Author/s:
Mendis, S;Beck, S;Lee, B;Lee, M;Wong, R;Kosmider, S;Shapiro, J;Yip, D;Steel, S;Nott, L;Jennens, R;Lipton, L;Burge, M;Field, K;Ananda, S;Wong, HL;Gibbs, P

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AUTHORS: Shehara Mendis[a], Sophie Beck[b], Belinda Lee[b-d], Margaret Lee[a-e], Rachel Wong[b,e,f], Suzanne Kosmider[a], Jeremy Shapiro[g], Desmond Yip[h,i], Simone Steel[j], Louise Nott[k], Ross Jennens[l], Lara Lipton[a,g], Matthew Burge[m], Kathryn Field[c,d], Sumitra Ananda[a], Hui-Li Wong[b], Peter Gibbs[a-d,n].

a. Footscray Hospital, Western Health, 160 Gordon Street, Footscray VIC 3011, Australia

b. Walter & Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville VIC 3052, Australia

c. Royal Melbourne Hospital, 300 Grattan St, Parkville VIC 3050, Australia

d. Faculty of Medicine & Health Sciences, University of Melbourne, Building 181, Grattan St, Melbourne VIC 3010, Australia

e. Box Hill Hospital, Eastern Health, 8 Arnold St, Box Hill VIC 3128, Australia

f. Monash University, Faculty of Nursing & Health Sciences, Wellington Rd, Clayton VIC 3800, Australia

g. Cabrini Health, 181-183 Wattletree Rd, Malvern VIC 3144, Australia

h. Canberra and Calvary Hospitals, Yamba Dr, Garran ACT 2605, Australia

i. ANU Medical School, Building 4, The Canberra Hospital, Hospital Rd, Garran ACT 2605, Australia

j. Peninsula Private Hospital, 525 McClelland Dr, Frankston VIC 3199, Australia

k. Royal Hobart Hospital, 48 Liverpool St, Hobart TAS 7000, Australia

l. Epworth Hospital, 89 Bridge Rd, Richmond VIC 3121, Australia

m. Royal Brisbane Hospital, Bowen Bridge Road &, Butterfield St, Herston QLD 4029, Australia

n. BioGrid Australia, Melbourne, Australia

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Corresponding author:

Dr Shehara Mendis[1]

Footscray Hospital, Western Health

160 Gordon Street, Footscray VIC 3011 Australia

Phone +61 423 020 001

Email Address: shehara_mendis@hotmail.com

ABSTRACT

Background

Metastatic colorectal cancer (mCRC) patients with a right sided primary (RC) have an inferior survival to mCRC arising from a left sided primary (LC). Previous analyses have suggested multiple factors contribute.

Methods

The Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) Registry prospectively captured data on consecutive mCRC patients. RC were defined as tumors proximal to the splenic flexure; LC were those at and distal to the splenic flexure and included rectal cancers. Patient, tumor, treatment and survival data were analysed stratified by side.

Results

Of 2306 patients enrolled from July 2009 – March 2018, 747 (32%) had a RC. Patients with RC were older, more likely to be female and have a Charlson score ≥ 3. RC were more frequently BRAF mutated, deficient in mismatch repair, associated with peritoneal metastases and less likely to receive chemotherapy. Progression-free survival on first line systemic therapy was inferior for RC patients (8.1 vs 10.8 months, hazard ratio [HR] 1.38, p<0.001). Median overall survival (OS) for all RC patients was inferior (19.6 vs 27.5 months, HR 1.44, p<0.001), and inferior within the treated (21 vs 29.5 months, HR 1.52, p<0.001) and untreated subgroups (5.9 vs 10.3 months, HR 1.38, p=0.009). Primary side remained a significant factor for OS in multivariate analysis.

Conclusion

Our data from a real-world population confirms the poorer prognosis associated with RC. Primary tumor location remains significantly associated with overall survival even when adjusting for multiple factors, indicating the existence of further side-based differences that are as yet undefined.

[1]Present address: Medical Oncology Dept, BC Cancer, 600 West 10th Avenue, Vancouver BC V5Z 4E6, Canada.

