteristics are listed in Table 1. There were 296 female patients (56.6%) and 227 male patients (43.4%), and the median age was 54 years (mean and standard deviation, 53 ± 12 years; range, 16 to 88 years). The PC arose from adenocarcinomas of the right colon (31%), transverse colon (4%), left colon (14%), sigmoid (28%), rectum (7%), and multiple locations (2%). The location of the primary was unknown in 73 patients (14%). Synchronous liver metastases were present (and were resected) in 77 patients (15%). Two hundred seventy-seven patients were treated in an experienced center, and 245 were treated in a inexperienced center. Three hundred seventy patients (70%) had been treated previously with systemic chemotherapy, which did not include new, targeted molecules.

Treatment

At completion of the best surgical effort at CRS, 439 patients had a CCR-0 resection (84%), 53 patients a CCR-1 resection, and 22 patients had a CCR-2 resection. Seventy-seven patients (17%) had undergone simultaneous resection of liver metastases. CRS was synchronous with the resection of the primary in 161 patients (35%). Four hundred forty-three patients (86%) had undergone HIPEC, and 84 patients (16%) had undergone EPIC. Nine patients had undergone both. All HIPEC procedures were performed intraoperatively after CRS but with many variations in exposure techniques (ie, open or closed wall), duration (30 to 90 minutes), intraperitoneal temperatures (40°C to 43°C), type of perfusate, and flow rates. Mitomycin-based regimens used mitomycin 30 to 50 mg/m^2 ± cisplatin 50 to 100 mg/m^2 during 60 to 120 minutes at 41°C. Oxaliplatin-based regimens used oxaliplatin 360 to 460 mg/m^2 ± irinotecan 200 mg/m^2 + intravenous fluorouracil and leucovorin during 30 minutes at 43°C. EPIC was delivered over 5 days, from day 1 to day 5 after surgery. The EPIC regimen delivered was mitomycin (10 mg/m^2) on day 1 and fluorouracil (600 mg/m^2) during the following four days in 0.8 to 1 L/m^2 of dialysis solution. Drains were clamped 23 hours of 24 hours.

Two hundred thirty-two patients (47%) had received postoperative adjuvant systemic chemotherapy when they achieved an objective response to preoperative chemotherapy (if administered) or when they exhibited poor prognostic factors (CCR-1 or -2 status, invaded lymph nodes, or liver metastases).

Table 1. Demographic and Clinical Characteristics of the 523 Treated Patients With Colorectal PC

Characteristic	Patients No.	Patients %
Age, years		
< 60	368	73
> 60	151	17
Sex		
Male	227	43
Female	296	57
Site of primary		
Right colon	162	31
Transverse colon	19	4
Left colon	71	14
Sigmoid	145	28
Rectum	36	7
Multiple	8	2
Unknown	73	14
Revealing symptom		
Discovered at surgery		36
Imaging examination		29
Abdominal pain		13
Digestive occlusion		6
Clinical ascites		4
CEA elevation		3
Worsening of general status		4
Inguinal hernia		2
Other		3
Preoperative IV chemotherapy		
Yes	370	71
No	153	29
Median No. of preoperative IV chemotherapy courses received	8	
PC synchronous with primary		
Yes	161	35
No	300	65
Primary lymph node status		
Positive	325	67
Negative	158	33
Histologic differentiation of the primary		
Well	165	39
Moderate	195	46
Poor	65	15
CEA level		
Normal	121	48
Elevated	112	52
Calcium 19.9 level		
Normal	119	60
Elevated	80	60
CA-125 level		
Normal	63	80
Elevated	16	20
WHO grade		
0	387	76
1	102	20
2	20	4
Synchronous liver metastases		
No	376	83
Yes	77	15
Type of intraperitoneal chemotherapy		
HIPEC		84
EPIC		16
Peritoneal cancer index		
1-6	181	37
7-12	132	28
13-19	96	21
> 19	69	14
Size of residual tumor after cytoreductive surgery, mm		
0 (CCR-0)	439	85
< 2.5 (CCR-1)	53	10
> 2.5 (CCR-2)	22	5
Intraperitoneal chemotherapy regimen		
Mitomycin based	287	55
Oxaliplatin based	235	45

Abbreviations: PC, peritoneal carcinomatosis; CEA, carcinoembryonic antigen; IV, intravenous; HIPEC, hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy; CCR, completeness of the cancer resection.

