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ORIGINAL REPORT

Cytoreductive Surgery Combined With Perioperative Intraperitoneal Chemotherapy for the Management of Peritoneal Carcinomatosis From Colorectal Cancer: A Multi-Institutional Study

O. Glehen, F. Kwiatkowski, P.H. Sugarbaker, D. Elias, E.A. Levine, M. De Simone, R. Barone, Y. Yonemura, F. Cavaliere, F. Quenet, M. Gutman, A.A.K. Tentes, G. Lorimier, J.L. Bernard, J.M. Bereder, J. Porcheron, A. Gomez-Portilla, P. Shen, M. Deraco, and P. Rat

From the Centre Hospitalo-Universitaire Lyon Sud, Pierre Bénite; Equipe Accueil 3738, Université Claude Bernard Lyon 1, Oullins; Centre Jean Perrin, Clermont-Ferrand; Institut Gustave Roussy, Villejuif; Centre Val d'Aurelle, Montpellier; Centre Paul Papin, Angers; Centre Hospitalo-Universitaire l'Archet 2, Nice; Centre Hospitalier de Bellevue, Saint-Etienne; Centre Hospitalo-Universitaire, Dijon, France; Shizuoka Cancer Centre, Shizuoka, Japan; Tel Aviv Medical Center, Tel Aviv, Israel; Didimotichon General Hospital, Didimotichon, Greece; San Giuseppe Hospital, Empoli, Florence; Regina Elena National Cancer Institute, Roma; Istituto Nazionale Tumori, Milano; Hospital Santiago Apostol, Vitoria, Spain; Washington Hospital Center, Washington, DC; Wake Forest University, Baptist Medical Center, Department of General Surgery, Winston-Salem, NC; and SharpHealthCare, San Diego, CA.

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Address reprint requests to Francois N. Gilly, MD, PhD, Surgical Department, Centre Hospitalo Universitaire Lyon Sud, 69495 Pierre Bénite cedex, France; e-mail: francogi@lyon-sud.univ-lyon1.fr.

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ABSTRACT

Purpose
The three principal studies dedicated to the natural history of peritoneal carcinomatosis (PC) from colorectal cancer consistently showed median survival ranging between 6 and 8 months. New approaches combining cytoreductive surgery and perioperative intraperitoneal chemotherapy suggest improved survival.

Patients and Methods
A retrospective multicenter study was performed to evaluate the international experience with this combined treatment and to identify the principal prognostic indicators. All patients had cytoreductive surgery and perioperative intraperitoneal chemotherapy (intraperitoneal chemohyperthermia and/or immediate postoperative intraperitoneal chemotherapy). PC from appendiceal origin was excluded.

Results
The study included 506 patients from 28 institutions operated between May 1987 and December 2002. Their median age was 51 years. The median follow-up was 53 months. The morbidity and mortality rates were 22.9% and 4%, respectively. The overall median survival was 19.2 months. Patients in whom cytoreductive surgery was complete had a median survival of 32.4 months, compared with 8.4 months for patients in whom complete cytoreductive surgery was not possible ($P < .001$). Positive independent prognostic indicators by multivariate analysis were complete cytoreduction, treatment by a second procedure, limited extent of PC, age less than 65 years, and use of adjuvant chemotherapy. The use of neoadjuvant chemotherapy, lymph node involvement, presence of liver metastasis, and poor histologic differentiation were negative independent prognostic indicators.

Conclusion
The therapeutic approach combining cytoreductive surgery with perioperative intraperitoneal chemotherapy achieved long-term survival in a selected group of patients with PC from colorectal origin with acceptable morbidity and mortality. The complete cytoreductive surgery was the most important prognostic indicator.

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INTRODUCTION

At initial diagnosis of colon cancer, the peritoneal surface is involved by tumor in 10% to 15% of patients.[1,2] Next to the liver, peritoneal surfaces are the most common sites for cancer recurrence after so-called curative colorectal cancer resections, occurring in as many 50% of patients.[3,4] In 10% to 35% of all patients with recurrent disease, tumor recurrence is confined to the peritoneal surface only.[1,5] Peritoneal carcinomatosis arising from colorectal cancer has long been considered a terminal condition with no curative treatment options. The prognostic study of Chu et al[2] in 1989 reported 45 patients with a median survival of 6 months after treatment with fluorouracil and leucovorin. A French multicenter prospective study[6] reported 118 patients studied from

1995 to 1997, with a median survival of 5.2 months. In a recent retrospective analysis of 3,019 patients with colorectal cancer, 13% of patients presented with carcinomatosis and had a median survival of 7 months.[7] Despite the development of new, more effective chemotherapeutic agents and combinations, the results of systemic chemotherapy treatment remain disappointing, with a limited impact on survival.[8-10] Interesting survival results were obtained with the use of irinotecan or oxaliplatin on metastatic colorectal patients, but a great majority of patients had liver metastasis without peritoneal carcinomatosis.[11,12]