Key words

Colonic neoplasms

Multivariate Analysis

Proportional Hazards Models

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BACKGROUND

Colorectal cancer (CRC) is the second leading cause of cancer related death in men and the third leading cause in women.[1] Primary tumor side-based differences in outcome for patients with metastatic disease have long been noted.[2, 3] A systematic review and meta-analysis of 66 studies found that left sided colorectal cancers (LC) (left colon and rectum) have a 20% reduced risk of death as compared to those arising from the right colon (RC).[4] Rectal cancers have been shown to be biologically indistinguishable from colon cancers in RNA expression analyses, have been shown to have similar survival outcomes as the left colon, and are commonly included with the left colon in comparisons of sidedness.[5-8]

Recent analyses of trial data[6, 7, 9-12], now in the era of biologic therapies for metastatic disease, have shown major survival gains with the addition of Epidermal Growth Factor (EGFR) inhibitors in RAS wild-type LC but limited impact for RAS wild-type RC. In contrast, the benefit of adding bevacizumab appears similar for RC and LC.[13-15] Consistent with this, SEER registry data demonstrate that recent improvements in overall survival have favoured LC over RC.[16]

Significant differences in patient profile (age and gender)[3, 16-19], molecular characteristics such as RAS, RAF and mismatch repair (MMR) status[20-24], and metastatic pattern[14, 16, 19] have previously been reported for RC versus LC. Previous studies, including a mixture of clinical trial and registry data, have reported on some of these findings but typically not all key data points have been available within each cohort.

Only within the past 10 years has registry and trial data routinely included key molecular data such as extended RAS, BRAF and MMR status. Clinical trials may not have prospectively collected primary tumor location data[11] and sites of metastatic disease may not have been fully documented, with case report forms often recording only liver versus other sites or the total number of metastatic

sites. Patients with peritoneal disease have also been excluded from many bevacizumab studies,[25, 26] however bevacizumab was a commonly used first line biologic until the recent availability of EGFR inhibitor therapy in the first line setting in Australia. Finally, the impact of factors that vary with age may not be fully appreciated in the select young and fit patients enrolled on trials, with an age-related increase in RC and in the frequency of MMR and BRAF being particularly noteworthy.[17, 21, 27, 28]

Here we undertook a review of registry data to further explore the specific impact on overall survival of differences between patients with a RC and those with a LC, including the use of first line biologic therapies. As many of these are inter-related, such as age, ECOG performance status (ECOG PS) and co-morbidity, careful analysis is required to better define the major drivers versus associated factors.

PATIENTS and METHODS

Patients

This study utilised data from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) Registry. TRACC has prospectively collected data on metastatic colorectal cancer patients from July 2009 onwards, now enrolling consecutive patients at 32 sites between Australia and Hong Kong. In the earliest version of the data set primary tumor side data and some molecular data was not recorded. Where possible this was retrieved retrospectively, including primary tumor side for almost all patients. As per the most commonly used definition, RC were tumors arising proximal to the splenic flexure. LC were defined as a primary tumor that occurred at or distal to the splenic flexure and included rectal tumors. All other data items have been collected on all patients from registry initiation.

Source data was accessed to determine primary tumor site where possible. Patients in whom site of primary tumor was unavailable and those with multiple primary tumors were excluded. Otherwise all patients were included, whether or not they received active treatment.

Patient age, gender, ECOG PS, Charlson score, and all individual sites of metastasis at diagnosis of metastatic disease was collected. In addition, whether presentation with metastatic disease was synchronous or metachronous to localized disease, RAS status, BRAF status and mismatch repair status was collected. RAS data was entered as per the changing standards of care, initially KRAS exon 2 only, later extended KRAS and NRAS. Surgical data included primary tumor resection and any resection of metastatic disease.

Statistical Analysis

The primary objective was to evaluate the overall survival of RC as compared to LC in the metastatic setting. Secondary objectives were to evaluate the difference in progression-free survival, patient demographics, clinicopathologic features, surgical interventions and systemic therapy use between RC and LC. Survival analyses were also performed stratified by use of biologic therapies in the first line setting.

Overall survival (OS) was defined as time from diagnosis of mCRC to death from any cause. Progression-free survival (PFS) was defined as time from diagnosis of mCRC to first objective evidence of disease progression or death from any cause, whichever occurred first. Patients undergoing metastasectomy were censored at their surgery date for PFS only. Data for patients who did not have disease progression or were lost to follow-up were censored at the time of their last clinical contact. Overall survival and progression-free survival were estimated using the Kaplan-Meier method and median survivals calculated using the log-rank test. Cox regression was used to calculate hazard ratios and their associated 95% confidence intervals.

When comparing demographics, tumor clinicopathologic features and treatments received stratified by side, Chi-squared testing was used. Where n≤10, Fisher's exact test was used. A univariate analysis using Cox regression was undertaken to assess for factors impacting on overall survival. Covariates found to be associated with survival in the univariate analysis at a significance level of <0.05 then underwent multivariate analysis using Cox multiple regression. All tests were performed at the two-sided 0.01 significance level to adjust for multiple testing.

RESULTS

A total of 2427 patients were entered in the TRACC registry between July 1st 2009 and March 8th 2018 *(Supplementary Figure 1).* Of these 2324 had primary tumor side data recorded. Eighteen patients with multiple primary tumors were excluded from the analysis. Ultimately data on 1,559 (68%) patients with LC and 747 (32%) patients with RC were analysed.

Patient and disease characteristics

Clinical characteristics of RC and LC patients are shown in *Table 1*. Patients with RC were more likely to be older (median age 71 years for RC vs 65 years for LC, p<0.001), female (50% vs 37%, p<0.001),

trended towards having a poorer ECOG PS of 2 or more (20% vs 16%, p=0.02) and had a higher Charlson score of 3 or more (67% vs 55%, p<0.001).

RC were more likely to be diagnosed at a later stage than LC, even when excluding locally advanced rectal cancers, where pathologic stage is not available at diagnosis (p=0.001). For those patients with mutation status and mismatch repair status available, RC were more likely to be BRAF mutated (22% vs 7%, p<0.001) and have deficient mismatch repair (13% vs 4%, p<0.001). Frequency of all-RAS mutation status did not reach statistical difference between sides (49% vs 43%, p=0.02). At metastatic diagnosis, RC patients were more likely to have peritoneal/omental metastases (30% vs 15%, p<0.001), and less likely to have lung metastases (22% vs 34%, p<0.001). Number of metastatic sites did not differ significantly between sides.

Surgical and systemic therapy

As shown in *Table 2*, RC patients were more likely to have their primary tumor resected (78% vs 71%, p<0.001), but resection of metastatic sites did not differ between sides (28% vs 31%, p=0.10). RC patients were less likely to receive systemic treatment (72% vs 79%, p=0.001), and when they did receive systemic treatment, it was less likely to be doublet chemotherapy (50% vs 56%, p=0.008). Use of biologic therapies in the first line setting and use of second line chemotherapy did not differ significantly between sides.

Progression-free and overall survival

Median progression-free survival for patients receiving first line therapy was 8.1 months for the RC cohort and 10.8 months for LC (hazard ratio [HR] from univariate Cox regression for RC vs LC was 1.38, 95% confidence interval [CI] 1.22-1.57, p<0.001*, Figure 1A)*. Progression-free survival and overall survival in patients receiving first line chemotherapy with bevacizumab was inferior in the RC group (HR 1.33, 95% CI 1.13-1.56, p<0.001 for progression-free survival, *Supplementary Figure 2A*; HR 1.56, 95% CI 1.32-1.84, p<0.001 for overall survival, *Supplementary Figure 2B)*. Progression-free survival and overall survival in patients receiving first line chemotherapy without bevacizumab was also inferior in the RC group (HR 1.44, 95% CI 1.17-1.77, p<0.001 for progression-free survival, *Supplementary Figure 3A*; HR 1.45, 95% CI 1.17-1.80, p=0.001 for overall survival, *Supplementary Figure 3B)*. Due to small patient numbers an analysis of side and EGFR inhibitor impact was not undertaken.

Median overall survival for the entire RC cohort was 19.6 months versus 27.5 months for the entire LC cohort *(Figure 2A)*. The HR for overall survival of RC vs LC was 1.44 (95% CI 1.29-1.62, p<0.001). Of the patients who received any systemic therapy in the metastatic setting, overall survival was 21 months for the RC cohort and 29.5 months for LC, with a hazard ratio of 1.52 (95% CI 1.33-1.73 p<0.001, *Figure 1B)*. For those patients receiving only best supportive care, that is no systemic treatment or resection of metastatic disease, overall survival was 5.9 months for the RC cohort and 10.3 months for LC cases (HR 1.38, p= 0.009, *Figure 2B*).

Univariate analysis of factors associated with overall survival

Variables included in the univariate analysis for overall survival were factors previously reported to impact treatment and survival: primary tumour side, patient age, gender, ECOG PS, Charlson score, KRAS status, BRAF status, mismatch repair status, presentation with synchronous metastases, sites of disease, number of metastatic sites at diagnosis of stage IV disease, whether the primary or metastases were resected, and receipt of first or second line chemotherapy (*Table 3)*.

Factors that were significant in the univariate analysis were primary tumor side (HR 1.44 for RC, p<0.001), age (HR 1.71 for age ≥ 70, p<0.001), ECOG PS ≥ 2 (HR 3.88, p<0.001), Charlson score ≥ 3 (HR 1.32, p<0.001), presence of a BRAF mutation (HR 2.42, p<0.001), presentation with synchronous metastases (HR 1.49, p<0.001), number of metastatic sites (HR 1.36, p<0.001), presence of peritoneal/omental metastases (HR 1.65, p<0.001), primary tumor resection (HR 0.40, p<0.001), metastatic disease resection (HR of 0.22, p<0.001), and receipt of any palliative chemotherapy (HR 0.50, p<0.001).

Multivariate analysis of factors associated with overall survival

Multivariate analysis using Cox multiple regression was conducted using the variables found to be associated with overall survival in the univariate model at a significance level of <0.05 (*Table 3)*. Complete cases analysis was performed; those who had covariate data missing were excluded. In total, 886 cases were included. In this analysis, side (HR 1.55 for RC, p<0.001), ECOG PS (HR 2.63 for ECOG PS ≥ 2, p<0.001), presence of a BRAF mutation (HR 1.97, p<0.001), presence of peritoneal/omental metastases (HR 1.49, p=0.003), resection of the primary tumor (HR 0.60, p<0.001), and resection of metastases (HR 0.27, p<0.001) remained associated with overall survival.

DISCUSSION

Our analysis of data from a metastatic colorectal cancer registry confirms the findings from prior analyses of clinical trial and other data sets: patients with a RC have an inferior progression-free and overall survival compared to those with a LC primary. A large part of this can be attributed to the multiple poor prognostic factors that are associated with RC. We have defined the frequency and impact of each of these prognostic factors in a real-world population and performed, to our knowledge, the first analyses of a dataset that includes all the clinical and molecular factors reported to contribute to primary side-based differences in survival. We have examined patients who received active systemic therapy and those not treated, with similar findings of poorer outcomes for RC in both populations. Notably, patients with a RC still have an inferior prognosis in multivariate analysis (HR 1.55, p<0.001, *Table 3*), indicating that there are as yet undefined drivers of this poor prognosis.

Median overall survival outcomes were substantially different when comparing sides: 19.6 months for RC and 27.5 months for the LC cohort (HR 1.44, p<0.001*, Figure 2A)*. There are consistent differences in survival outcome by primary tumor side in patients who are actively treated (HR 1.52, p<0.001, *Figure 1B*) and those who receive only best supportive care (HR 1.38, p=0.009, *Figure 2B*). The inferior progression-free survival achieved by RC patients receiving first line therapy (HR 1.38, p<0.001, *Figure 1A)* suggests that RC patients may derive less benefit from chemotherapy. Very similar hazard ratios for RC versus LC PFS were observed for patients who did and did not receive bevacizumab (*Supplementary Figures 2A & 3A)*, which is consistent with an earlier analysis of this dataset[14] and with the literature overall.[13, 15, 29] Analysis of side and anti-EGFR therapy impact could not be undertaken due to small patient numbers in these subgroups.

There are many factors associated with a RC and with poor prognosis. These include patient factors such as older age, poor performance status and high Charlson co-morbidity index. Of these, only ECOG PS (HR 2.63, p<0.001) retained statistical significance in multivariate analysis, again highlighting the importance of this prognostic marker in oncology. Of the molecular markers examined, BRAF mutations were significantly associated with RC (9% vs 3% for LC, p<0.001) and with poor outcomes (HR 1.97, p<0.001). Other molecular data were not clearly prognostic, including MMR status, as has been reported by others.[30, 31] There was a trend for more RAS mutations in RC (p=0.02) but RAS mutations were also not prognostic. A limitation of our study however is that molecular data are incomplete for a proportion of patients, and the multivariate analysis could only include 886 of the total 2306 cases, so these analyses might be confounded by unknown biases related to patients selected for testing.

Another significant driver of the poor survival outcomes in RC is the site of metastatic disease, with peritoneal disease being more frequent (30% vs 15%, p<0.001) and associated with poor outcomes (HR 1.49, p=0.003). The only other significant metastatic site association with RC was a lower rate of lung metastases (22% vs 34%, p<0.001) but lung metastases were not significantly associated with overall survival in the multivariate analysis. Clear differences in treatment received were seen, with RC patients less likely to receive any chemotherapy and less likely to receive doublet chemotherapy. While statistically significant the absolute differences were modest (7% and 6% respectively). In univariate analysis first line therapy was a strong predictor of overall survival (HR 0.5, p=0.001), but this was not maintained in a multivariate analysis. There were no significant differences seen in the proportions who received biologic therapy.

There was very limited first line use of EGFR inhibitors in the patient population overall. This reflects the period of patient enrolment, initial limited availability of EGFR inhibitors for first line treatment in Australia, and until recently uncertainty regarding the relative benefit of these agents versus bevacizumab as the first line biologic. We anticipate greater survival differences by tumor side will be observed over time, given the recently observed increased uptake of EGFR targeted therapy in Australia as part of first line therapy for RAS wild type LC.[32]

In future other treatment strategies may be shown to have an impact in this registry cohort. A recent side-based analysis of the TRIBE study indicated that the overall survival benefit for triplet chemotherapy was largely driven by improved outcomes in RC patients.[33] In a combined analysis of first line studies of selective internal radiation therapy for colorectal liver metastases an overall survival benefit was observed in RC but not in LC patients.[34] The use of immunotherapy for mismatch repair deficient tumors is also likely to increase moving forward. All three of these approaches to date have had very limited uptake in our registry population but may impact other side-based analyses where these options are more commonly used.

The strengths of our analysis are the comprehensive data available on a large number of real-world patients, including many patients who are excluded from clinical trials and therefore from side-based analyses of trial cohorts. While recent, large analyses of survival of LC vs RC have included all stages of disease,[3, 4, 16, 18] importantly our dataset focuses on patients who develop metastatic disease. Major factors include age, poor performance status and sites of metastatic disease, notably peritoneal disease. Given the interaction between many factors a comprehensive data set allows a more robust appreciation of the major drivers of poor outcomes, such as BRAF V600E mutations. The proportion of patients with a RC and with a BRAF mutation increases with age, in line with the

marked increase in deficient mismatch repair cancers.[35] This likely explains the relatively high proportions of each in our registry in comparison to analyses of clinical trial populations.

There are several further potential drivers of differences in RC versus LC that we could not examine in our dataset. There are other molecular classifications, not available within the TRACC database, that may have prognostic implications. These includes PIK3CA mutations, consensus molecular subtypes (CMS), and CpG island methylator phenotype (CIMP), which relates to epigenetic silencing with hyper-methylation.[36, 37] At present testing for CMS and CIMP remains outside the scope of routine clinical practice and the precise contribution to RC versus LC outcome differences is yet to be defined. Other side-based differences have been reported, such as differences in bacterial flora[38] but again remain of uncertain prognostic impact. The anatomic definitions of RC and LC that we have utilised here is used extensively in the literature and is clearly a reproducible way to define tumor location, but whether this is the optimal border between right and left or whether the transition from a "RC" to a "LC" is gradual or sudden continues to be debated.[39]

CONCLUSION

Our analysis confirms that patients with mCRC arising from a RC have inferior survival outcomes. This is clearly multifactorial and some poor prognostic features are strongly associated, which does confound analysis of which features are drivers of poor outcome and which may simply be passengers, due to an association with a driver. However, primary tumor side retains a significant association with overall survival in multivariate analysis, indicating that there remain other inherent, as yet undefined differences between RC and LC.

