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Clinicopathological Differences and Survival Outcomes with First-Line Therapy in Patients with Left-Sided Colon Cancer and Rectal Cancer: Pooled Analysis of 2,879 Patients From AGITG (MAX), COIN, FOCUS2, OPUS, CRYSTAL, and COIN-B Trials in the ARCAD Database

Running Head: Pooled analysis of metastatic left-sided colon vs. rectal cancer

Authors: Mohamed E. Salem, MD[1*], Jun Yin, PhD[2], Benjamin A. Weinberg, MD[3], Lindsay R. Renfro, PhD[2], Levi D Pederson, MS[2], Timothy S. Maughan, MD[4], Richard A. Adams, MD[5], Eric Van Cutsem, MD[6], Alfredo Falcone, MD[7], Niall C. Tebbutt, MD[8], Matthew T. Seymour, MD[9], Eduardo Díaz-Rubio, MD[10], Enrique Aranda, MD[11], Carsten Bokemeyer, MD[12], Volker Heinemann, MD[13], Harpreet Wasan, MD[14], Aimery de Gramont, MD[15], Axel Grothey, MD[16], Qian Shi, PhD[2], Daniel J. Sargent, PhD[2], and John L. Marshall, MD[3]

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Affiliations:

[1]Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

[2]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA

[3]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA

[4]CRUK/MRC Oxford Institute for Radiation Oncology, Oxford, UK

[5]Cardiff University, Cardiff, UK

[6]University Hospitals Gasthuisberg Leuven, and KU Leuven, Leuven, Belgium

[7]Department of Oncology, University of Pisa, Pisa, Italy

[8]Austin Health, Heidelberg, Australia

[9]Gastrointestinal Cancer Research Unit, Cookridge Hospital, Leeds, UK

[10]Department Oncology, Hospital Clínico San Carlos, Madrid, Spain

[11]Reina Sofia Hospital, University of Cordoba, Maimonides Institute of Biomedical Research, Spanish Cancer Network, Instituto de Salud Carlos III, Avenida de Menendez Pidal, Cordoba, Spain

[12]Department of Oncology, Haematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[13]Comprehensive Cancer Center, Ludwig-Maximilian-University of Munich, Munich, Germany.

[14]Imperial College Healthcare NHS Trust, London, UK

[15]Department of Medical Oncology, Franco-British Institute, Levallois-Perret, France

[16]Department of Oncology, Mayo Clinic, Rochester, MN, USA

[*]Corresponding author:

Mohamed E. Salem, MD

Assistant Professor

Levine Cancer Institute

Carolinas HealthCare System

1021 Morehead Medical Drive

Charlotte, NC 28204, USA

Tel: (704) 403-1370

Fax: (704)-403-3241

E-mail: Mohamed.Salem@carolinashealthcare.org

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Abstract

Purpose

Patients with left-sided colon tumors have better survival and respond differently to biologics compared to patients with right-sided tumors. Left-sided colon tumors and rectal cancers are often grouped together. Herein, we examined the clinicopathological differences and outcomes between left-sided colon and rectal cancers.

Patients and Methods

Data from 2,879 metastatic colorectal cancer patients enrolled on six first-line clinical trials during 2004-2010 were pooled. Patients were included if the primary tumor origin was clearly defined. Progression-free and overall survivals were compared in the two groups after adjusting for patient and tumor characteristics, metastatic sites, and the first-line regimen.

Results

In total, 1,374 patients with metastatic left-sided colon cancer and 1,505 patients with metastatic rectal cancers were evaluated. Left-sided colon cancer patients were more likely to be female (40.1% vs. 32.6%; P < .0001) and older (31.0% ≥ 70 years vs. 25.8%; P = .0033) compared to rectal cancers patients. Patients with left-sided colon cancer had higher rates of liver metastases (80.9% vs. 72.3%, P < .0001) but lower rates of lung metastases (34.2% vs. 53.8%, P < .0001). KRAS mutations were slightly less frequent among left-sided tumors (34.8% vs. 40.5%; P = 0.0103). Patients with left-sided tumors had approximately similar PFS (median 7.4 vs. 6.9 months; hazard ratio [HR] 0.92, 95% CI 0.87-1.03; P = .1998) and OS (median 17.4 vs. 16.6 months; HR 0.99, 95% CI 0.91-1.07; P = .7597) compared to rectal cancer patients.

Conclusion

The site of tumor origin within the left side was not prognostic of outcomes. Moreover, neither bevacizumab nor cetuximab impacted, differently, the findings of the comparisons in outcomes between patients with left-sided colon tumors or rectal cancers.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death in the USA [1-2]. The standard first-line treatment for metastatic colorectal cancer (mCRC) is combination chemotherapy with an oxaliplatin- or irinotecan-based fluoropyrimidine-containing regimen, commonly combined with a biological agent—either the anti-VEGF inhibitor bevacizumab, or, for patients with RAS wild-type tumors only, the anti-EGFR inhibitors cetuximab or panitumumab.

Until recently, bevacizumab and cetuximab were believed to have comparable efficacy when added to chemotherapy in the frontline treatment of RAS wild-type patients [3]. However, this belief has now changed in light of the retrospective analyses of the pivotal CALGB/SWOG 80405 and FIRE-3 studies [4-5]. The authors reported that in the first-line treatment of mCRC patients, the anatomic location of the primary tumor within the colon not only has an impact on patient survival but also on response to biological therapy: patients with right-sided primary tumors (from cecum to proximal transverse colon) have inferior overall survival (OS) and do not appear to benefit from first-line use of anti-EGFR therapy as patients do with left-sided tumors (distal transverse to sigmoid colon and rectum) [4-5]. Similar results were seen in other studies including a meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405 and the PEAK study [6-9].

Hence, tumor location (right vs. left) has emerged as an important prognostic and predictive factor in the treatment of mCRC, and shortly thereafter guidelines were updated to highlight the prognostic and predictive role of primary tumor location and to suggest that the site of tumor origin should be taken into account when selecting biological therapy in patients with RAS wild-type tumors [10,11].