Postoperative Mortality and Morbidity

Seventeen patients (3.3%) died postoperatively. The causes of death were septic shock (n = 9), respiratory complications (n = 4), hematologic toxicity (n = 2), pulmonary embolism (n = 1), and acute renal insufficiency (n = 1).

Grades 3 to 4 complications occurred in 156 patients (31%), and 11% of all the patients underwent reoperation; 9% had a digestive fistula, 4% had a profound abscess, 6% had hemorrhage, 6% had a lung infection, and 12% had grades 3 to 4 hematologic toxicity. The median duration of hospitalization was 18 days (first-to-third quartile range, 14 to 26 days).

The logistic regression analysis of factors that significantly increased the risk of postoperative mortality and morbidity identified two primary factors—the peritoneal index (odds ratio, 1.067; 95% CI, 1.035 to 1.099; $P < .001$) and the center in which treatment was performed ($P < .0001$).

Survival

With a median follow-up of 45 months (first-to-third quartile range, 23 to 79 months), the overall 1-year, 3-year, and 5-year survival rates were 81%, 41%, and 27%, respectively (Fig 1; respective 95% CIs, 77% to 85%, 36% to 47%, 21% to 33%). Disease-free survival rates were 47%, 15%, and 10%, respectively (respective 95% CIs, 43% to 52%, 11% to 19%, 6% to 14%). Median survival was 30.1 months.

Among the clinical factors in the univariate analysis (Table 2), sex, age, histologic grade, and also the presence of liver metastases did not have a prognostic impact. In contrast, the extent of carcinomatosis (ie, PCI; $P < .001$) and invaded lymph nodes ($P = .02$) had significant prognostic impacts.

Among the therapeutic factors, neoadjuvant chemotherapy and use of HIPEC or EPIC did not have a statistically significant prognostic impact. In contrast, the completeness of surgery had a strong impact ($P < .001$), and the center where the procedure was performed ($P < .001$) and the use of adjuvant chemotherapy ($P = .04$) had significant influences on the risk of death. The impact of the PIC

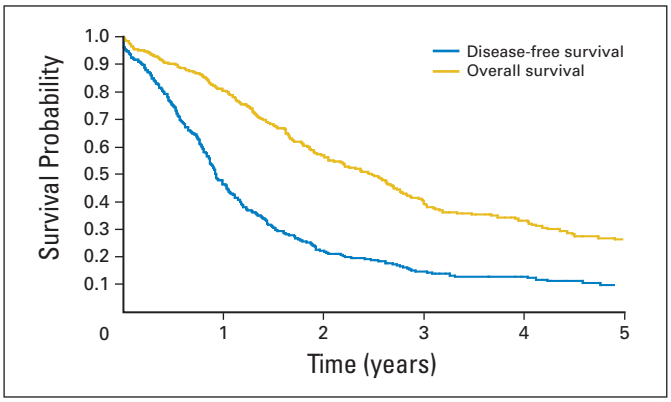

Fig 1. Overall and disease-free survival rates of the 523 patients with peritoneal carcinomatosis of colorectal origin.

techniques (ie, drugs, drug concentration, temperature, duration) could not be analyzed well, because there were too many variations across centers.

A multivariate analysis (Table 3) with a Cox regression model was performed to determine which clinical or therapeutic variables were more strongly correlated with overall survival. There were four independent prognostic indicators: the PCI, which reflected the extent of peritoneal disease (Fig 2), the completeness of surgery (Fig 3), the lymph node status, and adjuvant chemotherapy.

