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Prognosis of colorectal peritoneal metastases:

An analysis of 10,553 patients treated

with systemic therapy in prospective randomized trials (ARCAD database)

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ABSTRACT

BACKGROUND: Patients with peritoneal metastases from colorectal cancer (pmCRC) have reduced overall survival (OS) compared to mCRC patients without peritoneal involvement. Here we further investigated the impact of number and location of metastases among patients receiving first-line systemic chemotherapy.

METHODS: Individual patient data were available on 10,553 patients enrolled onto 14 first-line randomized trials. Stratified multivariable Cox models were used.

FINDINGS: There were 9,178 (87%) patients with non-peritoneal mCRC (4,385 with one disease site, 4,793 with ≥2 disease sites), 194 (2%) patients with isolated pmCRC, and 1,181 (11%) with pmCRC and other organ involvement. These groups were similar in age, race, and use of targeted therapy. Patients with pmCRC compared to those with non-pmCRC were more likely to be female (41% vs. 36%, p<0.001), have colon primary tumors (84% vs. 66%, p<0.0001), and have performance status 2 (10% vs. 6%, p<0.0001). Higher proportion of mutated *BRAF* was seen among patients with peritoneal-only (8/44 cases with available data, 18.2%) and pmCRC with other disease sites (34/289, 11.8%), compared to patients with non-peritoneal mCRC (194/2230, 8.7%; p=0.028).

Compared to patients with isolated pmCRC, patients with isolated non-peritoneal sites had significantly better overall survival (HR_{adj}=0.75; CI, 0.63-0.91, p=0.003) while patients with ≥2 non-peritoneal sites fared similarly (HR_{adj}=1.04; CI 0.86-1.25, p=0.69). Patients with pmCRC and one other disease site survived similarly to those with isolated pmCRC (HR_{adj}=1.10; CI 0.89-1.37, p=0.37), but those with pmCRC and ≥2 additional disease sites had the shortest survival (HR_{adj}=1.40; CI 1.14-1.71, p=0.0011).

INTERPRETATION: pmCRC patients have significantly worse survival than those with other isolated organ/site mCRC. Among patients with multiple metastatic organs/sites, poorer survival

is a function of both increased number of metastatic sites and peritoneal involvement. The pattern of metastasis and in particular, peritoneal involvement, results in prognostic heterogeneity of mCRC.

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RESEARCH IN CONTEXT

Evidence before this study

Presence of peritoneal metastases/carcinomatosis from colorectal cancer (CRC) is associated worsened overall survival. It has been unclear whether worsened survival is due to the increased number of metastatic sites typically observed with peritoneal metastases or inherent feature of peritoneal involvement. Mutated *BRAF* is more common among patients with peritoneal metastases, but it has been unknown whether $BRAF^{mut}$ drives worsened prognosis seen among patients with peritoneal metastases.

Added value of this study

Peritoneal metastases from CRC are associated with significantly worse prognosis, whether found as the only disease site, or in combination with other disease sites. Prognosis of patients with peritoneum-only involvement is significantly worse as compared to those with liver-only or lung-only metastases. Prognosis in mCRC is influenced both by number of disease sites and presence of peritoneal involvement. These findings are largely stable even when analysis is limited to BRAF wild-type mCRC cases.

Implications of all the available evidence

Diligent clinical investigation and recording of peritoneal involvement is necessary to accurately prognosticate patients with mCRC. Stratification of mCRC patients according to number or organs involved and presence of peritoneal metastases should be considered in future studies. Further molecular characterization of mCRC and it metastatic patterns is necessary.

INTRODUCTION

Peritoneal carcinomatosis represents malignant metastatic spread along the surface of specialized coelomic epithelium of the peritoneal cavity. Progression of peritoneal disease burden commonly results in intestinal stenoses and dysmotility, thus producing inter-related symptoms of early satiety, diet intolerance, bloating, nausea and emesis. Culmination of this 'carcinomatosis syndrome' is characterized by cachexia, loss of performance, and death.

Keen interest remains associated with prognosis and management of colorectal peritoneal carcinomatosis, herein further referred to as *peritoneal metastases* (pmCRC). We and others have previously shown that pmCRC is associated with considerably shortened overall survival by 30-40% [1-3], although some retrospective studies have not identified worsened prognosis [45]. Increased number of metastatic sites is a recognized negative prognostic factor in mCRC [6,7]. Peritoneal metastases are associated with increased number of metastatic sites in mCRC patients.[1] Therefore, it is unclear whether worsened prognosis of pmCRC patients is due to its association with more widespread metastases or an inherent feature of pmCRC. Additionally, relative prognosis of patients with peritoneal-only involvement as compared to other isolated disease sites (e.g. liver-only) has been understudied.[4]

We utilized the ARCAD Foundation (Aide et Recherche en Canérologie Digestive) database of pooled individual patient data from randomized studies of advanced colorectal cancer [8] to investigate effect of peritoneal metastases on outcomes among mCRC patients treated on first-line systemic chemotherapy trials. Our main objective was to compare overall survival and clinical characteristics of such patients with isolated pmCRC, non-isolated pmCRC and mCRC patients without peritoneal involvement.

METHODS

We included individual patient data from first-line prospective controlled randomized phase III trials treating patients with metastatic colorectal cancer. The ARCAD colorectal cancer database integrates individual patient-level data from a large collection of clinical trials for the purpose of endpoint evaluation and development, as well as variety of prognostic studies. We considered only trials which protocols explicitly pre-specified and solicited for peritoneal involvement in the trial data collection process or a formal peritoneum-focused review of individual pre-treatment scans was performed (CAIRO studies). Patients were excluded if disease sites were unknown. The presence of ascites was not considered as evidence of peritoneal involvement for the purpose of this analysis. For the purpose of this study we defined disease site as anatomic organ or space, i.e. liver, lung, distant lymph nodes, peritoneum, and others. We do not use this term to describe number of different metastatic foci in any disease site. Therefore, a patient with one disease site may have had one or more metastases in that site.

