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Association of Genomic Profiles and Survival in Early-Onset and Screening-Age Colorectal Cancer Patients with Liver Metastases Resected Over 15 Years

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Abstract

Background: This study explores whether genomic profiles of colorectal liver metastasis (CRLM) patients with early-onset (EO, <50-years-old) and screening age (SA) primary diagnosis are associated with overall survival (OS).

Methods: All patients undergoing hepatectomy between 2002–2017 were identified and tumor specimens with next-generation sequencing data were catalogued. Gene and signaling-level alterations were checked for association with OS from primary diagnosis accommodating for left-truncated survival.

Results: Of 1822 patients, 333 were sequenced—127 (38%) EO-CRLM and 206 (62%) SA-CRLM patients. More aggressive features presented in EO-CRLM patients—synchronous metastatic presentation (83% vs 75%, $p < 0.001$) and primary node-positive disease (71% vs 61%, $p < 0.001$). The median OS from primary diagnosis was 11.8 years (95% CI=7.94-NA). Five-year OS did not differ by age ($p = 0.702$). On multivariable analysis, altered *APC*[EO-CRLM:(HR=0.37, $p = 0.018$) vs SA-CRLM:(HR=0.61, $p = 0.260$)], *BRAF*[EO-CRLM:(HR=4.38, $p = 0.007$) vs SA-CRLM:(HR=4.78, $p = 0.032$)], and *RAS-TP53*[EO-CRLM:(HR=2.82, $p = 0.011$) vs SA-CRLM:(HR=2.35, $p = 0.003$)] associated with OS.

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Conclusions: Despite bearing more aggressive features, EO-CRLM patients had similar genomic profiles and survival as SA-CRLM patients. Better performance status in younger patients leading to increased treatment tolerance may partly explain this. As screening and treatment strategies from older patients are applied to younger patients, genomic predictors of biology identified historically in older cohorts could apply to early-onset patients.

Keywords

Colorectal neoplasms; hepatectomy; cancer genes; precision medicine; cancer biomarker

INTRODUCTION

The incidence and mortality from colorectal cancer are rising among patients diagnosed before the screening age of 50-years-old.¹ At presentation, younger patients more commonly have colorectal liver metastases (CRLM) due to delayed detection from the lack of screening.² In response, the American Cancer Society recently updated their guidelines to recommend beginning colonoscopy screening at 45-years-old for average risk adults.³ In support of this change are multiple reports indicating that younger patients with colorectal cancer have more aggressive features on presentation relative to older patients such as advanced primary tumor T-stage, more frequent node-positive specimens, and higher grade disease.^{2,4,5}

Despite bearing more aggressive features at diagnosis, younger patients do not have significantly different overall survival compared to their older counterparts.^{2,6} Comparable outcomes in younger patients despite delayed diagnosis could reflect more indolent biology or increased feasibility for aggressive interventions in this cohort. Expanding beyond traditional clinical profiles of colorectal cancer tumor biology, growing interest in novel genomic profiles are beginning to guide selection of therapies. For example, patients with tumors bearing *KRAS* alteration resist epidermal growth factor receptor inhibitors and CRLM patients with *BRAF*-altered tumors have poor prognosis with some exceptions.⁷⁻⁹ A recent report on genomic differences between colorectal cancer patients below 40-years-old and above 50-years-old found few genomic differences but did not explore overall survival based on detected alterations.¹⁰

Little is known regarding the genomic profiles of CRLM tumors of younger patients and their clinical correlates. The aim of this study is to determine whether unique genomic profiles predict survival for early-onset (EO) compared to screening-age (SA) CRLM patients.

METHODS

Patient Selection

All patients with CRLM undergoing resection by the Hepatopancreatobiliary service with a primary colorectal tumor diagnosis between January 2002 and October 2017 were identified from a prospectively maintained hepatectomy database. Any patients that died or were lost to follow up within 30 days of their operation were excluded. Race and ethnicity data

were not recorded into this database during the study period. Recorded data regarding clinicopathologic characteristics, surgical history, and follow up were retrieved. The clinical risk score (CRS) was defined as a composite of points added for a node-positive primary colorectal tumor, preoperative carcinoembryonic antigen (CEA) > 200 ng/mL, largest CRLM > 5 cm, multifocal disease, and disease-free interval from primary colon tumor diagnosis to liver metastasis detection < 12 months.¹¹ High CRS was defined as a score of 3 or higher. Primary tumors originating in the right colon were detected from the proximal cecum to the distal transverse colon and left colon tumors occurred anywhere from the splenic flexure to the distal sigmoid colon. Tumors arising in the rectosigmoid junction or distally were considered rectal. Preoperative chemotherapy was considered treatment with any local or systemic agent within 6 months before planned hepatectomy. Adjuvant chemotherapy was considered any local or systemic agent started within 6 months postoperatively without evidence for recurrent disease. This study was approved by the Institutional Review Board. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Genomic Analysis

