Treatment of Colorectal Peritoneal Carcinomatosis With Systemic Chemotherapy: A Pooled Analysis of North Central Cancer Treatment Group Phase III Trials N9741 and N9841

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Submitted June 14, 2011; accepted August 10, 2011; published online ahead of print at www.jco.org on December 12, 2011.

Supported by National Institutes of Health Grants No. CA25224 (North Central Cancer Treatment Group); CA32102 (Southwest Oncology Group); CA21115 (Eastern Cooperative Oncology Group); and CA38926 (Cancer and Leukemia Group B).

Presented in part at the 47th Annual Meeting of the American College of Clinical Oncology, June 3-7, 2011, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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0732-183X/12/3003-263/\$20.00

DOI: 10.1200/JCO.2011.37.1039

ABSTRACT

Purpose

Symptoms and complications of metastatic colorectal cancer (mCRC) differ by metastatic sites. There is a paucity of prospective survival data for patients with peritoneal carcinomatosis colorectal cancer (pcCRC). We characterized outcomes of patients with pcCRC enrolled onto two prospective randomized trials of chemotherapy and contrasted that with other manifestations of mCRC (non-pcCRC).

Methods

A total of 2,095 patients enrolled onto two prospective randomized trials were evaluated for overall survival (OS) and progression-free survival (PFS). A Cox proportional hazard model was used to assess the adjusted associations.

Results

The characteristics of the pcCRC group ($n = 364$) were similar to those of the non-pcCRC patients in median age (63 v 61 years, $P = .23$), sex (57% males v 61%, $P = .23$), and performance status (Eastern Cooperative Oncology Group performance status 0 or 1 94% v 96%, $P = .06$), but differed in frequency of liver (63% v 82%, $P < .001$) and lung metastases (27% v 34%, $P = .01$). Median OS (12.7 v 17.6 months, hazard ratio [HR] = 1.3; 95% CI, 1.2 to 1.5; $P < .001$) and PFS (5.8 v 7.2 months, HR = 1.2; 95% CI, 1.1 to 1.3; $P = .001$) were shorter for pcCRC versus non-pcCRC. The unfavorable prognostic influence of pcCRC remained after adjusting for age, PS, liver metastases, and other factors (OS: HR = 1.3, $P < .001$; PFS: HR = 1.1, $P = .02$). Infusional fluorouracil, leucovorin, and oxaliplatin was superior to irinotecan, leucovorin, and fluorouracil as a first-line treatment among pcCRC (HR for OS = 0.62, $P = .005$) and non-pcCRC patients (HR = 0.66, $P < .001$).

Conclusion

pcCRC is associated with a significantly shorter OS and PFS as compared with other manifestations of mCRC. Future trials for mCRC should consider stratifying on the basis of pcCRC status.

J Clin Oncol 30:263-267. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Symptoms and complications associated with metastatic colorectal cancer (mCRC) differ by metastatic sites. In clinical practice, the differences among several distinct types of mCRC have been apparent for decades. Best survival is achieved among those for whom a combination of contemporary systemic chemotherapy¹⁻³ and a surgical resection is possible. Respective 5-year survival rates for selected populations are nearly 60%, 40%, and 20% to 51% among those with resectable hepatic,⁴⁻⁶ pulmonary,^{7,8} and peritoneal metastases.⁹⁻¹¹

Peritoneal carcinomatosis from CRC (pcCRC) has been historically associated with a very poor prognosis. Studies including systemic chemotherapy and symptom-directed surgery without cytoreduction demonstrated a median survival ranging from 5.2 to 7 months in the era of fluorouracil (FU) -only treatment.¹²⁻¹⁵ A subset of patients presenting with bowel obstruction owing to peritoneal carcinomatosis have an even worse prognosis, with a median overall survival (OS) for those actively treated of approximately 3 to 4 months and a 17% 1-year survival rate.^{16,17}