The primary outcome was overall survival (OS) defined as time from randomization to death due to any cause. Progression-free survival (PFS), defined as time from randomization to first documented progression or death due to any cause, whichever occurred first, was also analyzed. The log-rank test, stratified by treatment-arm within trial, was used to compare OS and PFS among patients groups defined by presence of pmCRC and other metastatic sites. The distributions of survival outcomes were estimated by Kaplan-Meier curves. Stratified multivariable Cox models were used to assess the prognostic associations of pmCRC with OS and PFS, adjusting for other key clinical-pathological factors (age, gender, WHO performance score, primary tumor location [colon vs. rectum], prior treatment, and baseline body-mass index [BMI]). *KRAS* status was used to further stratify patients who received anti-EGFR therapy (i.e., cetuximab). Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and R

version 2.11 (http://www.r-project.org). Two-sided p-values of less than 0.05 were considered to be significant and were not adjusted for multiple comparisons.

Role of the funding source

ARCAD Foundation provided database and is credited with its conception, development, data collection from individual trials and database maintenance. Study concept, design, data analysis and interpretation, and manuscript writing was the responsibility of the lead authors (JF, QS, AG, DJS). Manuscript revisions and the decision to submit for publication was the responsibility of all authors.

RESULTS

Fourteen first-line randomized trials (5 of which tested targeted regimens, Table 1) in the ARCAD database solicited data collection of peritoneal metastasis and provided individual patient data for total of 10,635 patients. Metastatic sites data were available on 10,553 patients and 82 patients with absent disease site data were excluded. Non-targeted cytotoxic agents only were used in 8,185 (77.6%) patients, and 1,568 (14.9%) and 1,037 (9.8%) received anti-angiogenic and anti-EGFR agents, respectively (237 of these patients received both anti-angiogenic and anti-EGFR targeted therapy). Overall, 63% of the patients were male, the median age was 64 years, 94% of the patients had ECOG performance status of 0-1, and 68% presented with a colon primary tumor; Table 2.

There were 9,178 (87%) patients with non-peritoneal mCRC (4,385 with one disease site; 4,793 with ≥2 disease sites), and 1,375 patients with peritoneal metastases (194 patients with isolated pmCRC; and 1,181 with pmCRC plus another disease site(s)). Table 2 shows the distribution of demographic and clinical factors by subgroups defined per pmCRC status. These groups were similar in age, race, and use of biologics. Compared to non-peritoneal mCRC, patients with pmCRC were more likely to be female (41% vs. 36%, $p<0.001$), had colon primary tumors (84%

vs. 66%, p<0.0001), and an ECOG performance status 2 (10% vs. 6%, p<0.0001). Among patients with multiple metastatic sites, patients with pmCRC were less likely to have liver (74% vs. 84%, p = <0.0001) or lung (31% vs. 62%, p < 0.0001) metastases than patients with non-peritoneal mCRC.

Analysis of patients with isolated disease site

We initially analyzed patients with isolated/one disease site only – i.e. peritoneal-only, liver-only, and lung-only metastases (Figure 1 and Table 3). Patients with non-peritoneal metastases to a single disease site exhibited better survival compared to those with peritoneal-only involvement (liver-only metastases HR_{adj}=0.79, 95% CI 0.65-0.95, p=0.012; lung-only metastases HR_{adj}=0.61, 95% CI 0.49-0.76, p<0.001; lymph node as the only disease site HR_{adj}=0.73, 95% CI 0.58-0.92, p=0.008). These differences were greater in patients who received cytotoxic and targeted therapy combination: liver-only metastases (HR_{adj}=0.53, 95% CI 0.34-0.83, p=0.004), lung-only metastases (HR_{adj}=0.43, 95% CI 0.26-0.72, p=0.001) or lymph node as disease site (HR_{adj}=0.54, 95% CI 0.32-0.91, p=0.02) compared to disease limited to peritoneal metastases. Patients with isolated non-peritoneal sites had significantly better OS as compared to patients with isolated pmCRC (HR_{adj}=0.75; CI, 0.63-0.91, p=0.003).

Analysis of patients with two disease sites

We further analyzed patients with two disease sites and contrasted that with peritoneal-only metastases. Overall survival of patients with pmCRC and one additional disease site (n=455) was similar to patients with isolated pmCRC (HR_{adj}=1.10; CI 0.89-1.37, p=0.37). This remained true for patients with peritoneal and liver metastases (exactly 2 disease sites, n=252; HR_{adj}=1.15; CI 0.90-1.46, p=0.27), peritoneal and lung metastases (2 disease sites only, n=44; HR_{adj}=0.82; CI 0.52-1.31, p=0.412). Patients with exactly two non-peritoneal disease sites had similar survival to those with peritoneal-only involvement (n=3385; HR_{adj}=0.99; CI, 0.82-1.20, p=0.957). Similar

trends were observed for PFS, although magnitude of difference was smaller (Supplemental table 1).

Analysis of patients with ≥2 disease sites

Patients with pmCRC and ≥2 additional disease sites (n=726) had the shortest survival (HR_{adj}=1.40; CI 1.14-1.71, p=0.011) when compared to those with disease in the peritoneum only. Patients with ≥2 non-peritoneal sites had similar OS (HR_{adj}=1.04; CI 0.86-1.25, p=0.693) compared to those with mCRC involving peritoneum only; see Figure 2 and Table 4. A combination of peritoneal and liver metastases with or without other disease sites (≥ 2 disease sites, n=868; HR_{adj}=1.33, CI 1.09-1.63, p=0.004) was associated with poorer survival compared with isolated pmCRC. Subgroup analyses were performed for patients treated exclusively with cytotoxic chemotherapy (HR_{adj}=1.43, 95% CI 1.15-1.78, p=0.001) and for those treated with at least one targeted agent (HR_{adj}=0.96, 95% CI 0.60-1.53, p=0.87; not shown in tables/figures). Interestingly, the combination of peritoneal involvement with extrahepatic sites (≥2 disease site, n=313; HR_{adj}=1.13, CI 0.89-1.42, p=0.31) was not associated with poorer survival as compared to peritoneal disease only.