A subset of sequenced patients was identified from the larger clinical cohort excluding those with microsatellite instability, POLE mutations, or low tumor purity. When sequencing data from both the primary colorectal and CRLM tumor were available, the former was used given its proximity to the date of primary diagnosis. Genomic profiles of CRLM tumors were considered eligible for inclusion based on prior work noting high genomic concordance between matched primary and CRLM lesions, but not extrahepatic tumors.^{12,13} Patients with only extrahepatic specimens sequenced were thus excluded. Paired DNA from tumor specimens and matching normal tissue were reviewed by pathologists experienced in colorectal tumor and CRLM diagnosis, grading, and staging. These specimens underwent targeted next-generation sequencing using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay - a platform designed to identify point mutations, copy number alterations, and select gene fusions in 341 to 468 cancer-associated genes.¹⁴ Mutational burden was adjusted by megabase (mB) per IMPACT panel size based on precedent from prior work.¹⁵ Sequenced genomic data was stored for analysis on a secure server for large-scale cancer genomics data (cBioPortal for Cancer Genomics).¹⁶ Actionable genetic alterations were defined by the OncoKb database as somatic alterations conferring some heightened response or resistance to therapy relative to the wild-type configuration.¹⁷ In addition to signaling-level pathways, select genomic targets previously reported to be associated with oncologic outcomes such as amplification of 20q genes (*BCL2L1*, *DNMT3B*, *SRC*) and co-altered RAS-*TP53* were investigated.^{18–22}

Statistical Analysis

All patients with a primary colorectal tumor diagnosis before 50-years-old were considered EO; those diagnosed at 50-years-old or later were considered SA. Clinicopathologic characteristics of all patients were summarized using descriptive statistics and compared using Chi-square tests for categorical and Wilcoxon Rank-sum tests for the continuous variables between EO-CRLM and SA-CRLM patients. Genes altered in at least 3% of

the IMPACT sequencing data and known to be associated with oncologic outcomes were included for analysis.

Given recent changes to colorectal cancer screening guidelines³ and the homology of mutations identified from analysis of primary and liver metastasis specimens^{12,13}, overall survival (OS) was estimated from the date of primary diagnosis (as opposed to CRLM diagnosis) until the date of death or last follow up using Kaplan-Meier (KM) methods. Those alive at last follow up were censored at the date of last follow-up. Given that the risk of death began following hepatectomy and no deaths were observed during the interval between primary tumor and CRLM diagnoses, the numbers at risk from the time of primary tumor diagnosis under the survival curves were not provided. In addition, survival methodologies accommodating for the left-truncation data and different entry times into the risk set were applied.^{23,24} Cox proportional hazards models accounting for the left-truncated entry time were employed to study the association of clinical and genomic characteristics on OS. A Cox model was constructed for each gene with alterations associated with OS by including gene indicator, age-group, and an interaction term for both genomic alteration and age-group. Each of the models were further adjusted for CRS since this has been previously established as a potential confounder in this disease group.¹¹ Multiplicity testing correction was used to adjust the p-values. Two-sided p-values less than 0.05 were considered statistically significant. All analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) or SAS 9.3 (The SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics of All Resected and Sequenced CRLM Patients

Of 1822 CRLM patients, 1252 (68.7%) had a primary diagnosis at or after the SA and 570 (31.3%) were EO. In the EO-CRLM subgroup, 32 (5.6%) patients were 30-years-old or younger at diagnosis, 146 (25.6%) between 40 to 45-years-old, and 244 (42.8%) were 45 to 49-years-old. The EO-CRLM subgroup had notably more aggressive disease with more node-positive primary specimens (71% vs 61%, $p<0.001$), synchronous metastatic presentation (83% vs 75%, $p<0.001$), high CRS disease (51% vs 38%, $p<0.001$), preoperative systemic (75% vs 65%, $p<0.001$) and hepatic artery infusion (HAI) chemotherapy exposure (5% vs 2%, $p<0.001$), as well as shorter median time from primary tumor diagnosis to hepatectomy (35 vs 43 weeks, $p<0.001$), as noted in Table 1. Similar, but fewer significant differences were noted between the EO-CRLM and SA-CRLM subgroups in the subset of 333 sequenced CRLM patients as shown in Table 2.

Survival of All Resected and Sequenced CRLM Patients

The median follow up for all surviving patients ($n=928$) was 5.1 years (range=0.2–16.7). The median OS was 5.8 years (95%CI=5.5–6.2) and the 5-year OS was 55.9% (95%CI=53.3–58.7). No significant difference in OS was noted between the EO-CRLM and SA-CRLM subgroups (Figure 1A).

The median follow up after primary diagnosis among sequenced survivors was 3.8 years (range=0.5–15.8) and the median OS was 11.8 years (95%CI=7.94–NA). The 5-year OS was 71.6% (95%CI=65.2–78.6%). Again, no significant difference in OS was found when stratifying patients by age at primary diagnosis (Figure 1B).