The multivariate analysis of disease-free survival selected the following five factors: the PCI (hazard ratio [HR], 1.057; $P < .0001$), the completeness of surgery (HR, 0.446; $P = .05$), the experience of the center (HR, 2,389; $P = .0003$), the lymph node status (HR, 1.390; $P = .03$), and adjuvant chemotherapy (HR, 0.682; $P = .009$). Four of them were common with those of the overall survival, but the experience of the center appears in this analysis.

We specifically studied the prognostic factors in the 416 patients who had undergone complete CRS (ie, CCR-0 resection). The multivariate analysis identified five significant prognostic factors: the extent of carcinomatosis (HR, 1.054; $P < .0001$), the presence of liver metastases (HR, 1.623; $P = .01$), the experience of the center (HR, 1.841; $P = .01$), the lymph node status (HR, 1.44; $P = .07$), and adjuvant chemotherapy (HR, 0.719; $P = .03$). In this analysis, liver metastases had an impact on survival.

Table 2. Univariate Analysis of Overall Survival After Cytoreductive Surgery Plus Intraperitoneal Chemotherapy in Patients With Colorectal Peritoneal Carcinomatosis

Variable	Survival Data			Log-Rank *P*
	Median (months)	3-Year (%)	5-Year (%)	
Sex				.37
Male	30	39	26	
Female	30	42	27	
Preoperative systemic chemotherapy				.85
Yes	30	40.5	27	
No	30	42	26	
Performance status				.002
0-1	33	45	30	
2-3	16	0	0	
Synchronous resection of liver metastases				.15
Yes	23	34	21	
No	31	42	27	
Institution				.001
Best	31	44	29	
Worst	26	23	18	
Age, years				.07
≤ 60	31	43	28	
> 60	28	34	20	
Peritoneal cancer index				< .0001*
1-6	40	55	44	
7-12	29	39	22	
13-19	25	40	29	
> 19	18	18.5	7	
Size of remaining tumor nodules, mm				< .0001*
0	33	45	29	
< 2.5	20	21	14	
≥ 2.5	7	8.5	0	
Type of intraperitoneal chemotherapy				.965
EPIC	32	45	30	
HIPEC	31	40	25.5	
Positive lymph nodes				.02*
No	32	46	30	
Yes	24	36.5	22.5	
Using oxaliplatin inside peritoneum				.02
Yes	32	43	27	
No	25	38	23	
Adjuvant systemic chemotherapy				.04*
Yes	31	43	31	
No	27	40	23	
Degree of differentiation				1.0
Well	32	42	28	
Moderately	30	44	26	
Poorly	26	36	23	

Abbreviations: EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy.
*Variable also significant in multivariate analysis.

DISCUSSION

This retrospective, multicentric study that included 523 disease occurrences shows that combined treatment of CRS and PIC yields a 5-year survival rate of 27%. This rate attained 30% when CRS was complete.[6] It represents the worst results that will be obtained with this combined treatment approach against PC, because it takes into account all the learning curves of the different teams. This is also the largest series of selected patients with PC from colorectal carcinoma treated with combined CRS and PIC. The study was conducted in 25 centers in the French-speaking medical community and confirms a considerable part of the results obtained in the international retrospective study of 506 patients from 28 worldwide institutions, published in 2004 by Glehen et al.[7] Approximately one fourth of the patients were included in these two series.