In the context of the above-mentioned sidedness analyses, patients with metastatic left-sided colon tumors (distal transverse to sigmoid colon) and rectal cancers have been grouped together as one entity.

However, clinical differences have been observed between patients with left-sided colon tumors and rectal cancers [12]. Additionally, we have recently examined the molecular differences between left-sided colon tumors and rectal cancers [13]. We showed that rectal cancers exhibited a higher rate of TOPO1 and ERCC1 expression, as well as HER2/neu amplification compared to left-sided colon cancers. Moreover, left-sided colon cancers had higher rates of microsatellite instability, more frequent aberrant activation of the EGFR pathway including higher BRAF and PIK3CA mutation rates, and increased mutational burden compared to rectal cancers [14]. Similar findings were reported by Loree et al. [15].

It remains uncertain whether these molecular differences result in different biological behavior and whether rectal primary cancers respond differently to biologics (bevacizumab and cetuximab) as well as backbone chemotherapy compared to left-sided colon tumors. It is also remains unclear whether the site of tumor origin on the left side (left-sided colon tumors versus rectal tumors) should be considered when selecting treatment regimens and stratifying patients for future clinical trials.

Herein, we analyzed the Aide et Recherche en Cancérologie Digestive (ARCAD) Foundation database to determine whether metastatic rectal tumors are clinically different from left-sided colon tumors and whether primary rectal cancers respond differently to biologics as well as backbone chemotherapy compared to primary left-sided colon tumors.

Patients and Methods

Database

The ARCAD Foundation database contains patient-level data on over 33,000 patients enrolled on 39 clinical trials of mCRC from 1997 to the present day [16]. ARCAD is designed to pool

large quantities of data across many similar trials to standardize endpoints in CRC clinical trials and inform research on biomarkers and clinical trials design [16,17]. In our analysis, first-line trials in mCRC were included if there was data on primary tumor sidedness and location (six trials fulfilled these criteria). Thus, left-sided colon tumors were defined as arising from the splenic flexure to the sigmoid colon, and rectal cancers were those tumors that arose from the rectum only.

Recto-sigmoid junction tumors were excluded from the present analyses. Similarly, transverse colon tumors were also excluded [4]. Additionally, patients with both left-sided colon tumors and rectal cancers or with right-sided colon cancer were excluded.

Statistical Methods

Patient and tumor characteristics were described and compared between left-sided colon tumors and rectal cancers. Chi-square tests were used to compare categorical variables. Overall survival was defined as time from random assignment to death resulting from any cause. Progression-free survival was defined as time from random assignment to disease progression or death, whichever occurred first. The distributions of time-to-event outcomes were estimated using Kaplan-Meier methods and compared between left-sided colon and rectal tumors using a stratified log-rank test by treatment arm. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. Multivariate Cox proportional hazards models were used to assess associations, with adjustment for age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and prior surgical treatment. Subgroup analyses were further conducted by age group (< 60 years old, 60-69, 70 and older), treatment type by anti-VEGF inhibitors, anti-EGFR inhibitors and chemotherapy backbones (oxaliplatin-containing chemotherapy versus irinotecan-containing chemotherapy), metastatic sites (lung only metastases, liver only metastases, and both liver and lung metastases), BRAF and KRAS mutation status, and baseline CEA level.

In all analyses, the treatment arms nested within each trial were included as stratification factors in the Cox proportional hazards models in order to account for potential heterogeneity across trials and treatment arms. All analyses were conducted with two-sided tests and a significance level of 0.05.

Results

In total, 2,879 patients from six first-line trials, listed in **Table 1**, with available data on tumor location and sidedness were evaluated, with a median follow-up of 3.6 years. Accordingly, 1,374 patients were identified as having left-sided tumors and 1,505 patients were found to have rectal cancers. Descriptive demographic and disease data are summarized in **Table 2**. Compared to rectal cancers, patients with left-sided tumors were more likely to be female (40.1% vs. 32.6%; $P < 0.0001$) and more likely to have undergone prior surgery (73.1% vs. 66.4%; $P < 0.0001$). Median age (64 vs. 63 years) was similar in both groups; however, patients with left-sided tumors were more likely to be older (31.0% 70 years or older vs. 25.8%; $P = 0.0033$). Patients with left-sided tumors had higher rates of liver metastases (80.9% vs. 72.3%; $P < 0.0001$) but lower rates of lung metastases (34.2% vs. 53.8%; $P < 0.0001$) compared to patients with rectal cancers. KRAS mutations were slightly less frequent in left-sided tumors than rectal cancers (34.8 vs. 40.5%; $P = 0.0103$); however, the frequency of BRAF mutations was similarly low in both groups (5.3% vs. 3.8%; $P = 0.1239$). No significant differences were seen in PS or number of metastatic sites.

Prognostic Effect of Primary Tumor Site on Patient Outcomes

The site of the primary tumor within the left side (left-sided colon or rectum) was not prognostic of PFS or OS. Median PFS was approximately the same in patients with left-sided colon tumors and rectal cancers (**Fig 1A**; 7.4 vs. 6.9 months; $P = 0.1449$). Median OS was also similar between the two groups (**Fig 1B**; 17.4 vs. 16.6 months; $P = 0.6781$). In a multivariate analysis controlling for other potentially confounding variables, there was no significant difference

between left-sided tumors and rectal cancers for PFS (HR 0.94, 95% CI 0.87-1.03; P = 0.1998) or OS (HR 0.99, 95% CI 0.91-1.07; P = 0.7597) as shown in **Table 3**.

Analyses by Age, Treatment Type, Metastatic Site, and molecular markers Groups

Figure 2 shows comparisons of PFS and OS in left-sided tumors versus rectal cancer patients by subpopulation defined by age, treatment type, chemotherapy backbone and biological therapy, metastatic site groups and KRAS and BRAF status.