ADDITIONAL INFORMATION

Ethics Approval

Ethics Approval for data access was granted through BioGrid Australia, Project ID 201706/9, Application ID 389. The study was performed in accordance with the Declaration of Helsinki.

Availability of data and material

Data supporting these results can be accessed through the BioGrid database, access@biogrid.org.au.

Conflict of Interest

SM received accommodation funding from Merck. BL is honoraria for Roche and received travel, accommodation and expenses funding from Roche. ML received accommodation and expenses funding from Roche. RW received accommodation and expenses funding from AstraZeneca. JS received accommodation and expenses funding from Amgen and Merck Serono. SS is honoraria and on the speaker's bureau for AstraZeneca and received accommodation and expenses funding from AstraZeneca. LL has an advisory role for Amgen and is honoraria for Bayer. MB has an advisory role with Amgen and Roche, received accommodation and expenses funding from Ipsen and is honoraria for Sirtex Medical, Ipsen, Roche, Amgen, and Merck KGaA. MB has ownership interests in Bristol-Myers Squibb, Pfizer, Gilead Sciences and CSL Limited. KMF received accommodation and expenses funding from Amgen. HW has received research funding from Roche. PG is honoraria for Roche, Amgen, Merck, Sirtex Medical and Servier, and received research funding from Roche, Ventana Medical Systems, Amgen and Merck Serono.

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Author's contributions

Conception and design: SM and PG

Development of methodology: SM, SB and PG

Acquisition of data: SM, SB, BL, ML, RW, SK, JS, DY, SS, LN, RJ, LL, MB, KF, SA, HW and PG

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): SM, SB and PG

Writing, review, and/or revision of the manuscript: SM, SB, BL, ML, RW, SK, JS, DY, SS, LN, RJ, LL, MB, KF, SA, HW and PG

Administrative, technical, or material support: SB

Study supervision: PG

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FIGURE LEGENDS

Figure 1. *Patients receiving any systemic therapy. A) Median Progression-free Survival 8.1 vs 10.8 months, HR 1.38 (95% CI 1.22-1.57, p<0.001). B) Median Overall Survival 21 vs 29.5 months, HR 1.52 (95% CI 1.33-1.73, p<0.001)*

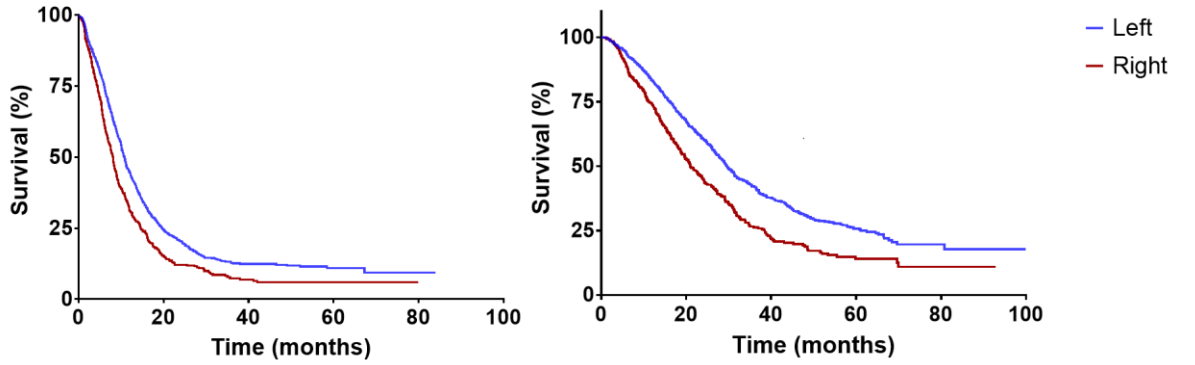

Figure 2: *Overall Survival (OS) A) Across entire cohort. Median OS: 19.6 vs 27.5 months, HR 1.44 (95% CI 1.29-1.62, p<0.001). B) In patients not receiving any systemic therapy. Median OS: 5.9 vs 10.3 months, HR 1.38 (95% CI 1.07-1.79, p=0.009).*

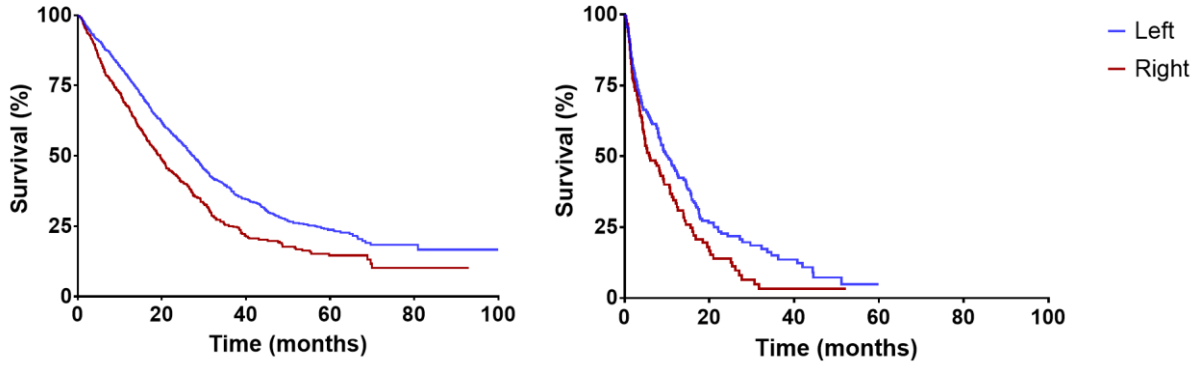

Table 1. Patient and tumor characteristics

Variable*		***Right-sided*** n=747	***Left-sided*** n=1559	***p value***
Primary Tumor Site	Right Colon	747 (100%)	N/A	
	Left Colon	N/A	665 (43%)	
	Rectum	N/A	894 (57%)	
Age (years)	< 50	63 (8%)	212 (14%)	<0.001 (<70 vs ≥ 70)
	50-59	107 (14%)	297 (19%)	
	60-69	170 (23%)	449 (29%)	
	≥70	407 (54%)	601 (39%)	
	Median	71	65	<0.001
	Min	24	18	
	Max	100	98	
Gender	Female	375 (50%)	576 (37%)	<0.001
	Male	372 (50%)	983 (63%)	
ECOG PS	0-1	594 (80%)	1299 (83%)	0.02
	≥2	152 (20%)	255 (16%)	
Charlson Score	0	48 (6%)	144 (9%)	<0.001 (<3 vs ≥ 3)
	1-2	194 (26%)	558 (36%)	
	≥ 3	504 (67%)	851 (55%)	
Tumor Stage at first presentation	LARC	N/A	141 (9%)	
	Stage I	10 (1%)	49 (3%)	0.001
	Stage II	82 (11%)	153 (10%)	
	Stage III	186 (25%)	276 (18%)	
	Stage IV	462 (62%)	918 (59%)	
	Unknown	7 (1%)	22 (1%)	
Mutation Status	KRAS mutated	225 (49%)	444 (43%)	0.02
	KRAS wild type	232 (51%)	600 (57%)	
	KRAS unknown	290	515	
	All-RAS mutated	233 (69%)	477 (62%)	0.02
	All-RAS wild type	105 (31%)	295 (38%)	
	All-RAS unknown	409	787	
	BRAF mutated	67 (22%)	46 (7%)	<0.001
	BRAF wild type	233 (78%)	589 (93%)	
	BRAF unknown	447	924	
Mismatch Repair Status (MMR)	deficient MMR	48 (13%)	24 (4%)	<0.001
	proficient MMR	321 (87%)	655 (96%)	
	MMR unknown	378	880	
CEA	Median	10	15.25	0.002

	(minimum:maximum)	(0.2:16000)	(0.5:67400)	
	Mean (Standard Deviation)	213.680 -1031.07	344.68 -2202.54	
Symptomatic Primary (synchronous metastases cohort)	Yes	273 (37%)	610 (39%)	0.01
Number of Metastatic Sites	1	394 (53%)	858 (55%)	0.35
	2	234 (31%)	468 (30%)	
	3	88 (12%)	188 (12%)	
	≥4	31 (4%)	45 (3%)	
Location of Metastases	Liver	439 (59%)	988 (63%)	0.03
	Lung	165 (22%)	532 (34%)	<0.001
	Peritoneal	222 (30%)	232 (15%)	<0.001
	Bone	19 (3%)	70 (4%)	0.02
	Brain	10 (1%)	16 (1%)	0.51
	Lymph nodes	148 (20%)	264 (17%)	0.09

*Variable measured at diagnosis of mCRC unless otherwise specified
mCRC: metastatic colorectal cancer; LARC: locally advanced rectal cancers

Table 2. Surgical and systemic therapies

Variable		***Right-sided*** (n=747)	***Left-sided*** (n=1559)	***p value***
Primary Tumor Resection	Entire cohort	582 (78%)	1100 (71%)	<0.001
	Metachronous metastases	277 (37%)	593 (38%)	0.001
	Synchronous metastases	298 (40%)	492 (32%)	<0.001
Metastatic disease resection	Entire cohort	207 (28%)	485 (31%)	0.10
	Metachronous metastases	96 (13%)	263 (17%)	0.03
	Synchronous metastases	110 (15%)	218 (14%)	0.97
Prior Adjuvant Chemotherapy	Stage II-III, inc LARC	154 (21%)	365 (23%)	0.07
	Stage II	15 (2%)	44 (3%)	0.08
	Stage III	139 (19%)	215 (14%)	0.43
	LARC*	N/A	106 (7%)	N/A
First Line Chemotherapy	Yes	539 (72%)	1227 (79%)	0.001
	FP alone	124 (17%)	245 (16%)	
	FP & oxaliplatin	309 (41%)	764 (49%)	
	FP & irinotecan	64 (9%)	106 (7%)	
	FP & oxaliplatin & irinotecan	11 (1%)	16 (1%)	
	Other	31 (4%)	95 (6%)	
Additional First Line Therapy	Bevacizumab	327 (44%)	665 (43%)	0.012
	Anti-EGFR therapy	7 (1%)	41 (3%)	0.016
Second Line Chemotherapy	Yes	272 (36%)	641 (41%)	0.49

Inc LARC: including locally advanced rectal cancers; FP: fluoropyrimidine;
EGFR: epidermal growth factor receptor

Table 3. Univariate and multivariate analysis for factors associated with overall survival

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Side (Right)	1.44 (1.29, 1.62)	<0.001	1.55 (1.25, 1.92)	<0.001
Age ≥ 70	1.71 (1.53, 1.91)	<0.001	0.97 (0.73, 1.29)	0.83
Gender (Male)	0.93 (0.83, 1.04)	0.18	-	-
ECOG PS ≥ 2	3.88 (3.41, 4.24)	<0.001	2.63 (1.93, 3.57)	<0.001
Charlson Score ≥ 3	1.32 (1.20, 1.44)	<0.001	1.21 (0.92, 1.58)	0.17
KRAS mutated	1.02 (0.89, 1.17)	0.75	-	-
BRAF mutated	2.42 (1.89, 3.12)	<0.001	1.97 (1.51, 2.59)	<0.001
Deficient Mismatch Repair Status	1.04 (0.73, 1.48)	0.84	-	-
Synchronous Metastases	1.49 (1.33,1.68)	<0.001	0.96 (0.76,1.22)	0.76
Lung Metastases	1.06 (0.95, 1.20)	0.31	-	-
Liver Metastases	1.12 (1.00, 1.26)	0.047	1.31 (1.04, 1.64)	0.02
Peritoneal/Omental Metastases	1.65 (1.46, 1.88)	<0.001	1.49 (1.14,1.95)	0.003
Number of metastatic sites	1.36 (1.30, 1.47)	<0.001	1.03 (0.91, 1.16)	0.67
Primary tumour resected	0.40 (0.36, 0.46)	<0.001	0.60 (0.47, 0.77)	<0.001
Metastatic disease resected	0.22 (0.19, 0.25)	<0.001	0.27 (0.21, 0.35)	<0.001
1st Line Chemotherapy	0.50 (0.44, 0.57)	<0.001	0.83 (0.59, 1.19)	0.31
2nd Line Chemotherapy	0.91 (0.81, 1.01)	0.08	-	-

HR: Hazard Ratio; CI: confidence interval