Table 1. Trial and Chemotherapy Description

Trial Label	Trial Name	Arm Label	Chemotherapy
N9741	A Randomized Phase III Trial of Combinations of Oxaliplatin, 5-Fluorouracil, and Irinotecan as Initial Treatment of Patients With Advanced Adenocarcinoma of the Colon and Rectum	Arm A: IFL (Saltz regimen)	Irinotecan 100 mg/m ² as a 90-minute infusion + CF 20 mg/m ² as a 15-minute infusion or IV push and FU 400 mg/m ² IV bolus weekly × 4, every 6 weeks
		Arm F: FOLFOX	OXAL 85 mg/m ² IV infusion in 500 mL of D5W over 120 minutes on day 1 and CF 200 mg/m ² IV infusion over 120 minutes and FU 400 mg/m ² IV bolus then 600 mg/m ² IV infusion in 500 mL of D5W over 22 hours on days 1 and 2, every 2 weeks
		Arm G: IROX	OXAL 85 mg/m ² IV infusion in 500 mL of D5W over 120 minutes on day 1 and irinotecan 200 mg/m ² IV over 30 minutes on day 1 every 3 weeks
N9841	A Randomized Phase III Equivalence Trial of Irinotecan Versus Oxaliplatin 5-Fluorouracil/Leucovorin in Patients With Advanced Colorectal Carcinoma Previously Treated with 5-FU	Arm A: IRI	Irinotecan 350 mg/m ² as a 90-minute infusion, day 1, every 3 weeks
		Arm B: FOLFOX	OXAL 85 mg/m ² as a 2-hour infusion, day 1, + CF 200 mg/m ² (2-hour infusion) followed by FU 400 mg/m ² followed by FU 600 mg/m ² (22-hour infusion), days 1 and 2, every 2 weeks

Abbreviations: CF, leucovorin; D5W, 5% dextrose in water; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; IFL, irinotecan, leucovorin, and fluorouracil; IROX, irinotecan and oxaliplatin; IV, intravenous; OXAL, oxaliplatin.

The combination of systemic chemotherapy after aggressive cytoreduction surgery with concurrent intraperitoneal chemotherapy has demonstrated a remarkable improvement in survival for highly selected patients with pcCRC (hazard ratio [HR] = 0.55) in a prospective randomized trial^{9,18} and in several retrospective surgical studies.^{10,11,19} Nevertheless, there is a paucity of prospectively collected outcome data for patients with peritoneal carcinomatosis treated with systemic chemotherapy. Therefore, we characterized the clinical course of patients with pcCRC enrolled in two cooperative group prospective randomized trials of systemic chemotherapy and contrasted that with mCRC with a different metastatic pattern (non-pcCRC). We hypothesized that pcCRC is associated with worse prognosis. If pcCRC is indeed a prognostic factor for mCRC, stratification of future systemic chemotherapy trials and exploration of other modalities for pcCRC should be considered.

METHODS

Prospective controlled randomized protocols of the North Cancer Central Treatment Group trials for patients with metastatic colorectal cancer were analyzed. Three trials collected information on site of metastatic disease. Data regarding the pcCRC status for an older trial (894652) were not available and therefore have not been included in this study. Two other trials met inclusion criteria (N9741 and N9841) and have available data (Table 1). N9741 examined multiple first-line chemotherapy regimens among patients with metastatic colorectal cancer.¹ This trial was modified during enrollment, resulting in the majority of patients treated with irinotecan, leucovorin, and fluorouracil (IFL); irinotecan and oxaliplatin (IROX); and infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimens (n = 1,691). N9841 (n = 491) enrolled patients for second-line systemic chemotherapy after prior FU treatment and randomly assigned between irinotecan and FOLFOX.³ Reported results are based on 2,101 cases without consent cancellations (n = 30), major protocol violations (n = 27), or ineligibility (n = 24). Analyses of pcCRC status are based on 2,095 cases as a result of missing data on metastatic sites in six patients (two cases for N9741 and four cases for N9841). Local institutional review boards approved the parent studies and the Mayo Clinic institutional review board approved the present analysis.

Most patients with pcCRC have radiologically nonmeasurable peritoneal disease, and progression may occur outside of peritoneum, making progression-free-survival (PFS) difficult to measure reliably. Therefore, we chose OS as the main clinical outcome, with limited reporting of PFS.

The stratified log-rank test was used to compare OS and PFS between pcCRC and non-pcCRC patients with combined data from two trials. The distributions of survival outcomes were estimated by Kaplan-Meier curves. The impact of systemic chemotherapy was analyzed separately for first- (N9741) and second-line treatment (N9841). A Cox proportional hazards model was used to assess the adjusted associations stratified by study. Analyses were done using SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.11 (<http://www.r-project.org>).

RESULTS

Of a total of 2,101 patients were included; the majority participated in the N9741 trial of first-line chemotherapy for mCRC (n = 1,646), and the remaining participated in the N9841 trial of second-line chemotherapy (n = 455). Although age statistically differed between the trials, the difference was clinically trivial (Table 2). There was no age difference when stratified by presence or absence of pcCRC (Table 3). pcCRC was more common among those enrolled in the second-line trial (22.6% v 15.9%, $P < .001$; Table 2), with a total of 17.4%. Patients with pcCRC as the sole presentation of mCRC were uncommon in this patient population (n = 44, 2.1%; Table 2). Despite having less hepatic and pulmonary metastases, the patients with pcCRC were more likely to harbor more metastatic disease sites (Table 3). Prior adjuvant chemotherapy (N9741) and prior systemic therapy (N9841) was collected differently between the two studies, had a high rate of missing data, and could not be factored into the analysis.

Patients with pcCRC had higher risk of death owing to all causes than patients without pcCRC (median OS 12.7 v 17.6 months, HR = 1.32, 95% CI, 1.15 to 1.50; $P < .001$; Fig 1, Table 4). Among patients treated with first-line FOLFOX, median OS was 15.7 months versus 20.9 months for pcCRC versus non-pcCRC patients, respectively ($P = .003$; Fig 2). After 7 years median follow-up on living patients, 2,009 (98.5%) of 2,095 patients with known pcCRC status have died. Both 5-year (6% v 4.1%) and 8-year (3.2% v 1.1%) survival rates were higher among those without pcCRC than with pcCRC. Data on tumor grade were not available. Involvement of regional lymph nodes did not predict OS (HR = 1.012, $P = .820$) or PFS (HR = 0.970, $P = .580$) in univariate Cox model stratified by study.

Table 2. Demographic Characteristics Stratified by Study: N9741 (first-line treatment) and N9841 (second-line treatment)

Characteristic	N9741 (N = 1,646)		N9841 (N = 455)		Total (N = 2,101)		P
	No.	%	No.	%	No.	%	
Age, years							.029
Mean	60.1		61.4		60.4		
SD	11.5		11.7		11.6		
pcCRC	262	15.9	102	22.6	364	17.4	< .001
pcCRC (solitary site)	28	1.7	16	3.5	44	2.1	.015
Liver metastases	1,347	81.9	295	65.4	1,642	78.4	< .001
Pulmonary metastases	513	31.2	176	39.0	689	32.9	.002
Male sex	998	60.6	267	58.7	1,265	60.2	.451
ECOG performance status							.286
0-1	1,569	95.3	439	96.5	2,008	95.6	
2	77	4.7	16	3.5	93	4.4	
No. of disease sites							.446
Missing data	2		4		6		
1	601	36.6	175	38.8	776	37.0	
2	572	34.8	160	35.5	732	34.9	
3+	471	28.6	116	25.5	587	27.9	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; pcCRC, peritoneal carcinomatosis colorectal cancer; SD, standard deviation.

Within N9741, there is no statistically significant evidence of interaction effect ($P = .799$) between pcCRC status and treatment groups on OS. Adjusting for status of pcCRC, IFL ($HR = 1.53, P < .001$) and IROX ($HR = 1.34, P < .001$) were associated with poorer OS than FOLFOX. Adjusting for treatments, patients with pcCRC had worse OS ($HR = 1.42, P < .001$) than patients with non-pcCRC.

Similar results were obtained when analyzing second-line treatment in N9841: There was no significant interaction ($P = .115$) between pcCRC status and treatment groups on OS. Adjusting for treatments, patients with pcCRC had worse OS than patients with non-pcCRC ($HR = 1.37, P = .006$). However, there is no statistically significant difference in OS between IRI and FOLFOX ($HR = 1.10, P = .321$) after adjusting for pcCRC status.

To estimate efficacy of various chemotherapy regimens on OS, separate analyses were performed by trial and pcCRC status (Fig 2 and Appendix Fig A1, online only). OS was similar for patients with pcCRC and non-pcCRC treated with second-line FOLFOX (Appendix Fig A1, online only). Patients with pcCRC fared significantly worse in all other settings.

PFS was not a primary objective of this analysis. Nevertheless, patients with pcCRC fared worse in both univariate analysis (median PFS 5.8 v 7.2 months, $P = .002$) and multivariate analysis ($HR = 1.16, P = .021$).

DISCUSSION

The prognostic impact of specific metastatic sites has been recognized and included in staging of patients with melanoma and ovarian cancer. Although less well studied in mCRC, available evidence suggests an especially poor prognosis in patients with peritoneal carcinomatosis¹²⁻¹⁵ treated by systemic chemotherapy. Reported median survival among selected patients with good performance status treated with cytoreductive

Table 3. Demographic Characteristics by Presence or Absence of pcCRC

Characteristic	Non-pcCRC (n = 1,731)		pcCRC (n = 364)		Total (N = 2,095)		P
	No.	%	No.	%	No.	%	
Age, years							.225
Mean	60.3		60.6		60.4		
SD	11.3		12.9		11.6		
Male sex	1,052	60.8	209	57.4	1,261	60.2	.234
ECOG performance status							.055
0-1	1,661	96.0	341	93.7	2,002	95.6	
2	70	4.0	23	6.3	93	4.4	
Disease status							.069
Measurable	1,443	83.4	289	79.4	1,732	82.7	
Evaluable	288	16.6	75	20.6	363	17.3	
Liver metastases	1,414	81.7	228	62.6	1,642	78.4	< .001
Pulmonary metastases	590	34.1	99	27.2	689	32.9	.011
No. of disease sites							< .001
1	734	42.4	42	11.5	776	37.0	
2	615	35.5	117	32.1	732	34.9	
3+	382	22.1	205	56.3	587	27.9	
Treatment group							.6188
FU	52	3	7	1.9	59	2.8	
IFL or IRI	585	33.8	120	33.0	705	33.7	
IROX	304	17.6	70	19.2	374	17.9	
FOLFOX	790	45.6	167	45.9	957	45.7	
Prior adjuvant therapy*							
Missing info	349		102		451		
Given	187	13.5	53	20.2	240	14.6	
Not given	1,195	86.5	209	79.8	1,404	85.4	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; IFL, irinotecan, leucovorin, and fluorouracil; IRI, irinotecan; IROX, irinotecan and oxaliplatin; pcCRC, peritoneal carcinomatosis colorectal cancer; SD, standard deviation.
*Only available for N9741.

surgery plus intraperitoneal and systemic chemotherapy is 22.3 months in a prospective randomized trial^{9,18} and 33 to 61 months in the most recent retrospective comparative studies.^{10,11}

Although a few prospective studies on peritoneal carcinomatosis are available,^{15,18,20} this report is by far largest and is, to our knowledge, the

Fig 1. Overall survival by peritoneal carcinomatosis colorectal cancer (pcCRC) status.

Table 4. Stratified Multivariable Cox Regression Modeling on the Entire Study Cohort

Parameter	P	Hazard Ratio	95% CI
pcCRC (present v absent)	< .0001	1.316	1.152 to 1.504
Age (per year increase)	.0072	1.005	1.001 to 1.010
PS (2 v 0 & 1)	< .0001	1.796	1.453 to 2.220
Disease status (evaluable v measurable)	.4269	0.953	0.847 to 1.073
Liver metastases (present v absent)	< .0001	1.284	1.133 to 1.455
Other metastases* (present v absent)	.0009	1.263	1.100 to 1.449
Grouped current sites of disease			
No. of sites, 0-1	—	Ref	—
No. of sites, 2	.1339	1.107	0.969 to 1.263
No. of sites, 3+	.1568	1.141	0.950 to 1.371

Abbreviations: pcCRC, peritoneal carcinomatosis colorectal cancer; PS, performance status.

*Refers to those outside lung, liver, and peritoneum (pcCRC).

only study that analyzes survival differences on the basis of pcCRC status. The negative prognostic impact of pcCRC on OS observed in this study has been consistently shown in univariate (both unadjusted and adjusted) and multivariate analysis. The magnitude of this impact was consistent (HR = 1.3) and is clinically relevant.

We observed no differential impact of systemic chemotherapy on the basis of presence or absence of pcCRC. To our knowledge, the only observation of this phenomenon in mCRC comes from Folprecht et al,²⁰ who observed the absence of benefit from infusional FU as opposed to bolus FU among patients with pcCRC. Second, they noted less benefit from an FU/irinotecan combination among those with pcCRC as compared with those with other forms of mCRC for OS.²⁰ The present study suggests superiority of FOLFOX versus IFL and IROX in the first-line setting and no difference between irinotecan and FOLFOX in the second-line setting after initial FU treatment. Therefore, the presence or absence of pcCRC should not affect the choice of systemic chemotherapy regimen.

We realize several apparent limitations of the present study, including the retrospective nature of the analysis and some missing data. Moreover, carcinomatosis burden is known to substantially influence survival,^{18,19,21} but cannot be estimated in this study population. Also, selective consideration of mCRC for randomized trials may affect the number of patients with pcCRC involved in such trials. Indeed, prevalence of isolated pcCRC has been reported at 10% to 15%,^{13,14} but was found in only 2.1% cases in this study population.

The clinical manifestation of peritoneal carcinomatosis is unusually variable, and caution should be exercised when applying these results in clinical practice. More than 90% of the patients in these two studies had excellent performance status, and inclusion criteria required expected survival of more than 3 months. These criteria are certainly not met among patients with pcCRC presenting with malignant bowel obstruction or ascites, for whom expected median survival remains less than 4 months.^{16,17} Status of regional lymph nodes did not predict survival in this study. Among studies of cytoreduction with systemic and regional chemotherapy, some have found nodal involvement predictive of OS,²¹ but others have not.^{10,22} Although tumor grade is recognized as an important survival predictor in retrospective studies on cytoreduction,^{10,21} we had no available data to examine this factor.

Documented long-term survival (> 5 years) of patients with unresectable mCRC has been approximately 1.1%²³ in the FU-only

Fig 2. Survival of N9741 (first-line chemotherapy for metastatic colorectal cancer) by regimen used and peritoneal carcinomatosis colorectal cancer (pcCRC) status. Survival of patients with pcCRC was inferior in all chemotherapy arms. (A) infusional fluorouracil, leucovorin, and oxaliplatin; (B) irinotecan, leucovorin, and fluorouracil; (C) irinotecan and oxaliplatin.

era and has increased with newer chemotherapeutic agents.¹⁻³ In the present study, the 5-year OS was 6% for those without pcCRC and 4.1% for those with pcCRC. On the other hand, retrospective surgical series document nearly 60% actuarial survival among those with liver resection^{5,6} and 20% to 51% among those treated with cytoreductive surgery and intraperitoneal and systemic chemotherapy for pcCRC.⁹⁻¹¹ Of note, these studies were limited to patients amenable to surgical consideration. It remains unclear how these considerations relate to the population in the current study, mainly because of different selection bias associated with randomized trials on systemic chemotherapy versus cytoreduction studies. Consequently, reported outcomes among patients

with carcinomatosis vary far and wide. The median survival was less than 4 months among those presenting with obstruction and treated with symptom-directed surgery and systemic chemotherapy,^{16,17} whereas the majority of cytoreduction studies report median survival of more than 19 months after cytoreduction,^{10,21} and the highest reported median survival is 63 months.¹⁰

In summary, peritoneal carcinomatosis among patients with mCRC is associated with a 30% reduction in OS. Choice of systemic chemotherapy should be independent of presence or absence of peritoneal carcinomatosis. The FOLFOX regimen is superior to IFL and IROX irrespective of carcinomatosis status. Stratification of future prospective randomized trials based on carcinomatosis status should be considered. Continued research on bimodality treatment combining surgery and alternative chemotherapy delivery routes may be warranted. Molecular and genetic profiling of colorectal cancers may establish a gene signature that is predictive of a propensity for pcCRC and lead to selection of alternative adjuvant or advanced disease management strategies.

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.

Employment or Leadership Position: None **Consultant or Advisory**

Role: Richard M. Goldberg, Genentech (C), Eli Lilly (C), sanofi-aventis

(C) **Stock Ownership:** None **Honoraria:** None **Research Funding:**

Richard M. Goldberg, Abbott Laboratories, Amgen, Bayer

Pharmaceuticals, Bristol-Myers Squibb, Genentech, Medimmune **Expert**

Testimony: None **Other Remuneration:** None

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Manuscript writing: All authors

Final approval of manuscript: All authors

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