There were no significant differences between left-sided tumors and rectal cancers with regard to PFS or OS by age groups (**Fig 2**). Additionally, multivariate models by age group did not demonstrate a difference in primary site for PFS when controlling for other covariates (**Supplemental Table S1**). Among patients under 60 years of age, the adjusted HR of PFS was 0.90 (95% CI, 0.77-1.05; P = 0.1658) for left-sided colon tumors vs. rectum cancers, 0.98 (95% CI, 0.85-1.14; P = 0.8388) for patients age 60-69 years, and 0.95 (95% CI, 0.80-1.12; P = 0.5085) for patients age 70 years and older. Similarly, for OS, multivariate models by age group did not demonstrate a difference in primary site.

No significant differences were observed between left-sided tumors and rectal cancers when we examined the impact of primary tumor on response to biological therapy (anti-VEGF inhibitors and anti-EGFR inhibitors) or chemotherapy backbones (irinotecan-based vs. oxaliplatin-based therapy) as shown in **Fig 2**.

Among patients who received cetuximab, patients with left-sided tumors had similar PFS (median 8.3 vs. 7.8 months; HR 0.93, 95% CI 0.79-1.08; P = 0.3137) and OS (median 19.4 vs. 18.5 months; HR 0.99, 95% CI 0.86-1.14; P = 0.8505) compared to rectal cancer patients.

Similarly, patients with primary tumors originating in the left-side colon who were treated with bevacizumab had a similar outcome to patients with primary tumors originating from the rectum, both for PFS (median PFS 8.6 vs. 8.7 months; HR 0.87, 95% CI 0.64-1.19; P = 0.3972) and for OS (median OS 19.2 vs. 21.8 months; HR 1.01, 95% CI 0.71-1.43; P = 0.9696).

Moreover, the anatomic location of the primary tumor did not appear to have an impact on PFS or OS when stratified by the type of chemotherapy backbone (**Fig 2**), whereby the findings on the comparisons between left-sided colon tumors and rectal cancers were consistent among patients treated with oxaliplatin- and irinotecan-based therapy. In patients treated with oxaliplatin-based therapy, patients with left-sided tumors had similar PFS (median 6.4 vs. 6.3 months; HR 1.05, 95% CI 0.93-1.18; P = 0.4513) and OS (median 15.0 vs. 16.4 months; HR 1.10, 95% CI 0.97-1.24; P = 0.1365) compared to rectal cancer patients. Likewise, among patients treated with irinotecan-based therapy, patients with left-sided tumors had similar PFS (median 8.4 vs. 8.8 months; HR 0.97, 95% CI 0.79-1.19; P = 0.7672) and OS (median 20.5 vs. 18.5 months; HR 0.92, 95% CI 0.79-1.08; P = 0.3305) compared to rectal cancer patients.

We further compared PFS and OS in the two groups according to the pattern of metastasis. Overall, there were no significant differences in PFS or OS between left-sided tumors and rectal cancers when we analyzed outcomes according to the metastatic location (**Fig 2).**

Finally, we examined the association between outcomes and baseline CEA level, KRAS and BRAF mutation status. Progression-free survival and OS were similar between left-sided tumors and rectal cancers regardless of the baseline CEA level or KRAS mutation status (**Fig 2)**.

A shorter OS was observed in patients with BRAF mutant left-sided colon tumors (median OS 9.1 vs. 14.7 months; HR 1.94, 95% CI, 1.11-3.37; P = 0.0178) compared to patients with BRAF mutant rectal tumors. However, no significant difference was seen in PFS (HR 1.84, 95% CI, 0.99-3.41; P = 0.0505). It is important to note that only 83 patients with BRAF mutant tumors were identified and included in this subgroup analysis.

Discussion

In the last two decades, major advances in the treatment of patients with mCRC have led to significant improvement in outcomes and prolonged OS. This progress can be attributed to several factors including increased access to novel, more diverse and selective therapies, and a

better understanding of the disease biology, which in turn has enabled us to better select patients, inform therapeutic choices, and individualize therapy.

The differences in outcome between patients with left-sided and right-sided colon cancer are likely the result of underlying differences in molecular and tumor biology, which is an area of active, vigorous research [19-21]. However, the prognostic and predictive effects of primary tumors within the left side have not been comprehensively studied.

In the current study, we examined the clinical and pathological characteristics, as well as the survival outcomes among patients with left-sided colon cancers vs. rectal cancers. The major objective of our study was to determine whether metastatic rectal tumors are clinically different and if rectal primary cancers respond differently to backbone chemotherapy from left-sided colon tumors.

In the present pooled analysis of individual patient data from six large mCRC trials, we showed that PFS and OS are remarkably similar between patients with left-sided colon tumors and rectal cancers, regardless of the biological agent or backbone chemotherapy administered.

In previous years, some studies examined the relationship between ERCC1 and TOPO1 expression and response to oxaliplatin and irinotecan. It was shown that high TOPO1 levels are associated with survival benefit on administration of first-line irinotecan-containing chemotherapy [22], and patients with a low expression level of ERCC1 have longer PFS and OS than patients with overexpression of ERCC1 when treated with oxaliplatin based regimens [23].

As rectal cancers exhibit higher expression of TOPO1 and ERCC1 than left-sided colon tumors, one can hypothesize that left-sided colon cancers benefit more from platinum-based chemotherapy (e.g., oxaliplatin), whereas rectal cancers benefit more from topoisomerase inhibitors (e.g., irinotecan). However, our data suggest that neither oxaliplatin nor irinotecan impact patient survival differently according to patient CRC tumor location, and PFS and OS

were similar between patients with left-sided colon tumors and rectal cancers, regardless of the backbone chemotherapy. Similar findings were seen with regard to biological therapy.

Despite similar outcomes, there are clinical differences between patients with left-sided colon tumors and rectal cancers. For instance, patients with rectal cancers were more likely to be younger and have a higher tendency to metastasize to the lungs while patients with left-sided colon tumors metastasized more often to the liver. This is likely a reflection of venous drainage, confirming results from other analyses [24-27]. Our results also demonstrate the increased risk of death for patients with liver only metastases compared to lung only metastases, raising the question of whether to use more intensive treatment for patients diagnosed with CRC and liver metastases.