Subanalysis of patients with known *KRAS* and *BRAF* status

KRAS and *BRAF* status data were available on a limited number of patients. $KRAS^{mut}$ status was equally distributed among patients with peritoneal-only (19 out of 44 cases with available data, 43.2%), pmCRC with other disease sites (144/308, 46.8%), and those with non-peritoneal mCRC (1060/2551, 41.6%; p=0.22). A significantly higher proportion of *BRAF* mutations was observed among patients with peritoneal-only (8 out of 44 cases with available data, 18.2%) and pmCRC with other disease sites (34/289, 11.8%), compared to patients with non-peritoneal mCRC (194/2230, 8.7%; p=0.028). Because prior evidence established *BRAF* status as an important prognostic factor among mCRC patients, we performed exploratory analysis of overall survival limited to those with $BRAF^{wt}$ (Table 5 and Supplemental Table 2). Similar adjusted hazard ratios

were observed, although statistical significance was not observed for peritoneal-only metastases, likely due to small numbers of cases available for this subanalysis.

DISCUSSION

The present study represents the largest analysis focusing on survival outcomes among patients with colorectal peritoneal metastases treated in randomized trials. Our main goal was to assess prognostic implication of peritoneal metastases as the only disease manifestation and contrast that to other isolated disease sites and peritoneal involvement in combination with other metastatic sites.

Our major finding is that mCRC patients with peritoneal-only involvement have significantly worse survival than those with other isolated site mCRC (e.g. isolated liver or lung metastases). Patients with lung-only metastases fared best, while those with peritoneum-only mCRC fared worst among patients with mCRC confined to one organ/disease site (Figure 1).

Survival of mCRC patients worsens as number of metastatic organs/sites increases – a well-established finding [6,7]. However, here we demonstrate that a combination with peritoneal involvement further worsens this prognosis. Therefore, poorer survival among mCRC patients with multiple disease sites is a function of both increased number of metastatic sites and peritoneal involvement. This indicates prognostic heterogeneities in this group (all current TNM stage IVB; M-stage 1b). Analysis of progression free survival paralleled that of overall survival, although the magnitude of difference was smaller.

Outcomes of individual mCRC patients are highly variable. Metastatic disease site and possible resectability are among the most important predictors, with cure possible among those with completely resected liver or lung colorectal metastases [6,9,10]. Complete resection of peritoneal metastases may be achieved by peritoneal cytoreductive surgery, [11] a treatment often combined with intraperitoneal and systemic chemotherapy. Resection of liver-only, lung-only or even

combined liver and lung metastases has been associated with improved survival in retrospective studies, and is guideline-recommended [6,9,10,12,13]. Resection of peritoneal metastases by cytoreductive surgery, with or without intraperitoneal therapy remains controversial. While supported by a single prospective randomized trial [11] and a few retrospective studies [14,15], it lacks broad acceptance [13]. Reported overall survival of pmCRC patients can reach as long as 62 months if optimal cytoreduction is achieved and subsequent systemic chemotherapy is delivered [14]. Therefore, in-depth knowledge of prognosis among mCRC patients with different metastatic profile is important, so one can put it into perspective with other therapies seeking wider approval.

Systemic chemotherapy is active in pmCRC [1,16-19]. Unfortunately, survival of those patients is markedly shorter (with HR around 1.4) as compared to those without pmCRC, an observation quite consistent among several studies of pooled randomized trials [1-3,16] and population studies [18-20].

Efficacy of individual agents or combinations in pmCRC has not been studied comprehensively. Improvements in overall survival were observed with exposure to modern cytotoxic agents, irinotecan and oxaliplatin [1,16,18-20] and added benefit was observed with the addition of targeted agents [2]. We have refrained from a specific exploratory analysis of the activity of individual agents, but noted an increased difference in outcomes between non-peritoneal and peritoneal cohorts with the use of biologic agents (Table 3 and 4).

What factors govern the poor prognosis of patients with peritoneal metastases? While limited data are available, plausible explanations may include poor tolerance of chemotherapy and under-treatment, chemotherapy resistance, and steeper performance decline – the later perhaps related to cancer cachexia associated with carcinomatosis-related bowel dysfunction. Additionally, a degree of treatment related resistance of peritoneal metastases was observed both before and after irinotecan/oxaliplatin introduction [2,16,21]. However, under-treatment was not observed in a

secondary analysis of the CAIRO trials, where the number of treatment cycles between patients with and without peritoneal metastases was similar [2]. At this time, we were unable to include a similar analysis in the present study.

While pmCRC is associated with worse performance status at the time of trial registration in this and prior studies [1,2], subsequent performance decline among patients receiving multiple line of systemic chemotherapy is an understudied but well observed clinical reality. Moreover, some histological types of mCRC (e.g. signet ring cell type) may contribute more to mortality compared to other types. A large contemporary autopsy study (n=5,817) demonstrated that signet ring cell carcinoma has a very high propensity for peritoneal metastases, and poor survival despite benefits from chemotherapy [17,22]. We were unable to assess the contribution of specific histological subtypes in the present study. Nevertheless, signet ring cell colonic carcinoma is rare with incidence around 1%, and therefore unlikely to skew survival in current study.