Over the past decade, novel therapeutic approaches to peritoneal carcinomatosis have emerged, combining cytoreductive surgery and peritonectomy procedures[13] with perioperative intraperitoneal chemotherapy, including early postoperative intraperitoneal chemotherapy (EPIC) and/or intraperitoneal chemohyperthermia (IPCH).[14-16] Several phase II studies reported the use of this combined therapeutic strategy for patients with colorectal carcinomatosis, with interesting 3-year survival rates ranging between 25% and 47%.[14,16-20] Recently, the Netherlands Center Institute reported a phase III study comparing standard treatment with palliative surgery followed by systemic fluorouracil and leucovorin as first-line chemotherapy with maximal cytoreductive surgery with IPCH followed by the same regimen in patients with known colorectal carcinomatosis.[21] It strongly demonstrated the benefit of the combined procedure and was stopped for ethical reasons.

Despite many phase II and a phase III study suggesting benefit, the oncologic community remains skeptical regarding this combined therapeutic approach. To provide further data, a collaborative effort of 28 institutions involved in the treatment of peritoneal surface malignancies provided information on a large number of patients with colorectal carcinomatosis to evaluate the efficiency of this treatment, to answer questions regarding patient selection, and to identify principal prognostic indicators.

PATIENTS AND METHODS

Patient Population

Five hundred six patients who had undergone 533 pro cedures combining cytoreductive surgery and perioperative intraperitoneal chemotherapy for treatment of colorectal carcinomatosis between May 1987 and December 2002 made up the study population. The inclusion criteria were peritoneal carcinomatosis from colorectal origin confirmed by pathologic examination; IPCH, EPIC, or both administrated within 7 days of surgery; and treatment before January 1, 2003. The exclusion criteria were appendiceal malignancy, intraperitoneal chemotherapy performed more than 7 days after the surgery, and extra-abdominal metastases.

Standardized clinical data on consecutive patients from each of 28 institutions were received and entered into a central database. One institution recorded more than 100 patients, three institutions recorded 50 to 100 patients, four institutions recorded 15 to 25 patients, five institutions recorded 10 to 15 patients, and 15 institutions recorded fewer than 10 patients. Confidentiality prevents our stating the exact number of patients from each hospital. However, we can confirm that each institution recorded all consecutive procedures performed in the study period by participating surgeons. The same author reviewed all data sheets before their entry into the database in an effort to make this a uniform interpretation of retrospective data.

Data Forms

A standard data form was created to retrieve information on the primary colorectal tumor, including the location of the primary tumor, the presence or absence of metastases to draining mesenteric lymph node, and the differentiation of primary tumor. The form also recorded information on the status of the patient before undergoing the combined procedure, including the sex, the age, the extent of peritoneal carcinomatosis, and the previous treatment with systemic chemotherapy. The extent of peritoneal carcinomatosis was assessed by intraoperative exploration. Individual institutions used two different tools (Gilly's classification[22,23] and Peritoneal Cancer Index [PCI] of Sugarbaker[16,24]) to assess the extent of carcinomatosis. By Gilly's classification, carcinomatosis is classified into four stages: stage I and II, malignant tumor nodules less than 5 mm in diameter localized in one part of the abdomen and diffuse to the whole abdomen, respectively; stage III, tumor nodules 5 mm to 2 cm in diameter; stage IV, large ($>$ 2 cm in diameter) tumor deposits. The PCI is described in Fig 1. To accommodate the two assessments in a single database, two groups were formed: carcinomatosis with limited extent, corresponding to the stage I and II from the Gilly's classification and PCI less than 13, and carcinomatosis with extensive extent, corresponding to the stage III and IV from the Gilly's classification and PCI $\geq$13. Information recorded about the combined procedure included the date, the completeness of cytoreductive surgery, the simultaneous resection of primary tumor or of liver metastasis, the presence or absence of lymph node metastases (draining mesenteric, celiac, hepatic, or retroperitoneal), the type of perioperative intraperitoneal chemotherapy (IPCH, EPIC, or both), and treatment with adjuvant systemic chemotherapy, including the drugs used. The assessment of the completeness of cancer resection (CCR) by cytoreductive surgery was performed by the surgeon at the end of the procedure and classified into three categories: CCR-0 indicated no macroscopic residual cancer remained, CCR-1 indicated no residual nodule greater than 5 mm in diameter remained, and CCR-2 indicated that the diameter of residual nodules was greater than 5 mm. Information was obtained regarding the postoperative course, including postoperative death (within 30 postoperative days) and its etiology, major complications (grade 3 and 4 complications according to the National Cancer Institute's Common Toxicity Criteria), and reoperations. Follow-up data recorded included the data of the most recent follow-up, the status of the patient (alive with disease, alive without disease, dead with disease, dead without disease), the site of initial recurrence, and all other sites of recurrence after the initial site of recurrence.

Statistical Analysis

To study relationships between variables, standard tests have been used: χ^2 with two qualitative variables, Pearson's correlation (or Spearman's ranks correlation) if quantitative, and analysis of variance, Student's t test, Kruskall-Wallis H test otherwise, depending on number of distributions, normality, and differences of

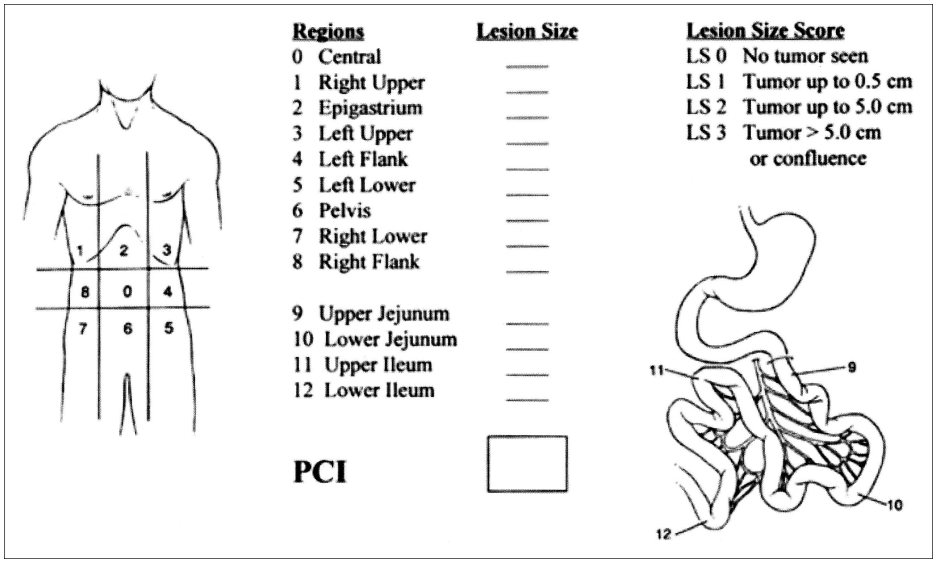

Fig 1. Peritoneal Cancer Index. The abdomen and the pelvis are divided into 13 regions. The lesion size of the largest sizes of the largest implants are scored (0 through 3) in each abdominopelvic region. They can be summated as a numerical score, which ranges from 1 to 39.

variances. Survival analysis was performed using the Kaplan-Meier method,[25] and comparisons of curves were made with the log-rank test.[26] Delays taken into account separated surgery from dates of recurrence, death, and/or last news. Cox model[27] enabled us to realize multiple analysis of survival and the logistic regression model to estimate complications risk of several factors together. Standard probability cutoff, $P \leq .05$, was chosen as the significance level. SEM software[28] was used to perform calculations. Disease-free survival was defined as time until recurrence or last news date if none. 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 CCR-2 resections with residual tumor nodules greater than 5 mm were considered as immediate relapse. The postoperative deaths were not excluded from the survival analysis.

RESULTS

Patients Characteristics

Patient characteristics are listed in Table 1. There were 273 female patients (53.9%) and 233 male patients (46.1%), with a median age of 51 years (range, 16 to 81 years). Three hundred twenty-two patients were treated in institutions that included more than 50 patients. The carcinomatosis arose from adenocarcinomas of right colon (39.5%), sigmoid (28.7%), left colon (12.5%), rectum (7.9%), transverse colon (7.0%), and of multiple locations (1.4%). The location of primary tumor was unknown for 15 patients (3%). The lymph node status of the primary tumor was established for 450 patients and was positive in 322 patients (71.6%) and negative in 128 patients (28.4%). Primary tumor was well differentiated in 122 patients (24.1%), moderately differentiated in 188 patients (37.2%), poorly differentiated in 122 patients (24.1%), and differentiation was unknown in 74 patients (14.6%). The extent of carcinomatosis was limited in 171 patients (34.2%), extensive in 329 patients (65.8%), and unknown in six patients. Two hundred seventy-five patients (54.3%) were previously treated with systemic chemotherapy.

Treatment

At the completion of a best surgical effort at cytoreduction, 271 patients were considered a CCR-0 resection, 106 patients were considered a CCR-1, and 129 patients a CCR-2. Sixty-one patients (12.1%) underwent a simultaneous resection of liver metastasis. The cytoreductive surgery was synchronous with the resection of the primary tumor in 99 patients (19.6%). Two hundred seventy-one patients (53.5%) underwent an IPCH alone, 123 patients (24.3%) underwent an EPIC alone, and 112 patients (22.2%) underwent both treatments. The drugs used for this perioperative intraperitoneal chemotherapy are reported in Table 2. All IPCH procedures were performed intraoperatively after cytoreductive surgery, but with many variations in exposure techniques (open or closed wall), drugs, drug doses, duration (30 to 90 minutes), intraperitoneal temperatures (40°C to 43°C), type of perfusate, and flow rates. EPIC was delivered during 5 days, from day 1 to day 5 after surgery. The main regimen delivered intraperitoneal fluorouracil at 15 mg/kg/d in 1 L of dialysis solution. Lymph node involvement was positive at the time of cytoreductive surgery in 263 patients (56.2%), negative in 205 patients (43.8%), and unknown in 38 patients (7.5%). Two hundred four patients (48.7%) received additional courses of systemic chemotherapy. The different drugs and regimens used are reported in Table 3. Twenty-six patients underwent a second combined procedure involving cytoreductive surgery and perioperative surgery, and one patient underwent a third procedure.

Table 1. Patient and Treatment Characteristics With Median Survival of Different Subgroups (univariate analysis)

Variable	No. of Patients	Median Survival (months)	*P*
Sex			
Male	233	16.8	.003
Female	273	21.6	
Age, years			
< 65	442	20.4	.04
≥ 65	64	15.6	
No. of inclusions			
< 50	230	18	—
≥ 50	276	18	
Location			
Right colon	200	16.8	.62
Sigmoid	145	24.0	
Left colon	63	20.4	
Rectum	40	19.2	
Transverse colon	36	19.2	
Lymph node involvement*			
Positive	363	18	.003
Negative	98	31.2	
Tumor differentiation			
Well	122	30	< .0001
Moderately	188	20.4	
Poor	122	14.4	
Unknown	74	18	
Extent of carcinomatosis			
Limited	171	34.8	< .0001
Extended	329	14.4	
Preoperative systemic chemotherapy			
Yes	275	19.2	.35
No	231	20.4	
Resection of concomitant liver metastasis			
Yes	61	16.8	.008
No	445	20.4	
Synchronous resection of primary tumor			
Yes	99	19.2	.27
No	407	19.2	
Completeness of cytoreduction			
CCR-0	271	32.4	< .0001
CCR-1	106	24	
CCR-2	129	8.4	
Perioperative intraperitoneal chemotherapy			
IPCH	383	19.2	.61
EPIC	235	19.2	
IPCH + EPIC	112	21.6	
Postoperative systemic chemotherapy			
Yes	204	25.2	.021
No	302	15.6	
Second procedure			
Yes	26	57.6	< .001
No	480	18	

Abbreviations: CCR, completeness of cancer resection; IPCH, intraperitoneal chemohyperthermia; EPIC, early postoperative intraperitoneal chemotherapy.
*Lymph node involvement was considered positive if lymph node was positive at the time of the resection of primary tumor or at the time of cytoreduction.

Table 2. Type of Drugs and Regimens Used for IPCH and EPIC

Drug	IPCH		EPIC	
	No. of Patients	%	No. of Patients	%
Mitomycin	274	71.4	2	0.9
Mitomycin + cisplatin	48	12.5	—	—
Oxaliplatin	32	8.4	—	—
Mitomycin + fluorouracil	—	—	113	52.1
Fluorouracil	—	—	95	43.8
Others	29	7.7	7	3.2
Total	383	100	235	100

Abbreviations: IPCH, intraperitoneal chemohyperthermia; EPIC, early postoperative intraperitoneal chemotherapy.

Survival

With a median follow-up of 53 months (range, 5 to 192 months), the overall 1-year, 3-year, and 5-year actuarial survival rates were 72%, 39%, and 19%, respectively. The overall 1-year, 3-year, and 5-year disease-free survival rates were 40%, 16%, and 10%, respectively (Fig 2). By univariate analysis, the principal clinical factors were age, sex, lymph node involvement, tumor differentiation, and carcinomatosis extent (Table 1). The median survival of male patients was 16.8 months, compared with 21.6 months for female patients ($P = .003$). The males were diagnosed more often with an extended carcinomatosis ($P = .023$; relative risk, 1.16). Patients older than 65 years had a significant lower survival rate than younger patients ($P = .037$). Age had significant influence on survival from 60 years. The lymph node involvement diagnosed at the time of the resection of primary tumor or at the time of cytoreduction was a significant prognostic indicator, as was tumor differentiation ($P = .003$ and $P < .0001$, respectively). The 1-year, 3-year, and 5-year survival rates of patients with limited carcinomatosis were 92%, 50%, and 33%, respectively, whereas they were 62%, 22% and 11%, respectively, for patients with extended carcinomatosis ($P < .0001$; Fig 3).

By univariate analysis, the principal therapeutic factors were the completeness of cytoreductive surgery, the synchronous resection of liver metastasis, the treatment with

Table 3. Type of Drugs and Regimens Delivered As Adjuvant or Palliative Systemic Chemotherapy

Regimen	No.	%
Fluorouracil plus leucovorin	75	36.7
Fluorouracil, leucovorin, and cisplatin	34	16.7
Fluorouracil, leucovorin, and oxaliplatin	20	9.8
Fluorouracil	20	9.8
Fluorouracil, leucovorin, oxaliplatin, and irinotecan	15	7.3
Others	14	7.0
Unknown	26	12.7

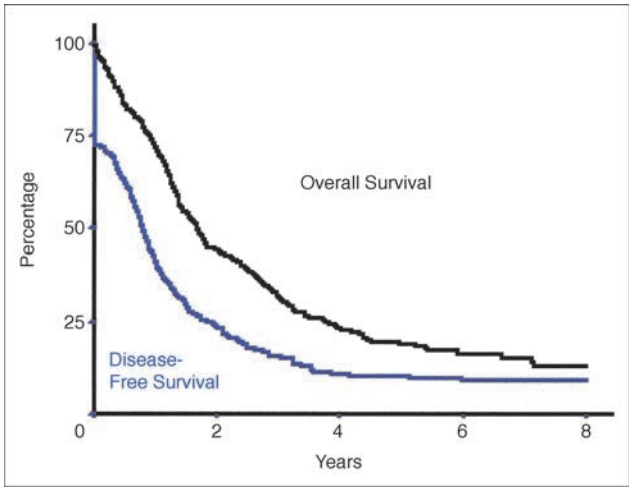

Fig 2. Overall survival and disease-free survival for 506 patients who had cytoreductive surgery combined with perioperative intraperitoneal chemotherapy.

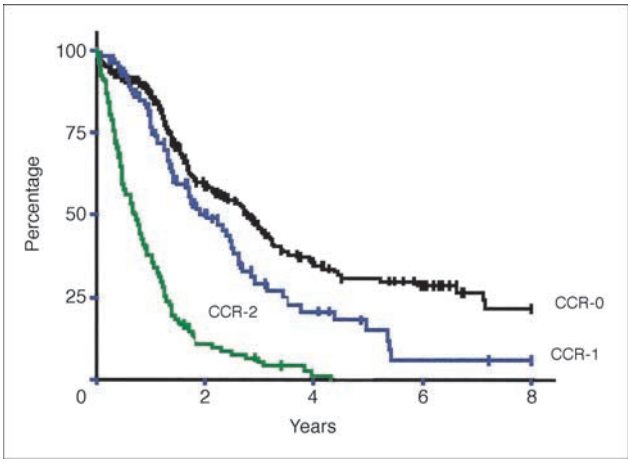

Fig 4. Actuarial survival of 506 patients who had cytoreductive surgery combined with perioperative intraperitoneal chemotherapy, according to the completeness of cytoreduction. CCR, completeness of cancer resection.

postoperative adjuvant systemic chemotherapy, and the use of a second surgical procedure. If postoperative deaths were excluded, the effect of adjuvant chemotherapy was no longer significant ($P = .24$). For CCR-0 patients, the 1-year, 3-year, and 5-year survival rates were 87%, 47%, and 31%, respectively, with a median survival time of 32.4 months (Fig 4). For CCR-1 patients, the 1-year, 3-year, and 5-year survival rates were 79%, 29%, and 15%, respectively, with a median survival time of 24 months. For CCR-2 patients, the 1-year and 3-year survival rates were 38% and 6%, respectively, with no patients alive at 5 years and a median survival time of 8.4 months ($P < .0001$). The synchronous resection of liver metastasis had a significant negative influence on survival ($P = .008$). Survival rates were higher with the perioperative association of IPCH with EPIC than with IPCH or EPIC alone, but this difference was not significant ($P = .61$). Patients who had a second procedure experienced significantly improved survival ($P < .0001$); median survival for such patients was 57.6 months. Survival rates were significantly higher with adjuvant systemic chemotherapy than without ($P = .021$).

A multivariate analysis using a Cox regression model was performed to determine which clinical or therapeutic variables were most strongly correlated with survival. The independent prognostic indicators were the completeness of cytoreduction, treatment with a second procedure, carcinomatosis extent, lymph node involvement, age, tumor differentiation, synchronous resection of liver metastasis, treatment with preoperative systemic chemotherapy, and treatment with adjuvant systemic chemotherapy (Table 4). The completeness of cytoreduction was the principal independent prognostic indicator ($P < .0001$) with the treatment with a second procedure ($P < .001$). Age ($<$ or ≥ 65

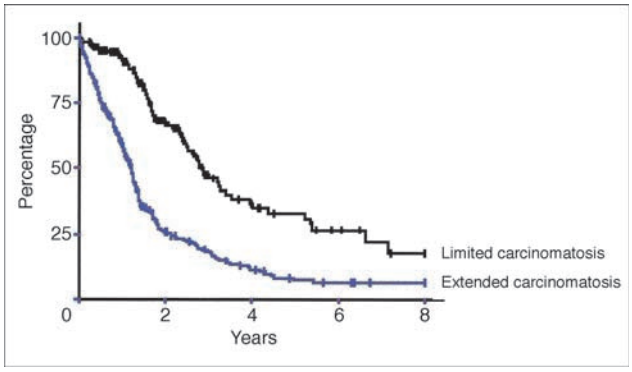

Fig 3. Actuarial survival of 506 patients who underwent cytoreductive surgery combined with perioperative intraperitoneal chemotherapy, according to the extent of carcinomatosis.

Table 4. Multivariate Survival Analysis of 506 Patients Treated With Cytoreductive Surgery Combined With Perioperative Systemic Chemotherapy

Variable	Cox Coefficient	*P*
Completeness of cytoreduction	0.71	< .0001
Treatment with second procedure	−1.10	< .001
Carcinomatosis extent	0.51	< .001
Lymph node involvement	0.23	.002
Age	0.54	.002
Tumor differentiation	0.26	.003
Synchronous resection of liver metastasis	0.52	.004
Preoperative systemic chemotherapy	0.33	.01
Adjuvant systemic chemotherapy	−0.26	.04
Treatment with IPCH	−0.33	.07
Treatment with EPIC	−0.22	.17
Sex	0.18	.12
Synchronous resection of primary tumor	0.05	.76

NOTE. A negative Cox coefficient indicates improved survival.
Abbreviations: IPCH, intraperitoneal chemohyperthermia; EPIC, early postoperative intraperitoneal chemotherapy.

years), which had significant influence on survival by univariate analysis, had no significant influence by multivariate analysis. Treatment with preoperative systemic chemotherapy kept its significant negative influence on survival ($P = .01$), as well as synchronous resection of liver metastasis ($P = .004$). As in univariate analysis, adjuvant chemotherapy lost its positive significance when postoperative deaths were excluded from Cox regression ($P = .13$).

Mortality and Morbidity

Twenty patients (4.0%) died postoperatively. The causes of death were septic shock (nine patients), respiratory complications (five patients), pulmonary embolism (one patient), aplasia (one patient), cerebral stroke (one patient), peritonitis (one patient), acute renal insufficiency (one patient), and unknown (one patient).

Major complications occurred in 116 patients (22.9%). Details of postoperative complications are reported in Table 5. A re-operation was necessary in 54 patients (10.7%). Digestive fistula was the principal complication and occurred in 42 patients (8.3%). It was involved in seven of the 20 postoperative deaths. Two factors significantly increased the risk of major complications: the extensive extent of carcinomatosis ($P = .005$) and the use of EPIC ($P = .032$), with relative risks of 1.7 (range, 1.2 to 2.5) and 1.4 (range, 1.0 to 1.9), respectively. When IPCH was combined with EPIC, the morbidity rate was nine (29.0%) of 31 patients.

Recurrences

Among all 506 patients, 371 recurrences (73.3%) were diagnosed. Among the 377 patients treated with CCR-0 or CCR-1 resection who did not die postoperatively, 242 recurrences (64.2%) were diagnosed. Peritoneal recurrences were detected in 158 patients (41.9%). The other sites of recurrence were systemic metastasis (liver, bones, lung, and/or brain). The site of recurrence was unknown in 16 patients.

DISCUSSION

In current surgical practice, peritoneal seeding from colorectal cancer found at the time of surgical exploration is treated by colectomy alone. The patient is given a poor prognosis and is usually referred for systemic chemotherapy. Unfortunately, in these patients, long-term survival is rarely, if ever, achieved. The three principal studies dedicated to the natural history of peritoneal carcinomatosis from colorectal cancer confirmed this poor prognosis, with a median survival ranging between 6 and 8 months and no 5-year survivors.[2,6,7] The carcinomatosis extent was found to be the principal prognostic indicator, but even with a limited extent, median survival of peritoneal carcinomatosis did not exceed 10 months. In the last decade, results of locoregional treatment giving a hope of cure in selected carcinomatosis patients emerged. This treatment combined cytoreductive surgery with perioperative intraperitoneal chemotherapy. Cytoreductive surgery attempts to remove all macroscopic visible tumor with comprehensive visceral resections and peritonectomy procedures, stripping involved portions of the peritoneum.[13] Perioperative intraperitoneal chemotherapy is used at the end of the operation to destroy residual microscopic disease, thereby preventing malignant cell implantation and cancer recurrence.[29] Institutions involved in the treatment of peritoneal surface malignancies developed two concepts of intraperitoneal chemotherapy that can be delivered alone or in association: the IPCH[14,18] and the EPIC.[16,19] Many phase II studies[16,18-21,30-36] involving a small number of patients reported interesting survival results with this combined approach

Table 5. Details of Major Postoperative Complications (grade 3/4 according to the National Cancer Institute's Common Toxicity Criteria)

Type of Complication	No.	%
Digestive fistula	42	8.3
Hematologic toxicity	12	2.4
Systemic sepsis	10	2
Postoperative bleeding	9	1.8
Intra-abdominal abscess	9	1.8
Respiratory distress	8	1.6
Pneumonia	8	1.6
Urinary fistula	5	1
Line sepsis	5	1
Bowel obstruction	5	1
Pulmonary embolism	2	0.4
Peritonitis	2	0.4
Other	6	1.2
Combined morbidity	116	22.9
Mortality	20	4

Table 6. Literature Data on Patients Treated With Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

Authors	Year	No. of Patients	Survival	
			Year When Measured	%
Fujimura et al[30]	1999	14	3	22
Beaujard et al[31]	2000	27	1	50
Cavaliere et al[32]	2000	14	2	64*
Pestiau and Sugarbaker[19]	2000	104	3	29
Elias et al[16]	2001	64	5	27†
Witkamp et al[20]	2001	29	3	23
Culliford et al[33]	2001	54	5	28*
Zoetmulder et al[21]	2002	48	2	63
Shen et al[18]	2003	40	3	25
Pilati et al[34]	2003	34	2	31
Elias et Pocard[35]	2003	34	3	65†
Cavaliere et al[36]	2003	69	4	45†

*Appendiceal malignancies included.
†Complete cytoreductive surgery.

(Table 6). Recently, preliminary results of a phase III study of IPCH combined with mitomycin was reported by the Netherlands Center Institute.[21] Patients with known colorectal carcinomatosis were preoperatively randomly assigned to standard treatment with palliative surgery followed by systemic fluorouracil and leucovorin or treatment with maximal cytoreductive surgery with IPCH. After a mean follow-up of 24 months, the 2-year survival rates were 43% in the experimental group and 16% in the standard group ($P = .01$). The study was stopped for ethical reasons. The present international registration, including a large population of 506 patients, confirmed the interesting survival results observed in all these single-institution studies using the combination of cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of colorectal carcinomatosis. With an overall median survival time of 19.2 months, the 3-year and 5-year survival rates were 39% and 19%, respectively. Thirty-eight 5-year survivors were observed, whereas no patient survived beyond 5 years in the studies dedicated to the natural history of colorectal carcinomatosis.

The combination of two aggressive locoregional therapeutic approaches can lead to increased morbidity and mortality rates. This study reported morbidity and mortality rates of 22.9% and 3.7%, respectively, with 8.3% of digestive fistula. These results are comparable to those previously reported by the two most important trials dedicated to the analysis of the complications that occur after cytoreductive surgery and perioperative intraperitoneal chemotherapy and that concluded that morbidity was correlated with the magnitude of surgery.[37,38] No evaluation of the magnitude of surgery was recorded in the present study, but we observed that extended carcinomatosis that required extensive cytoreductive surgery had a significant negative influence on the rate of complications. Elias et al,[16] who treated patients with the combined procedures only when complete cytoreductive surgery was possible, previously reported that morbidity rates were correlated with carcinomatosis extent. Surgeons must use their judgment to achieve a balance between the postoperative risk of extensive surgery and potential benefit in survival and quality of life. Extended carcinomatosis was also an independent negative prognostic indicator. Its association with other negative prognostic indicators, such as lymph node involvement, poor differentiation, and liver metastasis, may lead to contraindicate patients for aggressive surgery combined with perioperative intraperitoneal chemotherapy with a curative intent. The high but acceptable rate of complications emphasizes the necessity for careful patient selection. As age greater than 65 years seemed to be a significant negative prognostic indicator of survival, this aggressive combined procedure should be reserved for younger patients, without cardio-respiratory or renal failure, especially when carcinomatosis is extended and requires an extensive cytoreductive surgery to expect survival benefit.

As it was previously reported by single-institution studies,[14,16,18,19] the completeness of cytoreduction was the principal independent prognostic indicator. For patients treated with complete cytoreduction, the median survival reached 32.4 months, and the 5-year survival rate was 31%. These results should shake the skepticism of the oncologic community. In 1988, a multi-institutional study of 859 patients who had undergone liver resections for colorectal liver metastasis was reported.[39] The 5-year actuarial survival rate was 33%, whereas postoperative deaths were censored. Since that time, to our knowledge, no randomized trial has demonstrated the benefit of surgery for the treatment of resectable colorectal liver metastasis. However, is there any oncologist who will not refer one of his patients with resectable liver metastasis from colorectal cancer to the surgeon? Even if the study of peritoneal carcinomatosis is more difficult in that diagnostic tests to precisely assess the extent and the possibility of complete resection are lacking, each patient with colorectal carcinomatosis should be referred to centers involved in the management of peritoneal malignancies for evaluation. Peritoneum should be considered as organ and peritoneal carcinomatosis should be treated as well as other metastasis (liver, lung). Moreover, a procedure combining cytoreductive surgery and perioperative intraperitoneal chemotherapy does not contraindicate a second procedure for patients who presented with recurrence. Indeed, the few patient who underwent a second combined procedure reached a median survival of 57.6 months. This aggressive therapeutic strategy may lead to long-term survival for selected patients. Because locoregional recurrences occurred in 41.9% of patients treated with CCR-0 or CCR-1 resection, and because their median disease-free survival time was 13 months, a second-look procedure may be indicated at 1 year for patients who present without any evidence of recurrence on morphologic exams. Recurrences with limited carcinomatosis, often undetectable on the standard morphologic exams, could be treated with greater efficiency with a second combined procedure.

Independent negative prognostic indicators included lymph node involvement and synchronous resection of liver metastasis. Because they seemed to profoundly influence the prognosis, they must be carefully assessed with preoperative computed tomography scan and/or intraoperative ultrasonography for the detection of liver metastasis and multiple intraoperative biopsies for the assessment of lymph node involvement. They usually indicate systemic dissemination of the disease. An exclusive locoregional therapeutic approach for a disease that is not confined to the peritoneum cannot be sufficient. Additional systemic chemotherapy should be indicated in these cases. Many of the patients included in this registration underwent systemic chemotherapy before and after the procedures. In this retrospective review, the variability between administration and drugs used was too great to allow us a firm conclusion

regarding whether chemotherapy improved prognosis. It is beyond the capability of this analysis to confirm or deny the value of adjuvant or preoperative systemic chemotherapy. However, adjuvant systemic chemotherapy significantly improved survival in the group of patients treated with incomplete cytoreduction. Because of the recent development of and the interesting results achieved with new anticancer drugs such as oxaliplatin and irinotecan in patients with metastatic colorectal cancer,[11,12] systemic chemotherapy using these two drugs should be proposed to patients with carcinomatosis that cannot be completely resected or associated with liver metastasis and lymph node involvement and may be evaluated by randomized studies. The use of preoperative systemic chemotherapy had a significantly negative influence on survival. This could be explained by the fact that this chemotherapy delayed the combined procedure and the surgery and might have compromised the possibility of complete cytoreduction. However, patients given preoperative chemotherapy may also have had more disease burden, which would explain their course.

The question of which type of perioperative intraperitoneal chemotherapy to use remains controversial, but most of the centers involved in the treatment of peritoneal surface malignancies are currently using IPCH, which was part of treatment for 75.7% of patients in the registration. Unfortunately, as with EPIC, the procedure is not standardized, and many variations exist in exposure techniques, drugs, drug doses, duration, temperature, and flow rates.[40-42] There are some technical differences between EPIC and IPCH that may be exploited in different patient populations. EPIC has the advantage that it can be performed anywhere and at anytime because it does not necessitate any special apparatus. This is most relevant and useful when the carcinomatosis is a fortuitous discovery during laparotomy. Pestiau and Sugarbaker[19] reported the better prognosis of patients with colorectal carcinomatosis treated with concomitant management of primary tumor. The registration sought to demonstrate that synchronous treatment of carcinomatosis with the resection of primary tumor improved overall survival. The theoretical deficiencies of EPIC include a failure to uniformly treat all the peritoneal surfaces, failure to provide the additive effect of hyperthermia,[43,44] a requirement for 5 days of added patient discomfort, and the maintenance of high concentration of chemotherapy surrounding intestinal anastomoses, which increases the risk of complications, as it was observed in the present study. No significant differences in survival were observed between patients treated with IPCH alone, EPIC alone, or both, but survival results were better with the combination. Regarding the design and the bias of the study and the great heterogeneity of the techniques and drugs used, no conclusions on the more efficient perioperative intraperitoneal chemotherapy can be established.

The novel therapeutic approach combining cytoreductive surgery and perioperative intraperitoneal chemotherapy may be the most promising new treatment for colorectal cancer for the next decade. It offers hope for cure to patients who had in the past no escape for a terminal illness. This international registration, despite its bias owing to its design, identified several useful prognostic indicators for patient selection. The use of perioperative intraperitoneal chemotherapy and its modalities still need to be validated by randomized studies. A trial comparing IPCH with the most modern systemic polychemotherapy after maximal cytoreductive surgery is warranted. Although this trial would have a strong scientific and ethical rationale, the team undertaking it will probably face numerous recruitment difficulties resulting from patient refusal to be randomly assigned to the control group.[35]

Appendix

The appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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