Comparing patients with left-sided tumors and rectal cancers by metastatic site, there were trends toward improved OS in patients with lung but no liver metastases, followed by patients with liver but no lung metastases, and then patients with both lung and liver metastases (**Supplemental Figure S1**). Compared to patients with both lung and liver metastases (median 15.1 months), patients with lung metastases but no liver metastases (21.7 months; HR 0.75, 95% CI 0.64-0.88) and patients with liver metastases but no lung metastases (16.7 months; HR 0.85, 95% CI 0.76-0.95), had significantly longer OS (P = .0006; **Supplemental Table S2**). However, there were no significant interactions between primary site and site of metastatic disease in multivariate models of PFS (P = 0.4240) and OS (P = 0.3824).

Although CRC is predominantly a disease of older patients (the median age is 72 years), the incidence of CRC in younger patients is rising [28]. This increase is largely due to tumors arising from the distal colon and rectum. The impact of age on the clinicopathological features and outcomes among younger patients with left-sided colon tumors and rectal cancers is unknown.

Our analysis showed no significant differences between left-sided colon tumors and rectal cancers with regard to PFS or OS by age group. Of note, among patients with BRAF mutant

tumors, we observed a longer OS in patients with rectal cancers compared to patients with left-sided colon tumors. Although only 83 BRAF mutant patients were included in this subgroup analysis, this finding may still suggest a different biology according to tumor side, even among patients with the same mutations. Larger analyses are warranted to validate these results.

We acknowledge that there are several limitations to our study. Because only clinical trial patients were included, our study population was generally younger (71.7% were under the age of 70) and healthier (91.3% with ECOG PS 0-1) than the broader mCRC patient population of the past. Other limitations include the retrospective nature of the analysis and the differences between the clinical trials that were included. Moreover, later-line patient therapy details (post-disease progression) were not defined in our retrospective analysis. Irinotecan was used in only one of the trials included in our analysis (CRYSTAL). Additionally, data on multiple molecular markers such as RAS, HER2, and MSI-H were not available for the present analysis. Finally, data on synchronous mCRC and resection status of the primary tumors were also not obtainable.

Conclusion

Our study suggests that survival of patients with left-sided colon tumors and rectal cancers in past first-line mCRC clinical trials was similar. Thus, neither oxaliplatin- nor irinotecan-based therapy impacted PFS or OS of patients with left-sided colon tumors compared to rectal tumors, even following the inclusion of biological agents in the treatment regimens. Despite the clinical differences between left-sided colon tumors and rectal cancers, our results suggest that these diseases could share the same therapeutic strategy and grouping in clinical trials.

Nonetheless, further investigations into the biology, etiology, and optimal treatment of left-sided colon tumors and rectal cancers are still appropriate. Furthermore, an optimal biomarker to guide chemotherapy as well as targeted therapy selection in metastatic left-sided colon and

rectal cancers is yet to be determined, especially in the up-and-coming fields of precision medicine and immunotherapy.

Author Contributions

Conception and design: MES, JY, LRR

Financial support: ARCAD

Administrative support: AdG, DJS

Provision of study materials or patients: TSM, RAA, EVC, AF, NCT, MTS, EDR, EA, CB, AdG, AG, DJS

Collection and assembly of data: MES, JY, PDL, BAW, LRR

Data analysis and interpretation: MES, JY, PDL, BAW, LRR, QS

Manuscript writing: All authors

Final approval of manuscript: All authors

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FIGURE LEGENDS

Figure 1. Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) for patients with left-sided colon and rectal cancers. Kaplan-Meier curves are shown for PFS of all patients (A) and OS of all patients (B). CI, confidence interval; HR, hazard ratio.

Figure 2. Forest plot of progression-free survival (PFS) and overall survival (OS) for patients with left-sided colon vs rectal cancers by different subgroups. Forest plots are shown for PFS and OS of patients by treatment type, age, liver involvement and lung involvement, and biomarker status (BRAF, KRAS, and CEA). CI, confidence interval; HR, hazard ratio.

TABLES

Table 1. ARCAD Trials Included

Trial	Years of Accrual	Frontline Treatment Arms	Number of Patients
AGITG (MAX)	2005-2007	Cap	86
		Cap + Bev	93
		Cap + Bev+ Mitomycin	96
COIN	2005-2008	5-FU + LV + Ox	133
		Cap + Ox	257
		5-FU + LV + Cetuximab	128
		Cap +Ox + Cetuximab	268
		5-FU + LV(intermittent) + Ox	131
		Cap + Ox (intermittent)	266
FOCUS2	2004-2006	5-FU + LV	67
		5-FU + LV + Ox	72
		Cap	76
		Cap + Ox	68
OPUS	2005-2006	5-FU + LV + Ox + Cetuximab	124
		5-FU/FA+oxaliplatin	118
CRYSTAL	2004-2005	5-FU + LV + Irinotecan + Cetuximab	383
		5-FU + LV + Irinotecan	381
COIN-B	2007-2010	Intermittent FOLFOX + intermittent Cetuximab	67
		Intermittent FOLFOX + continuous Cetuximab	65
Total			2879

Abbreviations: 5-FU, 5-fluorouracil; AGITG, Australasian Gastrointestinal Trials Group; ARCAD, Aide et Recherche en Cancérologie Digestive; Cap, capecitabine; COIN, Combination Chemotherapy With or Without Cetuximab As First-Line Therapy in Treating Patients with Metastatic Colorectal Cancer; CRYSTAL, Cetuximab Combined With Irinotecan as First-Line Therapy for Metastatic Colorectal Cancer; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; IRI, irinotecan; LV, leucovorin; OPUS, Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer; Ox, oxaliplatin.