Molecular characterization of mCRC has already some impact on prognosis and treatment selection. Mutant *BRAF* status is associated with markedly worsened prognosis in prior studies [5,23]. We and others have observed a significantly higher proportion of $BRAF^{mut}$ cases among those with peritoneal involvement [5]. Sensitivity analysis was therefore performed excluding patients with known $BRAF^{mut}$ status and including only those with known wild-type *BRAF*. In this analysis, peritoneal-only involvement of $BRAF^{wt}$ cancers did not show statistical difference in OS as compared to other isolated mCRC sites, conceivably due to the small sample size for which *BRAF* mutation data were available. There were only 36 peritoneal-only metastatic patients with wild-type *BRAF* and the hazard ratio was nearly identical to that in the whole group analysis (1.33 versus 1.42, Table 4 and 5). Therefore, we infer, that *BRAF* status may not be the main driver of worsened prognosis associated with peritoneal metastases. In this context we acknowledge substantially limited availability of *BRAF* status in this cohort – only about one

quarter of cases had data available – yet there was some two thousand patients with known wild-type *BRAF* status.

The present analysis differs in conclusion from that provided by the only prior study investigating peritoneum-only metastatic involvement [4]. We observed that patient prognosis with peritoneal-only metastases was similar to those with two non-peritoneal disease sites (both M1b stage), while the other report suggested that peritoneal-only involvement carries prognosis similar to other isolated disease sites, and better as compared to multiple disease sites. It is likely that a larger patient sample and better data collection in context of randomized trials are primarily responsible for better discrimination in our study.

Strengths of the present report are its large sample size and superior data quality. Individual patient data were collected from prospective randomized studies that solicited for peritoneal involvement (peritoneal involvement was specified in the on-study data collection form) or a peritoneum-specific review of pretreatment scans was conducted. Presented multivariate analyses are adjusted for multiple influential clinical factors, including age, BMI, and performance status. On the other hand we were unable to adjust for socioeconomic factors, degree of physical activity and post-trial treatment, which all may significantly affect overall survival [24-27]. Peritoneal metastases and their extent are notoriously difficult to detect short of direct surgical observation. Additionally, this study did not evaluate volume-related disease burden. Higher metastatic volume burden is a well-recognized negative predictive factor, both for liver-only [6], and peritoneum-only disease sites [11,28,29]. Furthermore, pmCRC patients included in prospective randomized trials may not completely share the demographic profile of those found in the general population, potentially limiting generalizability. Indeed, upon comparison of randomized and population studies there appears to be a proportional inclusion of pmCRC patients in randomized trials, but possible under-representation of mCRC with peritoneal-only metastases. The proportion of patients with peritoneal-only metastases was 0.5% and 1.7% in prior pooled reports

investigating pmCRC among participants in randomized trials [1,2]. On the other hand, around 5% of patients with initial diagnosis of colorectal cancer have synchronous isolated pmCRC [20,30], representing some 24% with newly diagnosed mCRC. Among the other limitations, we have not examined post-trial treatment, which may significantly affect overall survival [24].

In conclusion, overall survival worsens with peritoneal metastases as well as with increasing number of metastatic sites. Peritoneal-only metastases are associated with significantly worse survival as compared with other single organ/isolated disease site mCRC. Peritoneal metastases are associated with worsened prognosis whether isolated or in combination with other metastatic locations. Prognostic heterogeneity among M1b patients with metastatic colorectal carcinoma is significant.

Contributors

AG, VH, AF, NCT, TM, MS, LS, CT, CJAP, MK, EDR, IS, BC, ADG, RAA recruited patients. QS, JF, JPM, JM, DJS analyzed and interpreted the data. JF, QS, AG, DJS wrote the manuscript. JF and QS designed the study. All authors revised and approved the manuscript.

Declaration of interests

Acknowledgments

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TABLES

Study	Accrual Period	Treatment Comparisons[#]	Number of patients[$]	% of Patients with pmCRC	First author and year of initial publication
N016966	02/2004-02/2005	FOLFOX4 vs. FOLFOX4+BEV vs. XELOX vs. XELOX+BEV	1965	12.8	Saltz – 2008
OPTIMOX1	01/2000-06/2002	FOFOLX4 vs. FOLFOX7->LV5FU2	612	6.05	Tournigand - 2006
OPTIMOX2	12/2002-06/2003	mFOLFOX7->CFI->mFOLFOX7 vs. mFOLFOX7->LV5FU2->mFOLFOX7	201	16.92	Andre - 2007
C97-3	12/1997-12/1999	FOLFIRI->FOLFOX6 vs. FOLFOX6->FOLFIRI	220	12.73	Tournigand - 2004
CAIRO	01/2003-12/2004	Cap+IRI->Cap+Ox vs. Cap->IRI->Cap+Ox	703	5.69	Koopman - 2007
CAIRO2	06/2005-12/2006	Cap+Ox+Bev vs. Cap+Ox+Bev+Cetuximab ($KRAS^{wt}$) vs. Cap+Ox+Bev+Cetuximab ($KRAS^{mut}$)	578	4.82	Tol – 2009
COIN	03/2005-05/2008	5FU+Ox vs. 5FU+Ox (Intermit) vs. 5FU+Ox + Cetuximab ($KRAS^{wt}$) vs. 5FU+Ox + Cetuximab ($KRAS^{mut}$) vs. CAPOX vs. 5FU+Ox (Intermit) vs. CAPOX+ Cetuximab ($KRAS^{wt}$) vs. CAPOX+ Cetuximab ($KRAS^{mut}$)	2271	14.58	Maughan - 2011
FOCUS	05/2000-12/2003	5FU->FOLFIRI vs. 5FU->FOLFOX vs. 5FU->IRI vs. FOLFIRI vs. FOLFOX	2070	15.12	Seymour - 2007
FOCUS2	01/2004-07/2006	FUFOL vs. FOLFOX vs. CAP vs. CAPOX	454	18.94	Seymour - 2011
03-TTD-01	04/2002-08/2004	FOLFOX vs. XELOX	338	3.84	Diaz-Rubio - 2007
AGITG MAX	07/2005-06/2007	CAP vs. CAP+BEV vs. CAP+BEV+Mitomycin	471	18.26	Tebbutt - 2010
HORG 99.30	10/2000-12/2004	FOLFIRI vs. FOLFOXIRI	282	25.53	Souglakos - 2006
GONO	11/2001-04/2005	FOLFIRI vs. FOLFOXIRI	242	14.46	Falcone - 2007
FIRE II	09/2004-12/2006	CAPIRI+Cetuximab ($KRAS^{mut}$) vs. CAPIRI+Cetuximab ($KRAS^{wt}$) vs. CAPOX+Cetuximab ($KRAS^{mut}$) vs. CAPOX+Cetuximab ($KRAS^{wt}$)	146	10.27	Moosmann - 2011