Genomic Profiles and Associations with Survival in Resected CRLM Patients

The most commonly altered genes were *APC* (n=283/333, 85%), *TP53* (n=267/333, 80%), *KRAS* (n=141/333, 42%), and *PIK3CA* (n=56/333, 17%, Figure 2). The most commonly altered signaling-level pathways were Wnt (n=291/333, 87%), p53 (n=273/333, 82%), RTK/RAS (n=211/333, 63%), RAS (n=154/333, 46%), and PI3K (n=86/333, 26%). No single gene or pathway alteration was enriched in either age group. Alterations in *APC* (p=0.029), *KRAS* (p=0.033), *BRAF* (p<0.001), *SMAD4* (p=0.026), *BCL2L1* (p=0.039), *DNMT3B* (p=0.049), and RAS-*TP53* co-alteration (p<0.001) were significantly associated with OS in the sequenced subset (Supplemental Figure 1).

Risk Factors Associated with Survival After Resection in CRLM Patients

On univariate analysis, the association between clinical and genetic factors with survival was significant for high CRS (HR=1.62, 95%CI=1.01–2.62, p=0.047), as well as alterations in *APC* (HR=0.51, 95%CI=0.29–0.88, p=0.015), *BRAF* (HR=4.21 95%CI=1.80–9.88, p=0.001), *KRAS* (HR=1.62, 95%CI=1.03–2.54, p=0.037), *SMAD4* (HR=1.87, 95%CI=1.07–3.25, p=0.027), and RAS-*TP53* co-alteration (HR=2.24, 95%CI=1.42–3.53, p<0.001). A significant association between age at primary diagnosis and OS was not detected.

Interaction models for mortality were constructed between altered genes and age at primary diagnosis adjusting for CRS (Figure 3). Similar magnitudes and directions for mortality were detected for EO-CRLM and SA-CRLM patients with altered *BRAF* (HR=4.32, 95%CI=1.46–12.77, p=0.008 and HR=4.80, 95%CI=1.14–20.17, p=0.032, respectively) and co-altered RAS-*TP53* (HR=2.76, 95%CI=1.24–6.16, p=0.013 and HR=2.36, 95%CI=1.32–4.21, p=0.004, respectively). Similar directions but different magnitudes for mortality were detected when EO-CRLM patients were altered compared to SA-CRLM patients at *APC* (HR=0.37, 95%CI=0.16–0.85, p=0.018 vs HR=0.61, 95%CI=0.26–1.45, p=0.264), *PIK3CA* (HR=3.06, 95%CI=1.34–6.98, p=0.008 vs HR=1.15, 95%CI=0.51–2.58, p=0.731), and *SMAD4* (HR=2.82, 95%CI=1.12–7.10, p=0.028 vs HR=1.64, 95%CI=0.79–3.42, p=0.184). No significant interaction was detected between age subgroup and the alterations. High CRS was independently associated with increased mortality in the presence of altered *KRAS* (HR=1.63, 95%CI=1.00–2.64, p=0.048), *BRAF* (HR=1.66, 95%CI=1.03–2.70, p=0.039), *PIK3CA* (HR=1.70, 95%CI=1.05–2.76, p=0.031), *SMAD4* (HR=1.68, 95%CI=1.04–2.74, p=0.035), and co-altered RAS-*TP53* (HR=1.72, 95%CI=1.06–2.80, p=0.029).

DISCUSSION

With the incidence and mortality from colorectal cancer rising among younger patients,¹ new discriminatory biomarkers for aggressive disease are needed to further investigate this phenomenon and guide therapeutic interventions. Despite the growing understanding of

genomic correlates for tumor biology, it remains unclear if findings from sequencing studies conducted in historically older cohorts can be applied to younger patients. This report explored differences in the clinical and genomic profiles of resectable CRLM patients with primary diagnosis at EO or SA as well as their associations with OS.

Although significant differences in clinical features were noted between EO-CRLM and SA-CRLM patients, no significant difference in survival was detected. Additionally, tumor alterations did not vary between these age groups possibly suggesting that presentation of EO-CRLM patients with more aggressive disease could be due to delayed diagnosis rather than a predilection for more hostile genomic profiles. Interestingly, the magnitude of risk for mortality with altered *APC*, *PIK3CA*, and *SMAD4* differed between the EO-CRLM and SA-CRLM subgroups.

The presentation of EO-CRLM patients with more aggressive clinical features recapitulates earlier work noting more aggressive clinical characteristics in CRLM patients diagnosed at a younger age.² Therapeutic factors may also have contributed to more aggressive malignant degeneration. Preoperative chemotherapy exposure was more common in the EO-CRLM subgroup and has been associated with more aggressive genomic profiles.²⁵ Additionally, HAI chemotherapy given at all sequences (preoperative, adjuvant, salvage) was more common in the EO-CRLM subgroup likely reflecting the pursuit of more aggressive interventions in younger patients with higher volume disease.