Table 2. Patient Baseline Characteristics

	Left Colon (N=1374)	Rectum (N=1505)	Total (N=2879)	P-value
Age Category, n (%)				0.0033[1]
<60	492 (35.8%)	544 (36.1%)	1036 (36.0%)	
60-69	456 (33.2%)	572 (38.0%)	1028 (35.7%)	
70+	426 (31.0%)	389 (25.8%)	815 (28.3%)	
Gender, n (%)				<.0001[1]
Female	551 (40.1%)	491 (32.6%)	1042 (36.2%)	
Male	823 (59.9%)	1014 (67.4%)	1837 (63.8%)	
Performance Score, n (%)				0.8707[1]
Missing	38	26	64	
0	630 (47.2%)	706 (47.7%)	1336 (47.5%)	
1	586 (43.9%)	648 (43.8%)	1234 (43.8%)	
2+	120 (9.0%)	125 (8.5%)	245 (8.7%)	
BRAF, n (%)				0.1239[1]
Missing	538	475	1013	
MT	44 (5.3%)	39 (3.8%)	83 (4.4%)	
WT	792 (94.7%)	991 (96.2%)	1783 (95.6%)	
KRAS, n (%)				0.0103[1]
Missing	498	433	931	
MT	305 (34.8%)	434 (40.5%)	739 (37.9%)	
WT	571 (65.2%)	638 (59.5%)	1209 (62.1%)	
CEA, n (%)				0.2003[1]
Missing	817	784	1601	
Normal (≤ 10 ng/mL)	97 (17.4%)	146 (20.2%)	243 (19.0%)	
Elevated (>10 ng/mL)	460 (82.6%)	575 (79.8%)	1035 (81.0%)	
Received Any Prior Surgery, n (%)				<.0001[1]
No	369 (26.9%)	505 (33.6%)	874 (30.4%)	
Yes	1005 (73.1%)	1000 (66.4%)	2005 (69.6%)	
Number of Metastatic Sites, n (%)				0.1258[1]
Missing	426	342	768	
0-1	359 (37.9%)	403 (34.7%)	762 (36.1%)	
2+	589 (62.1%)	760 (65.3%)	1349 (63.9%)	
Liver Involvement, n (%)				<.0001[1]
Missing	426	341	767	
No	181 (19.1%)	322 (27.7%)	503 (23.8%)	
Yes	767 (80.9%)	842 (72.3%)	1609 (76.2%)	
Lung Involvement, n (%)				<.0001[1]
Missing	426	341	767	
No	624 (65.8%)	538 (46.2%)	1162 (55.0%)	
Yes	324 (34.2%)	626 (53.8%)	950 (45.0%)	
Liver/Lung Involvement, n (%)				<.0001[1]
Missing	528	439	967	
Lung Involved, Liver not Involved	79 (9.3%)	224 (21.0%)	303 (15.8%)	
Liver Involved, Lung not Involved	522 (61.7%)	440 (41.3%)	962 (50.3%)	
Liver and Lung Involved	245 (29.0%)	402 (37.7%)	647 (33.8%)	
Includes Biologic Agent, n (%)				0.1549[1]
No	771 (56.1%)	884 (58.7%)	1655 (57.5%)	
Yes	603 (43.9%)	621 (41.3%)	1224 (42.5%)	
Treatment Type, n (%)				<.0001[1]
Missing	397	413	810	
OX-based chemo + biologics	228 (23.3%)	296 (27.1%)	524 (25.3%)	
IRI-based chemo + biologics	214 (21.9%)	169 (15.5%)	383 (18.5%)	
OX-based chemo	325 (33.3%)	456 (41.8%)	781 (37.7%)	
IRI-based chemo	210 (21.5%)	171 (15.7%)	381 (18.4%)	

[1]Chi-Square p-value;

Abbreviations: IQR, interquartile range; IRI, irinotecan; MT, mutant; OX, oxaliplatin; SD, standard deviation; WT, wild-type

Table 3. Multivariate Models for PFS and OS

	Progression-Free Survival			Overall Survival		
	Events/Total	Hazard Ratio (95% CI)	P-value	Events/Total	Hazard Ratio (95% CI)	P-value
Multivariate Model	2238/2768			2326/2810		
Primary Site			0.1998[1]			0.7597[1]
Left Colon	1016/1309	0.94 (0.87-1.03)		1098/1333	0.99 (0.91-1.07)	
Rectum	1222/1459	Reference		1228/1477	Reference	
Age at enrollment			0.5607[1]			0.3964[1]
10 Units Increase		0.99 (0.94-1.03)			1.02 (0.98-1.06)	
Performance Score			<.0001[1]			<.0001[1]
0	1029/1327	Reference		1026/1334	Reference	
1	998/1214	1.27 (1.16-1.40)		1077/1233	1.54 (1.41-1.69)	
2+	211/227	1.64 (1.40-1.92)		223/243	2.14 (1.83-2.50)	
Gender			0.0554[1]			0.2285[1]
Female	790/1000	1.09 (1.00-1.19)		841/1017	1.06 (0.97-1.15)	
Male	1448/1768	Reference		1485/1793	Reference	
Prior Surgery			<.0001[1]			<.0001[1]
No	731/800	1.23 (1.12-1.36)		737/811	1.55 (1.41-1.71)	
Yes	1507/1968	Reference		1589/1999	Reference	

[1]Stratified type 3 likelihood-ratio p-value

Abbreviations: CI, 95% confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Figure 1