Table 1. Description of included trials and chemotherapy. FOLFOX - infusional 5-fluorouracil, folinic acid and oxaliplatin. BEV – bevacizumab. FUFOL –bolus 5-fluorouracil and folinic acid administered daily over 5 consecutive days and repeated every 28 days. FOLFIRI - infusional 5-fluorouracil, folinic acid and irinotecan. CAPOX – capecitabine and oxaliplatin. FOLFOXIRI - infusional 5-fluorouracil, folinic acid, oxaliplatin and irinotecan. CAPIRI - capecitabine and irinotecan. CAP – capecitabine. pmCRC - colorectal peritoneal metastases; $KRAS^{wt}$ – wild-type *KRAS*; $KRAS^{mut}$ - mutant *KRAS*.

[#]Treatment arms within trials were the stratification factor in the Cox regression model. For the trails testing anti-EGFR agents, KRAS status was used to further stratify patients who received anti-EGFR agents.

[$]Total of 10,635 patients were included in these studies. Final dataset excluded 82 patients with missing data on metastatic sites leaving 10,553 for analysis.

	pmCRC-only N = 194	**pmCRC with ≥1 other sites** N = 1181	**Solitary Non-pmCRC sites (1 disease site)** N = 4385	**Multiple Non-pmCRC sites (≥2 disease sites)** N = 4793	**Total** N = 10,553	**p-value**
Age, years						**0.66[#]**
N	194	1181	4384	4789	10548	
Median	63.0	64.0	64.0	64.0	64.0	
Range	(22.0-84.0)	(18.0-85.0)	(18.0-86.0)	(19.0-87.0)	(18.0-87.0)	
Missing	0	0	1	4	5	
Gender, n (%)						**0.0011[$]**
Female	89 (45.9%)	476 (40.4%)	1602 (36.6%)	1710 (35.7%)	3877 (36.8%)	
Male	105 (54.1%)	701 (59.6%)	2778 (63.4%)	3079 (64.3%)	6663 (63.2%)	
Missing	0	4	5	4	13	
Primary site, n (%)						**<0.0001[$]**
Colon only	166 (86.0%)	950 (83.3%)	2782 (68.5%)	2821 (63.8%)	6719 (68.5%)	
Rectum only	24 (12.4%)	172 (15.1%)	1187 (29.2%)	1530 (34.6%)	2913 (29.7%)	
Both	3 (1.6%)	19 (1.7%)	91 (2.2%)	69 (1.6%)	182 (1.9%)	
Missing	1	40	325	373	739	
[*†]Tumor Sidedness, n (%)						**<0.0001[&]**
Distal colon only	26 (32.1%)	189 (33.0%)	596 (28.0%)	733 (27.0%)	1544 (28.1%)	
Proximal colon only	31 (38.3%)	211 (36.9%)	344 (16.2%)	450 (16.6%)	1036 (18.9%)	
Rectum only	24 (29.6%)	172 (30.1%)	1187 (55.8%)	1530 (56.4%)	2913 (53.0%)	
Missing data	113	609	2258	2080	5060	
Performance status, n (%)						**<0.0001[$]**
0	93 (47.9%)	489 (41.4%)	2396 (54.7%)	2357 (49.2%)	5335 (50.6%)	
1	79 (40.7%)	577 (48.9%)	1762 (40.2%)	2130 (44.5%)	4548 (43.1%)	
2	22 (11.3%)	114 (9.7%)	222 (5.1%)	299 (6.2%)	657 (6.2%)	
Missing	0	1	5	7	13	
BMI group, n (%)						**0.0498[$]**
<20	14 (8.6%)	91 (8.5%)	294 (8.2%)	312 (7.1%)	711 (7.7%)	
≥20 & <25	67 (41.4%)	453 (42.1%)	1414 (39.5%)	1689 (38.6%)	3623 (39.4%)	
≥25 & <30	49 (30.2%)	377 (35.0%)	1314 (36.7%)	1626 (37.1%)	3366 (36.6%)	
≥30	32 (19.8%)	155 (14.4%)	554 (15.5%)	752 (17.2%)	1493 (16.2%)	
Missing	32	105	809	414	1360	
Liver metastases, n (%)						**<0.0001[&]**
Present	0 (0.0%)	868 (73.5%)	3179 (72.7%)	4040 (84.4%)	8087 (76.7%)	
Absent	192 (100.0%)	313 (26.5%)	1196 (27.3%)	749 (15.6%)	2450 (23.3%)	
Missing data	2	0	10	4	16	
Lung metastases, n (%)						**<0.0001[&]**
Present	0 (0.0%)	361 (30.8%)	623 (14.4%)	2936 (61.7%)	3920 (37.5%)	
Absent	190 (100.0%)	812 (69.2%)	3714 (85.6%)	1819 (38.3%)	6535 (62.5%)	