Despite having different clinical features, a significant difference in OS was not observed between EO-CRLM and SA-CRLM patients. Most earlier reports found no significant difference in OS between younger and older colorectal cancer patients.^{2,6,26} The lack of a survival difference despite more aggressive disease presenting in EO-CRLM patients could be related to better performance status in this cohort or better tolerance for more aggressive systemic regimens and surgical interventions.^{4,27} Studies identifying survival differences by age dichotomized their cohorts to compare SA-CRLM patients with younger groups than reported herein. Lieu et al noted a parabolic relationship with risk for mortality where the youngest (under 20-years-old) and oldest (over 80-years-old) metastatic colorectal cancer patients had the worst outcomes.²⁶ Of note, age lost its association with OS in that study when the cohort was adjusted for metastatic site. Sultan et al reported outcomes for a 30-year cohort from the Surveillance, Epidemiology, and End Results (SEER) database noting diminished 5-year survival for colorectal cancer patients diagnosed under 20-years-old relative to older patients.²⁸ Khan et al similarly reported that colorectal cancer patients under 30-years-old undergoing resection had lower 5-year disease-specific survival compared to a cohort undergoing resection over 50-years-old.²⁹ While it is possible that the tumor biology of colorectal cancer specimens obtained from very young adults differs from those obtained from older EO-CRLM patients, this report was underpowered to detect this as only 32 patients of the overall clinical cohort were less than 30-years-old.

The genomic profile of the sequenced cohort resembles that of prior study cohorts of resectable CRLM patients reporting, for example, *TP53* and *KRAS* altered in 55–100%, and 34–62%, respectively.^{30–34} This predictable pattern of genomic alterations highlights the feasibility of using novel non-invasive methods developed in older cohorts, such as

circulating tumor cells or circulating DNA, in screening or surveillance strategies for high-risk EO-CRLM patients.^{35,36}

Despite EO-CRLM and SA-CRLM cohorts bearing similar genomic profiles, the impact of altered genes on OS varied. Notably, altered *SMAD4* and *PIK3CA* were associated with significantly greater risk for all-cause mortality on multivariate analyses in the EO-CRLM subgroup only. Earlier work concurs that *SMAD4* alteration is associated with worse OS in resectable CRLM patients.^{37,38} Altered *PIK3CA* was previously reported to have no association with survival,^{39,40} however, Yamashita et al noted an association between co-altered *APC-PIK3CA* and worse OS in resectable CRLM patients after chemotherapy exposure.⁴¹ In this study, altered *APC* alone was associated with increased risk for improved OS in the EO-CRLM group after accounting for CRS. A report from Jorissen et al revealed similar results, with wild-type *APC* associated with worse OS in patients with microsatellite stable primary tumors.⁴² An association between *APC* alteration and OS in CRLM patients, however, has not been previously reported.

Altered *BRAF* and co-altered RAS-*TP53* were associated with worse OS with a higher mortality hazard magnitude in both subgroups, recapitulating earlier work in CRLM patients.^{8,33,43} Co-altered RAS-*TP53* has been noted to be enriched in unresectable CRLM cohorts,⁴⁴ however, data describing outcomes for patients with co-alteration in otherwise low-risk, resectable disease is lacking. Published preclinical work supports a mechanism for interplay between loss-of-function p53 alteration and RAS activation in colorectal cancer.¹⁸ Additionally, altered *TP53* correlates negatively with cytolytic immune cell activity contributing to worse OS.¹⁹ Furthermore, altered *KRAS* was associated with significantly greater risk for worse OS in the SA-CRLM group but not the EO-CRLM group. Altered *KRAS* has been associated with worse outcomes in earlier work,^{45,46} however, select strategies (e.g. HAI chemotherapy) have been shown to result in better survival regardless of *KRAS* status.⁴⁷ Although multiple gene alterations were associated with OS in one age group and not the other, lack of a significant interaction between these genes and age as a covariate suggests that the impact on OS may not depend on age at primary diagnosis. Instead, other characteristics of patients in these age groups may be related to how tumor alterations impact survival. Future work investigating the interaction between tumor alterations and age-specific factors is necessary to clarify this.

Limitations

Several limitations to this study merit mention. First, the retrospective nature of this study introduces limitations inherent to this design including the selection bias of analyzing genomic data from patients chosen by their oncologists for next generation sequencing. For instance, although no significant difference in OS was detected between the EO-CRLM and SA-CRLM subgroups in the clinical and sequenced cohorts, several clinicopathologic differences were noted between these subgroups in the clinical cohort and fewer differences in the sequenced subset. The EO-CRLM subgroup had more aggressive features than the SA-CRLM patients in the clinical cohort and the sequenced EO-CRLM subgroup had relatively fewer differences compared to the sequenced SA-CRLM patients, suggesting that SA-CRLM patients with higher risk disease underwent sequencing. Conversely, this

change could represent removal of the fraction of EO-CRLM patients with microsatellite instability or POLE mutations that are associated with more aggressive tumor biology. Although multivariable analyses were performed to adjust for clinical and genomic selection differences, the presence of a significant relationship with a genomic profile and OS in one age subgroup and not the other should not be interpreted as an absence of association in the latter. This study was not powered to determine this. Second, use of next generation sequencing of tumor specimens, as utilized in this study, may not offer the optimal representation of genomic aberrations for metastatic disease. New interest in using circulating tumor cells or circulating DNA as a liquid biopsy is quickly becoming a competitive option to detect mutations.⁴⁸ Although there is strong concordance between alterations found in resected primary colon and CRLM tumors,^{12,13} some alterations (e.g. *TP53*⁴⁹) are more commonly found in metastatic CRLM tumors.