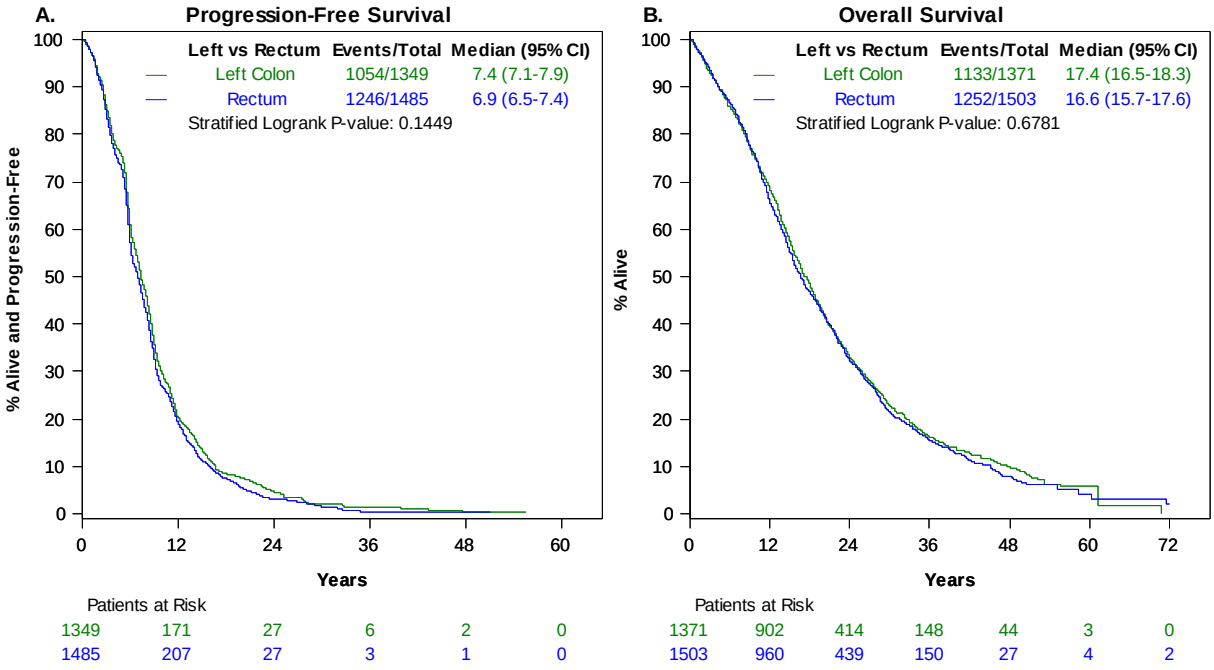
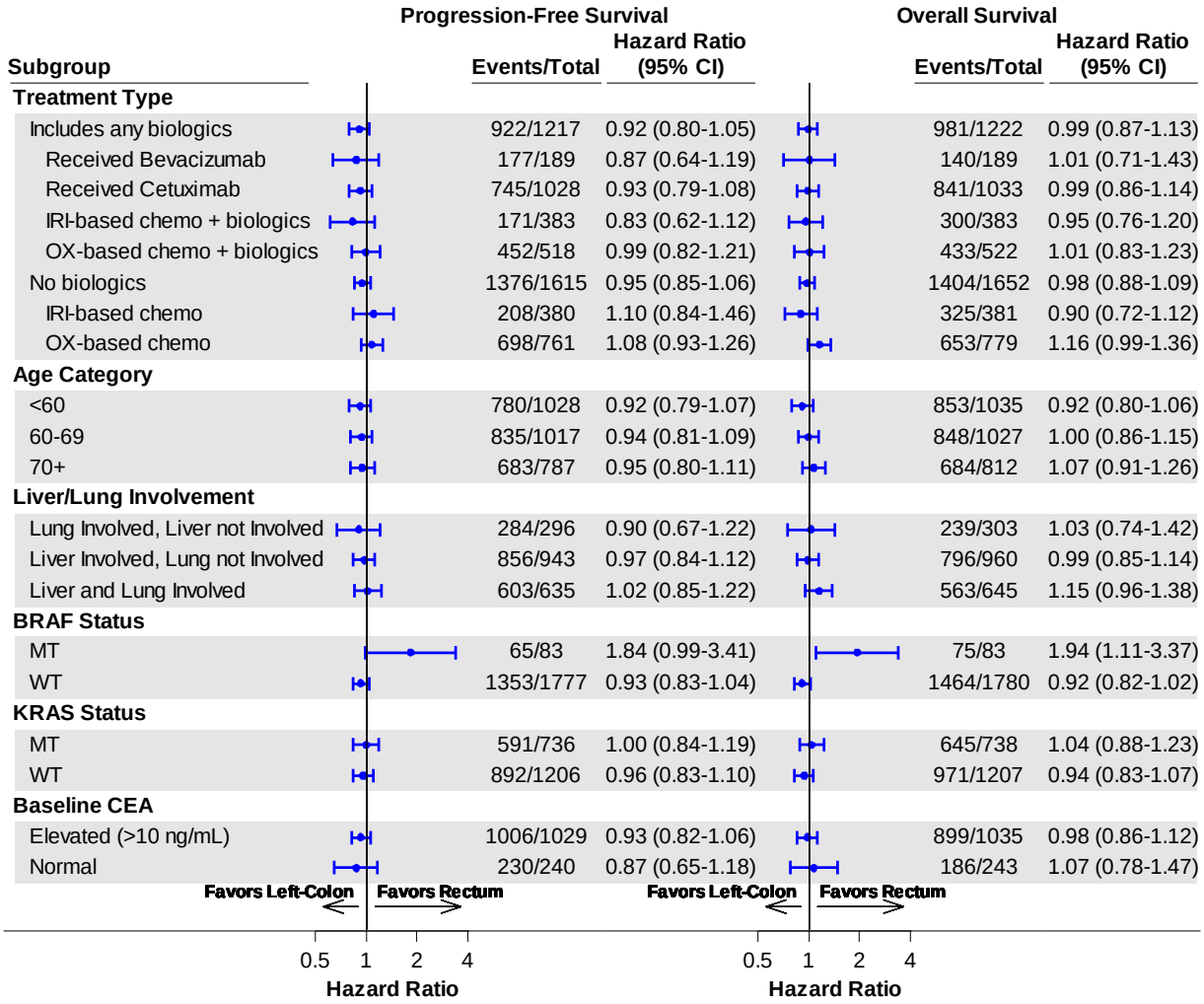