A comparison of these two series shows that mortality (3% and 4% for this study and the 2004 study, respectively) and morbidity (23% and 31%, respectively) are low and are no longer acceptable criticisms against this procedure. It also underlines the strong impact of the completeness of CRS on the survival rate: the 5-year survival rate was 19% in the series by Glehen et al[7]; 53% were CCR-0.[7] The 5-year survival rate was 30% in this study, and the CCR-0 in was 79%. Median survival rates were similar in the two series for

Table 3. Multivariate Analysis of Prognostic Factors for Overall Survival of 523 Patients Treated With Cytoreductive Surgery Combined With Perioperative Intraperitoneal Chemotherapy

Variable	Multivariate Analysis		
	P	Hazard Ratio	95% CI
Peritoneal cancer index*	< .001	1.052	1.029 to 1.076
Completeness of surgery†	.07	1.398	0.970 to 2.014
Positive lymph nodes‡	.02	1.534	1.058 to 2.224
Adjuvant chemotherapy‡	.002	0.578	0.407 to 0.820

*For each additional point in the peritoneal cancer index, the risk of death of the relative risk increases (ie, by 5.2%).
†Completeness was divided into three categories: completeness of the cancer resection (CCR)-0, CCR-1, and CCR-2. Passing from one category to another increases the risk of death by 39%.
‡Compared in two classes (ie, yes or no).

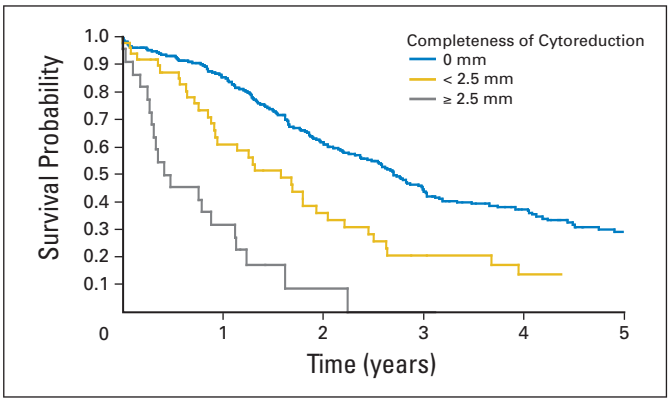

Fig 3. Prognostic impact of the completeness of the surgery ($P < .001$) on overall survival.

patients who had a similar CCR-0 resection (ie, 32.4 months and 33 months, respectively); this was, of course, reassuring. Future results will be better, as confirmed by the 5-year overall survival rates recently reported by expert centers after CCR-0 : 32% for the 100 patients reported by da Silva and Sugarbaker,[8] 43% for the 59 patients reported by Verwaal et al,[9] and 48% for the 30 patients reported by Elias et al.[10] In 2009, the completeness of CRS must be considered fundamental because of its strong prognostic impact and the because it is a prerequisite for the use of any kind of PIC.

The main criticism medical oncologists level against this combined treatment is that it is performed exclusively in highly selected patients. Their skepticism stems from the fact that they think systemic treatment alone could yield similar results in this selected population. A recent study in patients who had resectable PC in both groups compared the results of complete CRS and HIPEC with those of systemic chemotherapy. Median survival was 60 months in the first group versus 25 months in the second group,[11] which underlined, at least, the positive impact of CRS.

Additional important information was obtained in this study. First, mortality (3%) and morbidity (31%) are low and are no longer acceptable reasons for not using this combined treatment. The expertise of the center has a strong prognostic impact. The procedures required for aggressive cytoreduction are lengthy, challenging, and morbid, and they utilize a great deal of resources. Clearly, there is a significant learning curve, and this is not a procedure that can be undertaken by the occasional operator.[12,13] A high volume of treated patients per center resulted in lower morbidity and mortality (data not shown) in this series, as already proven in other complex surgeries.[14] This impact appears to be particularly strong in this series.

Second, there is a strong correlation between the PCI (ie, extent of peritoneal disease), the completeness of CRS, and also morbidity and mortality. When the PCI is greater than 20, the 5-year survival rate is less than 10%, which proves that extensive disease becomes a relative contraindication for this combined treatment. We currently believe that a PCI greater than 20 and associated with another poor prognostic factor, such as evidence of lymph node involvement or a poor general status or progression under chemotherapy, should be considered an absolute contraindication to this treatment.

Third, when liver metastases were resected concomitantly, there was no significant prognostic impact on the entire series. However, in patients who attained a CCR-0 status, the synchronous resection of liver metastases impacted negatively on disease-free survival in the multivariate analysis of prognostic factors. Liver metastases, therefore, should be considered before deciding to perform this combined treatment, and liver metastases could be a relative contraindication if associated with a high peritoneal index.

Fourth, it was surprising to discover that there was no statistical difference in survival rates between HIPEC or EPIC. In fact, the scientific rationale for using HIPEC is more solid than that supporting the use of EPIC,[15-19] but it has yet to be proven in humans. In this study, postoperative morbidity also appeared to be lower ($P = .03$) with HIPEC than with EPIC. A randomized study comparing the two techniques in terms of tolerance, survival, quality of life, and cost would be necessary. However, before conducting such a trial, it seems more important to prove unequivocally that HIPEC or EPIC impacts on the survival rate after complete CRS and is able to cure residual occult tumor seedings. This is, in fact, the objective of the randomized trial currently ongoing in France that is comparing HIPEC with no HIPEC after complete surgical resection of PC (ie, study Prodige 7 of Fédération Francophone de Cancérologie Digestive and Fédération Nationale des Centres de Lutte Contre Ie Cancer groups).

Fifth, HIPEC techniques are miscellaneous and nonstandardized. This is a constant criticism leveled against HIPEC. In this

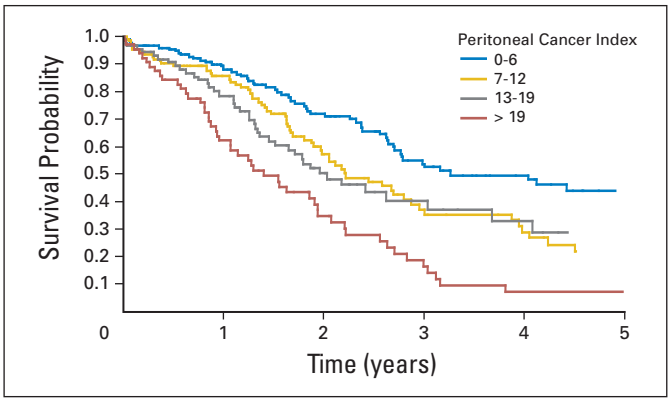

Fig 2. Prognostic impact of the extent of carcinomatosis (ie, peritoneal cancer index; $P < .001$) on overall survival.

multi-institutional study, although the use of oxaliplatin rather than mitomycin, and an intraperitoneal temperature greater than 42°C, seemed preferable (but more morbid) in the univariate analysis of prognostic factors for survival, the interpretation of these technical aspects appeared difficult. Clearly, more standardized and unified techniques should be used in the future.

Sixth, it is important for surgeons to realize that they play a decisive role in this treatment, which mainly is based on the peritoneal index and on the quality of the completeness of surgery. In this respect, their experience and perseverance during this long treatment will be determinative. In addition, because adjuvant systemic chemotherapy improved survival in this study, as in others,[7] surgeons must ensure that patients receive it.

Finally, it is important to consider the four prognostic factors for disease-free survival identified in the multivariate analysis in patients with completely resected disease, because they provide us with the keys for future improvements. These factors were the extent of PC, the presence of liver metastases (ie, a validated score incorporating the PCI and hepatic metastases is required to indicate or contraindicate complete CRS plus HIPEC.), the experience of the center (accreditation should only be delivered to a few centers), and adjuvant systemic treatment (which has improved dramatically).

In conclusion, the survival rate obtained in this multicentric study makes this combined treatment of PC the current gold standard therapy, when feasible. The analysis of prognostic factors allowed us to specify the contraindications. Future improvements in the selection of patients, in mastery of the technical process, and in the use of new molecules will rapidly increase its efficiency.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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