CONCLUSIONS

Although the incidence and mortality of colorectal cancer are rising in younger patients that present with more aggressive clinical characteristics, differences in genomic profiles or survival were not detected. Notably, differences in the impact of tumor alterations on survival were found to vary between age groups, however, the mechanism for this difference needs further clarification. As screening and treatment strategies from older patients are applied to younger patients, genomic predictors of biology identified historically in older cohorts could apply to early-onset patients as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SYNOPSIS

The incidence and mortality from colorectal cancer are rising among patients younger than the screening age of 50-years-old. Novel age-related genomic signatures among resected colorectal liver metastasis patients may have implications toward therapeutic decision making and are explored herein.

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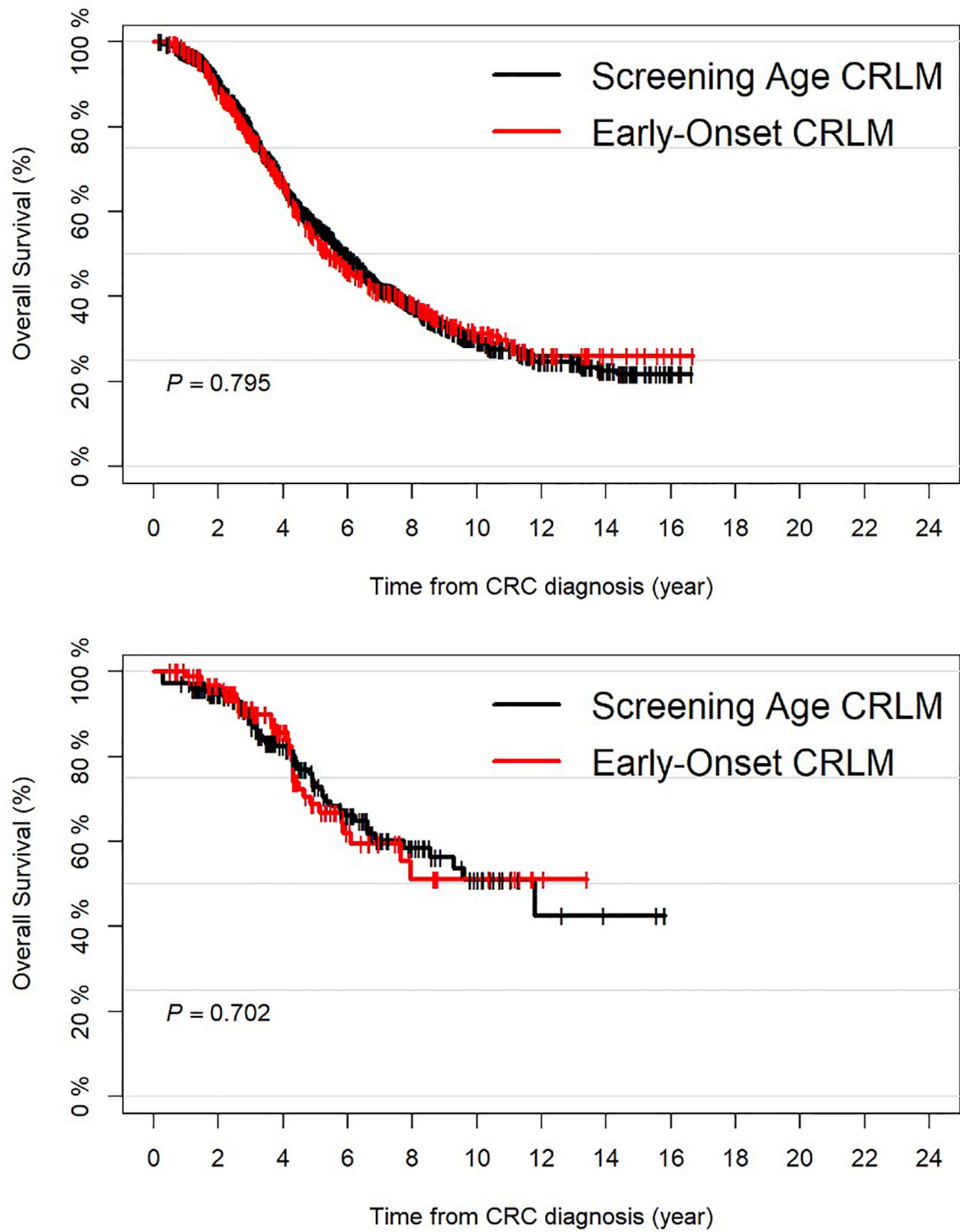


Figure 1.

A: Overall Survival for all Resected Colorectal Liver Metastasis (CRLM) Patients, Stratified by Age at Primary Colorectal Tumor Diagnosis; **B:** Overall Survival for all Sequenced and Resected Colorectal Liver Metastasis (CRLM) Patients, Stratified by Age at Primary Colorectal Tumor Diagnosis.

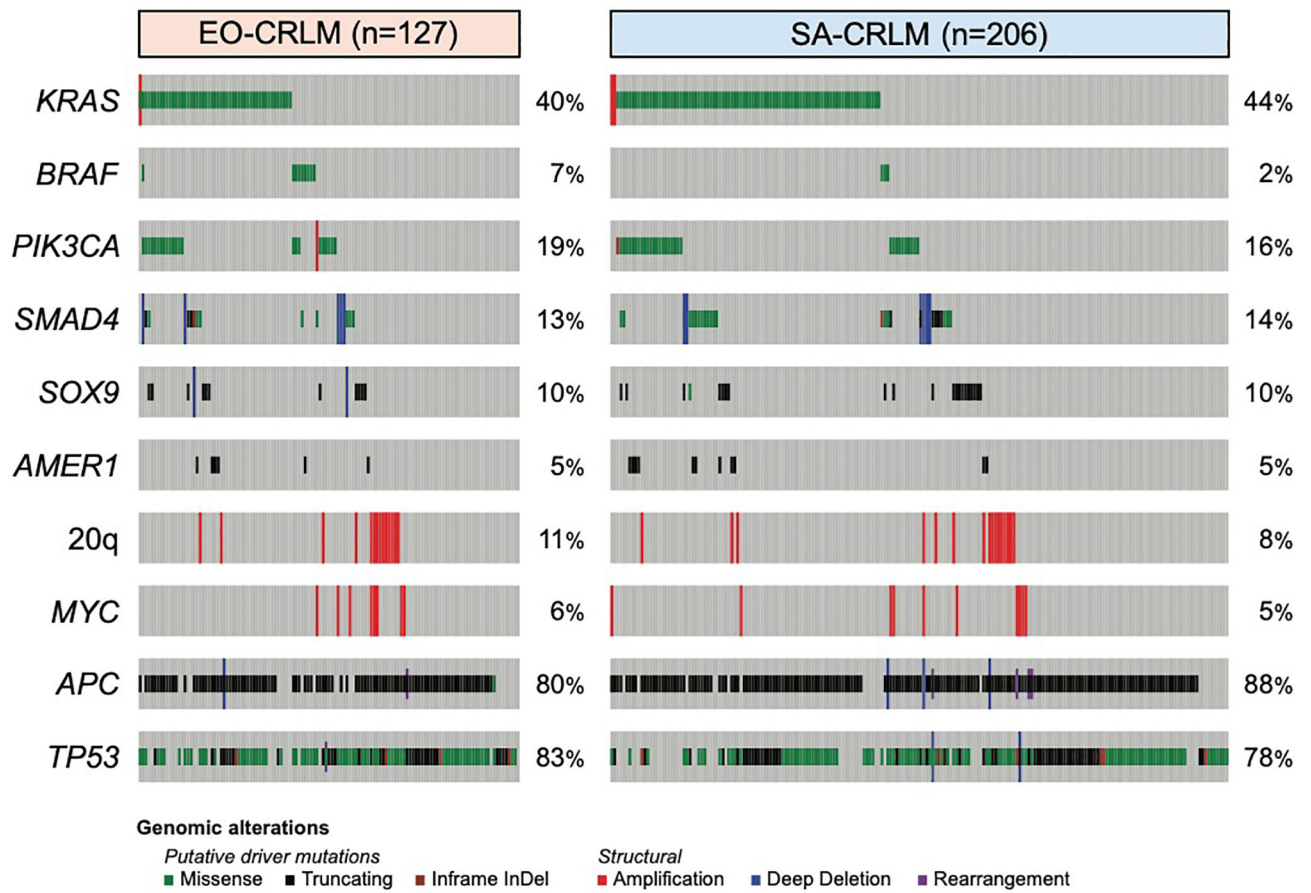


Figure 2: Heatmap of Sequenced and Resected Colorectal Liver Metastasis Patients Stratified by Age at Primary Colorectal Tumor Diagnosis. 20q alterations include mutations in *BCL2L1*, *DNMT3B*, and *SRC*.