Missing data	4	8	48	38	98	
KRAS Status, n (%)						**0.0326[&]**
Mutant	19 (43.2%)	144 (46.8%)	421 (38.8%)	639 (43.6%)	1223 (42.1%)	
Wild-type	25 (56.8%)	164 (53.2%)	663 (61.2%)	828 (56.4%)	1680 (57.9%)	
Missing data	150	873	3301	3326	7650	
[*]BRAF Status, n (%)						**0.0652[&]**
Mutant	8 (18.2%)	34 (11.8%)	81 (8.8%)	113 (8.6%)	236 (9.2%)	
Wild-type	36 (81.8%)	255 (88.2%)	836 (91.2%)	1200 (91.4%)	2327 (90.8%)	
Missing data	150	892	3468	3480	7990	
[*]Primary Tumor Resection Status, n (%)						**0.0030[&]**
Metachronous	6 (66.7%)	31 (36.0%)	279 (33.7%)	301 (36.8%)	617 (35.5%)	
Synchronous Unresected	0 (0.0%)	10 (11.6%)	121 (14.6%)	162 (19.8%)	293 (16.8%)	
Synchronous Resected	3 (33.3%)	45 (52.3%)	427 (51.6%)	355 (43.4%)	830 (47.7%)	
Missing data	185	1095	3558	3975	8813	

Table 2. Demographic and clinical characteristics of study population by disease site. pmCRC - colorectal peritoneal metastases

[#]Kruskal-Wallis test for comparing four groups; [$]Chi-squared test for comparing four groups; [&]Chi-squared test for comparing groups of patient with pmCRC with ≥1 other site and multiple non-pmCRC sites;

*Only a small portion of patients with available data

[†]Patients with multiple locations were excluded.

	Events/Total	Median OS [months] (95% CI)†	Hazard Ratio (95% CI)‡	P-value	Adjusted[1] Events/Total	Adjusted[1] Hazard Ratio (95% CI)‡	Adjusted[1] P-value
All patients with isolated organ/disease site ***Disease Sites***				<.0001#			<.0001#
Liver-only	2269/3179	19.1 (18.3-19.8)	0.75 (0.63-0.88)	0.0004+	1554/2240	0.79 (0.65-0.95)	0.0121+
Lung-only	391/623	24.6 (22.7-26.4)	0.53 (0.44-0.64)	<.0001+	277/450	0.61 (0.49-0.76)	<.0001+
Peritoneal-only	159/193$	16.3 (13.5-18.8)	Reference	--	119/147	Reference	--
Distant Lymph Nodes-only	281/405	19.4 (17.0-21.9)	0.69 (0.57-0.84)	0.0003+	201/299	0.73 (0.58-0.92)	0.0075+
Other Isolated Organ/Site	127/178	18.0 (14.4-20.5)	0.85 (0.67-1.07)	0.1707+	95/131	0.95 (0.73-1.25)	0.7354+
Multiple Organs/Sites‡	4757/5971	15.0 (14.6-15.3)	1.02 (0.87-1.20)	0.8058+	3768/4816	1.09 (0.91-1.31)	0.3644+
All Arms with Only Cytotoxic Agents ***Disease Sites***				<.0001#			<.0001#
Liver-only	1907/2543	18.3 (17.7-19.2)	0.78 (0.65-0.93)	0.0047+	1196/1610	0.85 (0.69-1.05)	0.1224+
Lung-only	332/511	23.8 (22.0-26.0)	0.55 (0.45-0.67)	<.0001+	219/339	0.65 (0.51-0.83)	0.0004+
Peritoneal-only	137/163	16.3 (12.9-19.2)	Reference	--	98/118	Reference	--
Distant Lymph Nodes-only	228/320	18.2 (16.5-21.3)	0.72 (0.58-0.89)	0.0025+	149/216	0.77 (0.60-1.00)	0.0482+
Other Isolated Organ/Site	107/147	18.4 (13.6-20.7)	0.84 (0.65-1.08)	0.1705+	75/100	0.95 (0.70-1.29)	0.7623+
Multiple Organs/Sites‡	3719/4498	14.5 (14.1-15.0)	1.04 (0.87-1.23)	0.6856+	2744/3362	1.13 (0.92-1.39)	0.2331+
All Arms with at Least One Targeted Agent ***Disease Sites***				<.0001#			<.0001#
Liver-only	362/636	22.2 (20.5-25.7)	0.58 (0.38-0.90)	0.0157+	358/630	0.53 (0.34-0.83)	0.0052+
Lung-only	59/112	27.4 (23.8-33.5)	0.42 (0.26-0.69)	0.0006+	58/111	0.43 (0.26-0.72)	0.0013+
Peritoneal-only	22/30	17.1 (13.0-22.1)	Reference	--	21/29	Reference	--

		Median OS [months]			Adjusted[1]	Adjusted[1] Hazard Ratio	Adjusted[1]
	Events/Total	(95% CI)[†]	Hazard Ratio (95% CI)[‡]	P-value	Events/Total	(95% CI)[‡]	P-value
Distant Lymph Nodes-only	53/85	22.0 (16.9-28.9)	0.55 (0.33-0.92)	0.0213+	52/83	0.54 (0.32-0.91)	0.0203+
Other Isolated Organ/Site	20/31	15.0 (14.4-34.8)	0.91 (0.49-1.68)	0.7601+	20/31	0.89 (0.48-1.66)	0.7220+
Multiple Organs/Sites[‡]	1038/1473	16.8 (15.9-17.6)	0.89 (0.58-1.36)	0.5882+	1024/1454	0.83 (0.54-1.29)	0.4067+

[†]Kaplan-Meier method; [‡]Cox model; [#]Likelihood-ratio test; [+]Wald Chi-Square test;
[1]Adjusted for gender, performance score, colon involved, rectum involved, prior chemotherapy, age, and BMI

Table 3. Unadjusted and adjusted prognostic overall survival differences among patients with isolated organ or disease site. A category of multiple organs/sites is provided for comparison[‡]. pmCRC - colorectal peritoneal metastases; OS - overall survival; CI - confidence interval; NR - not reached

[*]Reference is isolated non-peritoneal disease site (non-pmCRC with one disease site only).