A.
Progression-Free Survival
Left vs Rectum Events/Total Median (95% CI)
Left Colon 1054/1349 7.4 (7.1-7.9)
Rectum 1246/1485 6.9 (6.5-7.4)
Stratified Logrank P-value: 0.1449
% Alive and Progression-Free
Years
Patients at Risk
1349 171 27 6 2 0
1485 207 27 3 1 0
B.
Overall Survival
Left vs Rectum Events/Total Median (95% CI)
Left Colon 1133/1371 17.4 (16.5-18.3)
Rectum 1252/1503 16.6 (15.7-17.6)
Stratified Logrank P-value: 0.6781
% Alive
Years
Patients at Risk
1371 902 414 148 44 3 0
1503 960 439 150 27 4 2

Figure 2

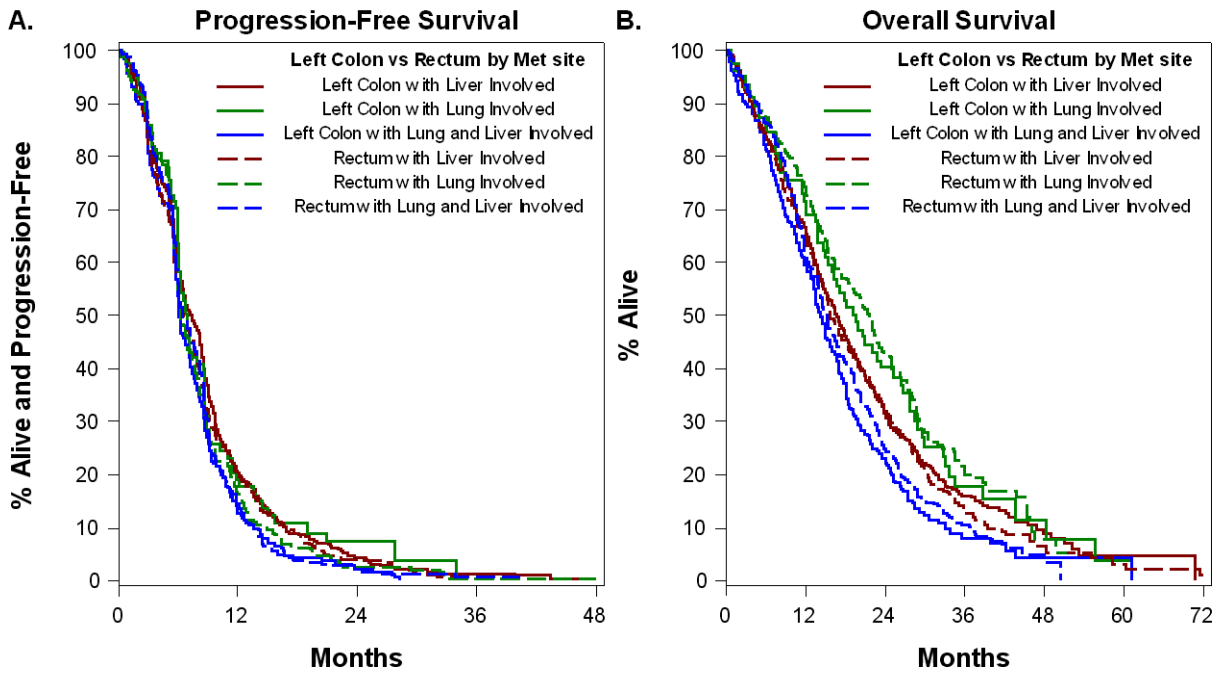

Progression-Free Survival
Overall Survival
Subgroup
Events/Total
Hazard Ratio (95% CI)
Events/Total
Hazard Ratio (95% CI)
Treatment Type
Includes any biologics 922/1217 0.92 (0.80-1.05) 981/1222 0.99 (0.87-1.13)
Received Bevacizumab 177/189 0.87 (0.64-1.19) 140/189 1.01 (0.71-1.43)
Received Cetuximab 745/1028 0.93 (0.79-1.08) 841/1033 0.99 (0.86-1.14)
IRI-based chemo + biologics 171/383 0.83 (0.62-1.12) 300/383 0.95 (0.76-1.20)
OX-based chemo + biologics 452/518 0.99 (0.82-1.21) 433/522 1.01 (0.83-1.23)
No biologics 1376/1615 0.95 (0.85-1.06) 1404/1652 0.98 (0.88-1.09)
IRI-based chemo 208/380 1.10 (0.84-1.46) 325/381 0.90 (0.72-1.12)
OX-based chemo 698/761 1.08 (0.93-1.26) 653/779 1.16 (0.99-1.36)
Age Category
<60 780/1028 0.92 (0.79-1.07) 853/1035 0.92 (0.80-1.06)
60-69 835/1017 0.94 (0.81-1.09) 848/1027 1.00 (0.86-1.15)
70+ 683/787 0.95 (0.80-1.11) 684/812 1.07 (0.91-1.26)
Liver/Lung Involvement
Lung Involved, Liver not Involved 284/296 0.90 (0.67-1.22) 239/303 1.03 (0.74-1.42)
Liver Involved, Lung not Involved 856/943 0.97 (0.84-1.12) 796/960 0.99 (0.85-1.14)
Liver and Lung Involved 603/635 1.02 (0.85-1.22) 563/645 1.15 (0.96-1.38)
BRAF Status
MT 65/83 1.84 (0.99-3.41) 75/83 1.94 (1.11-3.37)
WT 1353/1777 0.93 (0.83-1.04) 1464/1780 0.92 (0.82-1.02)
KRAS Status
MT 591/736 1.00 (0.84-1.19) 645/738 1.04 (0.88-1.23)
WT 892/1206 0.96 (0.83-1.10) 971/1207 0.94 (0.83-1.07)
Baseline CEA
Elevated (>10 ng/mL) 1006/1029 0.93 (0.82-1.06) 899/1035 0.98 (0.86-1.12)
Normal 230/240 0.87 (0.65-1.18) 186/243 1.07 (0.78-1.47)
Favors Left-Colon
Favors Rectum
0.5
1
2
4
Hazard Ratio
Favors Left-Colon
Favors Rectum
0.5
1
2
4
Hazard Ratio

Supplementary

Supplemental Table S1. Multivariate Models for Progression-Free and Overall Survival By Patient Age Group Using Covariates for Primary Site, Age, Performance Status, Sex, and Prior Surgery.