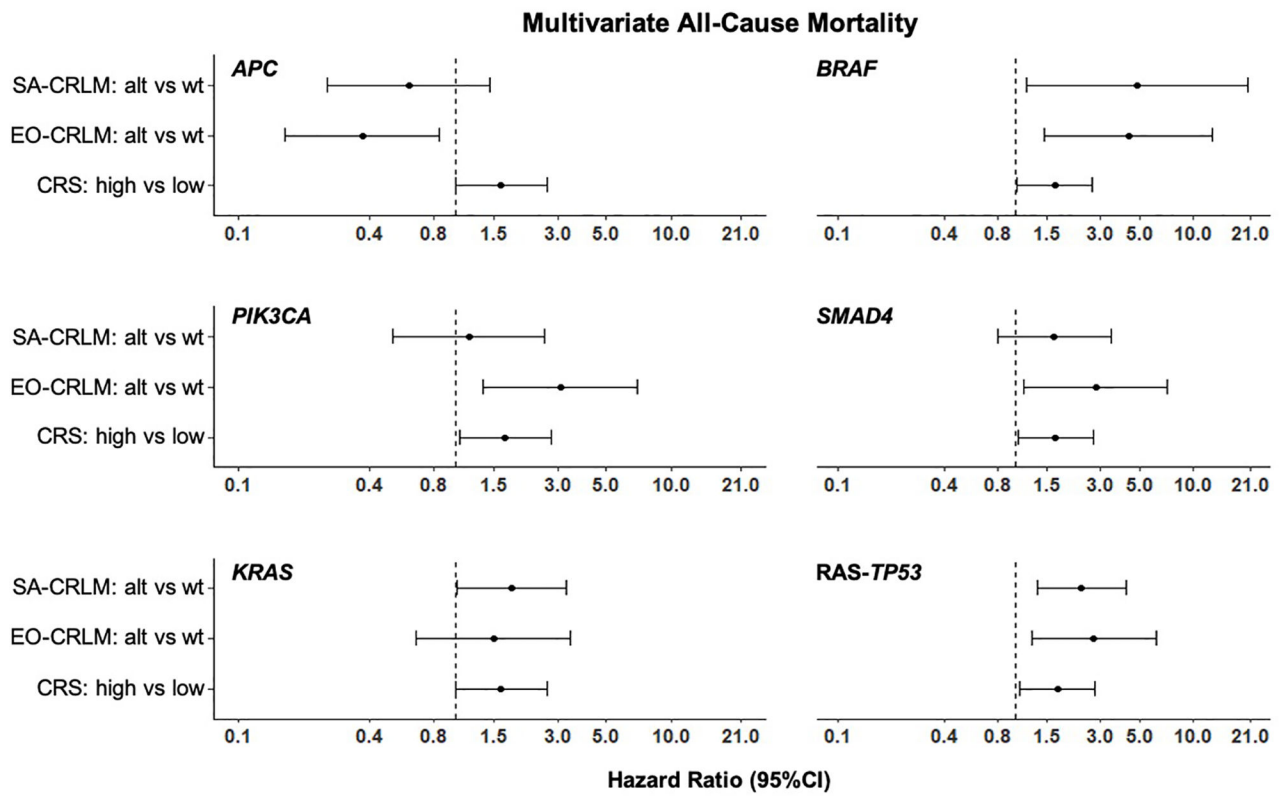


Figure 3: Forest Plots of Multivariable Survival Models. Each panel represents a multivariable regression model with genetic alteration, age (SA-CRLM vs EO-CRLM), interaction between genetic alteration/age, and CRS. SA=Screening Age, EO=Early-Onset, CRLM=Colorectal liver metastasis, CRS=Clinical risk score, alt=alteration, wt=wild-type.

Table 1:

Clinicopathologic characteristics of all resected colorectal liver metastasis (CRLM) patients, stratified by age at primary colorectal tumor diagnosis.

		All patients	Early-Onset	Screening Age	p-value
Number of patients		1822	570 (31.3)	1252 (68.7)	
Age at Diagnosis, years	Median (range)	57 (18, 90)	44 (18, 49)	62 (50, 90)	
Gender	Male	1008 (55.3)	306 (53.7)	702 (56.1)	0.400
	Female	814 (44.7)	264 (46.3)	550 (43.9)	
Primary Tumor Location	Right Colon	517 (28.4)	118 (20.7)	399 (31.9)	<0.001
	Left Colon	700 (38.4)	228 (40.0)	472 (37.7)	
	Rectum	597 (32.8)	223 (39.1)	374 (29.9)	
	Multifocal	6 (0.3)	1 (0.2)	5 (0.4)	
	Colon, NOS	2 (0.1)	0 (0.0)	2 (0.2)	
Primary Pathologic Nodal Status	N0	636 (34.9)	161 (28.2)	475 (37.9)	<0.001
	N+	1170 (64.2)	405 (71.1)	765 (61.1)	
	Unknown	16 (0.9)	4 (0.7)	12 (1.0)	
Disease Free Interval	< 12 months	1413 (77.6)	474 (83.2)	939 (75.0)	<0.001
	12 months	331 (18.2)	72 (12.6)	259 (20.7)	
	Unknown	78 (4.3)	24 (4.2)	54 (4.3)	
Preoperative CEA	< 200 ng/mL	1535 (84.2)	476 (83.5)	1059 (84.6)	0.058
	200 ng/mL	101 (5.5)	41 (7.2)	60 (4.8)	
	Unknown	186 (10.2)	53 (9.3)	133 (10.6)	
Largest CRLM Size	< 5 cm	1398 (76.6)	443 (77.5)	955 (76.1)	0.300
	5 cm	357 (19.8)	103 (18.2)	254 (20.4)	
	Unknown	67 (3.7)	24 (4.2)	43 (3.4)	
Number of CRLM	Solitary	606 (33.2)	156 (27.2)	450 (35.9)	<0.001
	Multifocal	1144 (62.8)	390 (68.6)	754 (60.2)	
	Unknown	72 (4.0)	24 (4.2)	48 (3.8)	
Clinical Risk Score (CRS)	Low Risk (0–2)	811 (44.5)	205 (36.0)	606 (48.4)	<0.001
	High Risk (3–5)	763 (41.9)	290 (50.9)	473 (37.8)	
	Unknown	248 (13.6)	75 (13.2)	173 (13.8)	
Preoperative Chemotherapy	Yes	1243 (68.2)	425 (74.6)	818 (65.3)	<0.001
	No	579 (31.8)	145 (25.4)	434 (34.7)	
Hepatic Artery Infusion Chemotherapy	None	995 (54.6)	246 (43.2)	749 (59.8)	<0.001
	Preoperative	61 (3.3)	31 (5.4)	30 (2.4)	
	Adjuvant	678 (37.2)	258 (45.3)	420 (33.5)	

		All patients	Early-Onset	Screening Age	p-value
	Salvage	88 (4.8)	35 (6.1)	53 (4.2)	
Time from Primary Diagnosis to Resection, weeks	Median (range)	40 (23, 82)	35 (20, 69)	43 (24, 90)	<0.001
Extent of Hepatectomy	Minor	1139 (62.5)	356 (62.5)	783 (62.5)	>0.900
	Major	683 (37.5)	214 (37.5)	469 (37.5)	
Ablation at Hepatectomy	Yes	337 (18.5)	107 (18.8)	230 (18.4)	0.900
	No	1485 (81.5)	463 (81.2)	1022 (81.6)	

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Table 2:

Clinicopathologic characteristics of sequenced resected colorectal liver metastasis (CRLM) patients, stratified by age at primary colorectal tumor diagnosis.

		All patients	Early-Onset	Screening Age	p-value
Number of patients		333	127 (38.1)	206 (61.9)	
Age at Diagnosis, years	Median (range)	54 (23, 84)	45 (23, 49)	60 (50, 84)	
Gender	Male	176 (52.9)	65 (51.2)	111 (53.9)	0.700
	Female	157 (47.1)	62 (48.8)	95 (46.1)	
Primary Tumor Location	Right Colon	80 (24.0)	28 (22.0)	52 (25.2)	0.700
	Left Colon	142 (42.6)	56 (44.1)	86 (41.7)	
	Rectum	104 (31.2)	42 (33.1)	62 (30.1)	
	Multifocal	6 (1.8)	1 (0.8)	5 (2.4)	
	Colon, NOS	1 (0.3)	0 (0)	1 (0.5)	
Primary Pathologic Nodal Status	N0	100 (30.0)	27 (21.3)	73 (35.4)	0.008
	N+	232 (69.7)	100 (78.7)	132 (64.1)	
	Unknown	1 (0.3)	0 (0)	1 (0.5)	
Disease Free Interval	< 12 months	266 (79.9)	106 (83.5)	160 (77.7)	0.300
	12 months	67 (20.1)	21 (16.5)	46 (22.3)	
Preoperative CEA	< 200 ng/mL	290 (87.1)	109 (85.8)	183 (88.8)	0.200
	200 ng/mL	28 (8.4)	14 (11.0)	14 (6.8)	
	Unknown	15 (4.5)	6 (4.2)	9 (4.4)	
Largest CRLM Size	< 5 cm	269 (80.8)	104 (81.9)	165 (80.1)	0.800
	5 cm	64 (19.2)	23 (18.1)	41 (19.9)	
Number of CRLM	Solitary	85 (25.5)	30 (23.6)	55 (26.7)	>0.900
	Multifocal	248 (74.5)	97 (76.4)	151 (73.3)	
Clinical Risk Score (CRS)	Low Risk (0–2)	146 (43.8)	43 (33.9)	103 (50.0)	0.005
	High Risk (3–5)	171 (51.4)	78 (61.4)	93 (45.1)	
	Unknown	16 (4.8)	6 (4.7)	10 (4.9)	
Preoperative Chemotherapy	Yes	216 (64.9)	85 (66.9)	131 (63.6)	0.600
	No	117 (35.1)	42 (33.1)	75 (36.4)	
Hepatic Artery Infusion Chemotherapy	None	76 (22.8)	16 (12.6)	60 (29.1)	<0.001
	Preoperative	0 (0)	0 (0)	0 (0)	
	Adjuvant	220 (66.1)	100 (78.7)	120 (58.3)	
	Salvage	37 (11.1)	11 (8.7)	26 (12.6)	
Time from Primary Diagnosis to Resection, weeks	Median (range)	32 (17, 69)	26 (16, 57)	35 (18, 75)	0.024

		All patients	Early-Onset	Screening Age	p-value
Extent of Hepatectomy	Minor	237 (71.2)	88 (69.3)	149 (72.3)	0.600
	Major	96 (28.8)	39 (30.7)	57 (27.7)	
Ablation at Hepatectomy	Yes	75 (22.5)	28 (22.0)	47 (22.8)	>0.900
	No	258 (77.5)	99 (78.0)	159 (77.2)	

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