[$]One pmCRC-only patient was lost to follow-up, therefore only 193 patients were available for survival analysis.

[†]Kaplan-Meier method; [‡]Cox model; [#]Likelihood-ratio test; [+]Wald Chi-Square test;

[1]Adjusted for gender, performance score, colon involved, rectum involved, prior chemotherapy, age, and BMI

	Events/Total	Median OS [months] (95% CI)[†]	Hazard Ratio (95% CI)[‡]	P-value*	Adjusted[1] Events/Total	Adjusted[1] Hazard Ratio (95% CI)[‡]	Adjusted[1] P-value*
All Patients							
Peritoneal Status				<.0001[#]			<.0001[#]
pmCRC-only	159/193[$]	16.3 (13.5-18.8)	1.42 (1.21-1.66)	<.0001+	119/147	1.33 (1.10-1.60)	0.0030+
pmCRC with ≥1 other site	999/1181	12.6 (12.0-13.1)	1.79 (1.67-1.93)	<.0001+	812/967	1.71 (1.57-1.86)	<.0001+
Isolated non-pmCRC sites (1 disease site)	3068/4385	20.0 (19.4-20.6)	Reference	--	2127/3120	Reference	--
Multiple non-pmCRC (≥ 2 disease sites)	3758/4790	15.7 (15.2-16.3)	1.37 (1.30-1.44)	<.0001+	2956/3849	1.38 (1.30-1.46)	<.0001+
All Arms with Only Cytotoxic Agents							
Perit*oneal Status*				<.0001[#]			<.0001[#]
pmCRC-only	137/163	16.3 (12.9-19.2)	1.36 (1.15-1.62)	0.0005+	98/118	1.24 (1.01-1.52)	0.0439+
pmCRC with ≥1 other site	815/936	12.3 (11.4-13.0)	1.76 (1.62-1.91)	<.0001+	629/725	1.67 (1.52-1.83)	<.0001+
Isolated non-pmCRC sites (1 disease site)	2574/3521	19.3 (18.5-20.0)	Reference	--	1639/2265	Reference	--
Multiple non-pmCRC (≥ 2 disease sites)	2904/3562	15.2 (14.7-15.8)	1.34 (1.27-1.41)	<.0001+	2115/2637	1.33 (1.24-1.42)	<.0001+
All Arms with at Least One Targeted Agent							
Peritoneal Status				<.0001[#]			<.0001[#]
pmCRC-only	22/30	17.1 (13.0-22.1)	1.79 (1.16-2.76)	0.0083+	21/29	1.92 (1.23-2.99)	0.0040+
pmCRC with ≥1 other site	184/245	13.2 (12.6-16.3)	1.96 (1.65-2.33)	<.0001+	183/242	1.88 (1.58-2.25)	<.0001+
Isolated non-pmCRC site (1 disease site)	494/864	22.7 (21.6-25.7)	Reference	--	488/855	Reference	--
Multiple non-pmCRC (≥ 2 disease sites)	854/1228	17.2 (16.5-18.4)	1.52 (1.36-1.70)	<.0001+	841/1212	1.53 (1.37-1.72)	<.0001+

Table 4. Unadjusted and adjusted prognostic overall survival differences among subgroups defined by pmCRC status. pmCRC - colorectal peritoneal metastases; OS - overall survival; CI - confidence interval

[*]Reference is isolated non-peritoneal disease site (non-pmCRC with one disease site only).

[$]One pmCRC-only patient was lost to follow-up, therefore only 193 patients were available for survival analysis.

[†]Kaplan-Meier method; [‡]Cox model; [#]Likelihood-ratio test; [+]Wald Chi-Square test;

[1]Adjusted for gender, performance score, colon involved, rectum involved, prior chemotherapy, age, and BMI

	Events/Total	Median OS [months] (95% CI)†	Hazard Ratio (95% CI)‡	P-value*	Adjusted[1] Events/Total	Adjusted[1] Hazard Ratio (95% CI)‡	Adjusted[1] P-value*
Peritoneal Status, BRAF wild-type only				<.0001#			<.0001#
pmCRC-only	30/36	16.1 (13.1-21.7)	1.57 (1.08-2.27)	0.0179+	26/32	1.42 (0.96-2.11)	0.0827+
pmCRC with ≥1 other site	228/255	13.1 (12.3-16.1)	1.58 (1.36-1.84)	<.0001+	225/252	1.52 (1.30-1.78)	<.0001+
Isolated non-pmCRC site (1 disease site)	642/836	21.5 (20.1-22.7)	Reference	--	627/816	Reference	--
Multiple non-pmCRC (≥ 2 disease sites)	1019/1200	17.0 (16.4-18.0)	1.30 (1.18-1.44)	<.0001+	1011/1186	1.30 (1.18-1.44)	<.0001+

Table 5. Unadjusted and adjusted prognostic overall survival differences among subgroups defined by pmCRC status among those with known *BRAF* wild-type status. pmCRC - colorectal peritoneal metastases; OS - overall survival; CI - confidence interval
*Reference is isolated non-peritoneal disease site (non-pmCRC with one disease site only).
†Kaplan-Meier method; ‡Cox model; #Likelihood-ratio test; +Wald Chi-Square test;
[1]Adjusted for gender, performance score, colon involved, rectum involved, prior chemotherapy, age, and BMI

FIGURES

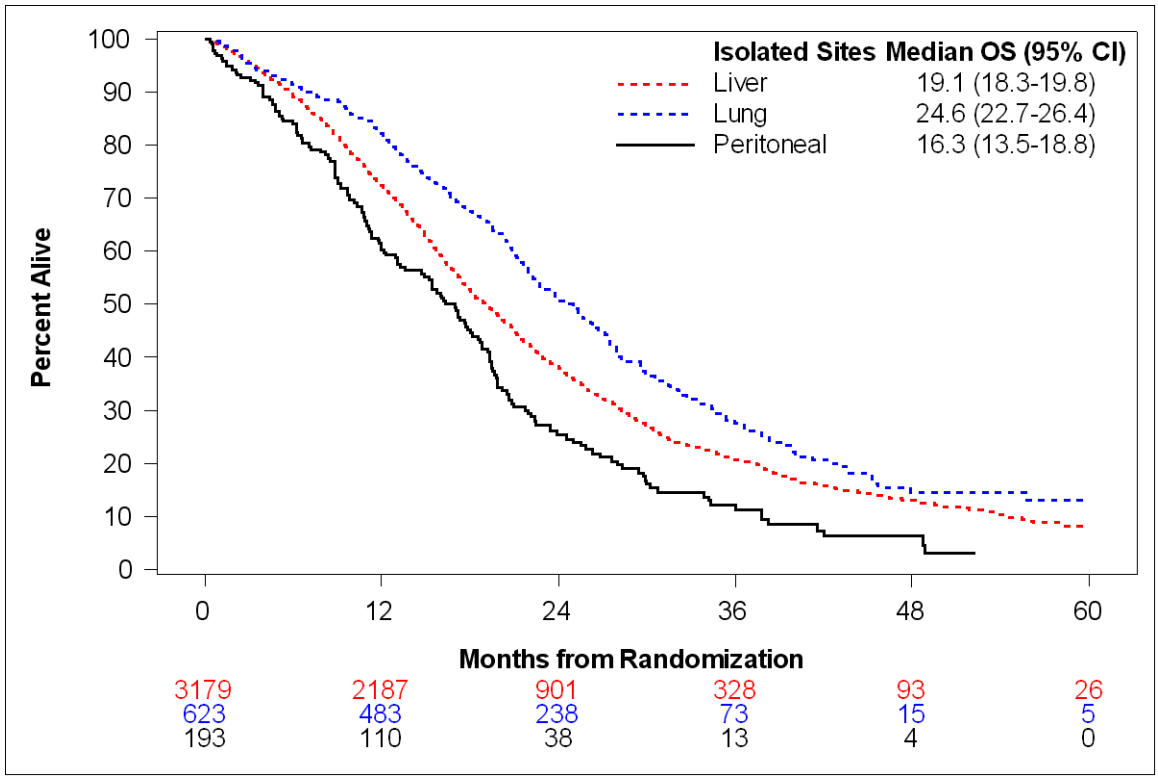

Figure 1. Overall survival among mCRC patients with isolated metastatic disease site at the time of trial enrollment. Median overall survival is provided in months.

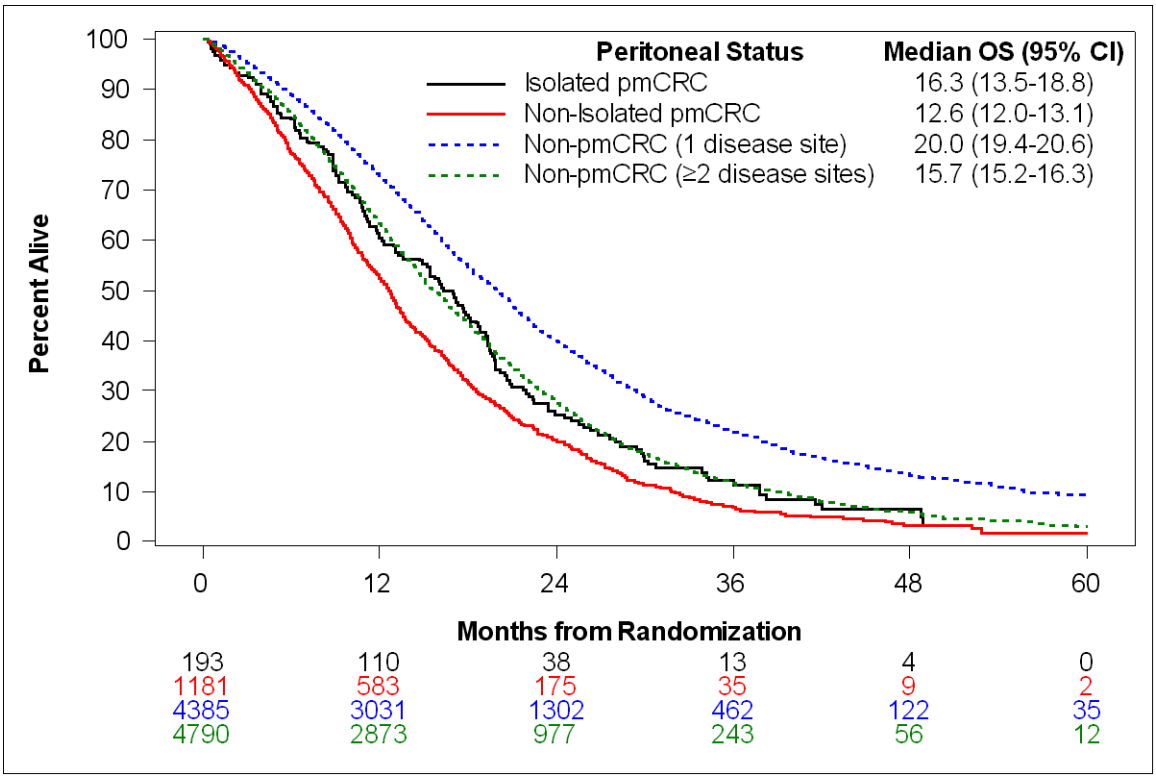

Figure 2. Overall survival among mCRC patients with isolated peritoneal metastatic disease site at the time of trial enrollment as compared to other subgroups (single-site involvement or ≥2 disease site). Median overall survival is provided in months.

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