		Progression-Free Survival			Overall Survival		
Age Category		**Events/Total**	**Hazard Ratio (95% CI)**	**P-value**	**Events/Total**	**Hazard Ratio (95% CI)**	**P-value**
<60	**Multivariate Model**	765/1011			839/1018		
	Primary Site			0.1658[1]			0.1036[1]
	Left Colon	341/477	0.90 (0.77-1.05)		386/481	0.89 (0.77-1.03)	
	Rectum	424/534	Reference		453/537	Reference	
	Performance Score			<.0001[1]			<.0001[1]
	0	394/535	Reference		407/537	Reference	
	1	309/409	1.39 (1.19-1.62)		369/412	1.81 (1.56-2.10)	
	2+	62/67	1.67 (1.24-2.24)		63/69	1.90 (1.41-2.57)	
	Gender			0.2164[1]			0.7814[1]
	Female	310/428	1.10 (0.95-1.28)		350/430	1.02 (0.89-1.18)	
	Male	455/583	Reference		489/588	Reference	
	Prior Surgery			0.0585[1]			<.0001[1]
	No	277/313	1.17 (1.00-1.38)		286/318	1.48 (1.26-1.73)	
	Yes	488/698	Reference		553/700	Reference	
60-69	**Multivariate Model**	808/989			821/999		
	Primary Site			0.8388[1]			0.3593[1]
	Left Colon	342/436	0.98 (0.85-1.14)		362/440	1.07 (0.93-1.24)	
	Rectum	466/553	Reference		459/559	Reference	
	Performance Score			0.0001[1]			<.0001[1]
	0	379/483	Reference		372/483	Reference	
	1	362/434	1.29 (1.10-1.50)		376/438	1.59 (1.37-1.85)	
	2+	67/72	1.67 (1.25-2.22)		73/78	2.33 (1.76-3.08)	
	Gender			0.0375[1]			0.2055[1]
	Female	261/314	1.18 (1.01-1.38)		265/318	1.11 (0.95-1.29)	
	Male	547/675	Reference		556/681	Reference	
	Prior Surgery			0.0013[1]			<.0001[1]
	No	300/321	1.30 (1.11-1.52)		294/323	1.62 (1.39-1.90)	
	Yes	508/668	Reference		527/676	Reference	
70+	**Multivariate Model**	665/768			666/793		
	Primary Site			0.5085[1]			0.7895[1]
	Left Colon	333/396	0.95 (0.80-1.12)		350/412	1.02 (0.87-1.21)	
	Rectum	332/372	Reference		316/381	Reference	
	Performance Score			0.0038[1]			<.0001[1]
	0	256/309	Reference		247/314	Reference	
	1	327/371	1.21 (1.01-1.44)		332/383	1.26 (1.05-1.50)	
	2+	82/88	1.59 (1.21-2.09)		87/96	1.92 (1.46-2.53)	
	Gender			0.9629[1]			0.3948[1]
	Female	219/258	1.00 (0.85-1.19)		226/269	1.08 (0.91-1.28)	
	Male	446/510	Reference		440/524	Reference	
	Prior Surgery			0.0617[1]			<.0001[1]
	No	154/166	1.22 (0.99-1.51)		157/170	1.58 (1.29-1.94)	
	Yes	511/602	Reference		509/623	Reference	

[1]Stratified type 3 likelihood-ratio p-value
Abbreviation: CI, confidence interval.



Supplemental Figure S1. Kaplan-Meier curves of progression-free survival and overall survival for patients with left-sided colon and rectal cancers by site of metastatic disease (lung, liver, or both). Met, metastatic.

Supplemental Table S2. Multivariate Models for Progression-Free and Overall Survival Using Covariates for Primary Site, Metastatic Site(s), Age, Performance Status, Sex, and Prior Surgery.

	Progression-Free Survival			Overall Survival		
	Events/Total	Hazard Ratio (95% CI)	P-value	Events/Total	Hazard Ratio (95% CI)	P-value
Multivariate Model	1692/1820			1548/1854		
Primary Site			0.6129[1]			0.6156[1]
Left Colon	725/795	0.97 (0.88-1.08)		671/813	1.03 (0.92-1.14)	
Rectum	967/1025	Reference		877/1041	Reference	
Liver/Lung Involvement			0.0086[1]			0.0006[1]
Lung Involved, Liver not Involved	274/286	0.93 (0.80-1.08)		229/293	0.75 (0.64-0.88)	
Liver Involved, Lung not Involved	828/912	0.84 (0.75-0.94)		769/929	0.85 (0.76-0.95)	
Liver and Lung Involved	590/622	Reference		550/632	Reference	
Age at enrollment			0.5960[1]			0.6138[1]
10 Units Increase		0.99 (0.93-1.04)			1.01 (0.96-1.07)	
Performance Score			<.0001[1]			<.0001[1]
0	772/836	Reference		649/841	Reference	
1	748/804	1.22 (1.10-1.36)		720/819	1.48 (1.32-1.65)	
2+	172/180	1.53 (1.28-1.82)		179/194	2.05 (1.72-2.46)	
Gender			0.1458[1]			0.2342[1]
Female	574/628	1.08 (0.97-1.20)		539/641	1.07 (0.96-1.19)	
Male	1118/1192	Reference		1009/1213	Reference	
Prior Surgery			0.0004[1]			<.0001[1]
No	609/627	1.23 (1.10-1.37)		582/635	1.60 (1.43-1.80)	
Yes	1083/1193	Reference		966/1219	Reference	

[1]Stratified type 3 likelihood-ratio p-value

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival