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ORIGINAL ARTICLE

Distinct molecular and clinical aggressiveness in very early-onset metastatic colorectal cancer: survival and genomic divergence between patients aged 30-39 versus 40-49 years

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Background: Early-onset colorectal cancer (EOCRC) is increasing worldwide and exhibits clinical heterogeneity. Patients younger than 40 years may constitute a biologically distinct subgroup within EOCRC. We investigated whether ‘very early-onset’ metastatic colorectal cancer (VEOCRC, ages 30-39) exhibits specific clinical and genomic features compared with EOCRC in patients aged 40-49 and whether these differences lead to variations in survival from the time of metastatic diagnosis.

Materials and methods: We analysed the data of metastatic EOCRC patients in a multi-institutional database, divided into two predefined age groups: 30-39 years and 40-49 years. Overall survival (OS) from metastatic diagnosis was estimated using Kaplan—Meier methods, and hazard ratios (HRs) were calculated with Cox regression. Comprehensive genomic profiling was carried out using the Foundation Medicine next-generation sequencing platform (FoundationOne®). Key molecular alterations were compared using odds ratios (ORs). Baseline clinicopathologic characteristics were assessed using χ^2 or two-sided Fisher’s exact tests.

Results: A total of 264 patients were included (aged 30-39: $n = 65$; aged 40-49: $n = 199$). Median OS was shorter in patients aged 30-39 years than in those aged 40-49 years (30.0 versus 38.0 months; log-rank $P = 0.0269$; HR 0.67). A distinct genomic profile appeared in patients with VEOCRC, characterised by higher *KRAS* mutation rates (55.4% versus 42.0%; OR 1.71; one-sided $P = 0.041$) and fewer *APC* alterations (69.2% versus 82.0%; one-sided $P = 0.024$). *NRAS*, *BRAF*, *PTEN*, and *POLE* alterations were directionally consistent with a more aggressive biology, although event counts were limited. Clinically, overall Eastern Cooperative Oncology Group performance status (ECOG PS) distribution was similar (χ^2 $P = 0.099$), but ECOG PS 0 was more common in VEOCRC (89.1% versus 76.8%; $P = 0.0468$). Peritoneal metastases occurred significantly more frequently in patients aged 30-39 (32.3% versus 19.6%; $P = 0.041$). No differences were observed regarding liver, lung, or nodal involvement.

Conclusions: Patients aged 30-39 years constitute a biologically distinct subgroup within EOCRC, with shorter survival, *KRAS* mutation enrichment, fewer *APC* alterations, and increased peritoneal involvement. These findings support the emerging idea of an ‘ultra-young’, genomically driven CRC subtype, with implications for disease biology, risk assessment, and treatment development.

Key words: early-onset colorectal cancer, metastatic colorectal cancer, molecular profiling, next-generation sequencing, precision oncology

INTRODUCTION

Colorectal cancer (CRC) remains a major driver of cancer morbidity and mortality worldwide, with a substantial global burden despite progress in prevention, screening, and systemic therapy.[1,2] In several high-income settings, CRC mortality has declined and outcomes have improved

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over time, likely reflecting earlier detection and advances in systemic therapy.[1,2] However, CRC epidemiology is shifting, with a sustained increase in diagnoses among adults younger than 50 years.[3-6]

This increase in early-onset CRC (EOCRC) has influenced prevention policies, including recommendations to initiate average-risk screening at age 45 years.[7,8] Even so, a substantial fraction of EOCRC arises in patients who are younger than age 45, and a clinically relevant subset younger than age 40, who are outside standard screening pathways.[4-6] Diagnosis in these patients is largely symptom-driven, and they may be vulnerable to delayed recognition and work-up.[9,10] EOCRC is often diagnosed at an advanced stage and has been reported as enriched for distal colon/rectal primaries and, in some cohorts, for mucinous or signet-ring histology.[6]

In the metastatic setting, real-world data increasingly support metastatic EOCRC as a distinctive clinical and biological phenotype, and large-scale molecular datasets suggest a cohort-level molecular ‘fingerprint’, supporting integrated clinicogenomic analyses.[11,12] Metastatic patterns are also clinically relevant: peritoneal metastases represent a challenging dissemination phenotype and are associated with poorer outcomes compared with other metastatic sites in patients treated with systemic therapy.[13]

EOCRC remains etiologically and biologically heterogeneous. Germline cancer predisposition is more frequent in younger patients, and multigene testing identifies pathogenic variants in a meaningful proportion of EOCRC cases, supporting systematic genetic assessment and counselling as part of standard management. International consensus recommendations reinforce structured hereditary risk evaluation and care pathways.[14,15] At the same time, hereditary syndromes alone cannot explain the rapid increase in EOCRC incidence, supporting a role for modifiable determinants and early-life exposures; a life-course framework has therefore gained momentum.[4-6,16] Somatic profiling further indicates that EOCRC is not a uniform molecular entity, with reported age-associated differences in selected driver events and pathways.[17-19] Mutational epidemiology provides additional mechanistic insight: colibactin-producing *E. coli* has been linked to a characteristic CRC mutational signature, and whole-genome analyses have reported enrichment of colibactin-associated signatures in younger patients, particularly those diagnosed before age 40 years.[20,21]

Against this background, we conducted a multicentre real-world analysis of metastatic EOCRC stratified by age at diagnosis (30-39 versus 40-49 years). We compared clinicopathologic characteristics, metastatic patterns with a focus on peritoneal involvement, and key molecular alterations derived from standard-of-care and/or comprehensive profiling, and explored their association with outcomes, aiming to improve risk stratification and inform future research directions for very young patients with metastatic CRC.

MATERIALS AND METHODS

Study design and patient population

This retrospective, multi-institutional study included patients with metastatic CRC diagnosed before the age of 50 years (EOCRC). Eligible patients were identified from participating centres and included if they had a confirmed diagnosis of metastatic disease and available clinical follow-up data. The tumours in all patients were mismatch repair proficient (pMMR) and microsatellite stable (MSS), according to standard diagnostic assessment performed at each participating centre. Patients were excluded if age at metastatic diagnosis was $\geq$50 years or if key clinical or molecular data were missing. For the purposes of this analysis, patients were stratified a priori into two predefined groups based on age at the time of metastatic diagnosis: 30-39 years, defined as very early-onset CRC (VEOCRC), and 40-49 years. The age cutoffs were prespecified based on biological plausibility and emerging evidence suggesting increasing heterogeneity within EOCRC at younger ages.

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of the participating centres. Given the retrospective nature of the study, the requirement for written informed consent was waived where applicable.

Clinical data collection

Clinical and pathological data were extracted from medical records and institutional databases. Collected variables included sex, age at metastatic diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS) at baseline, primary tumour location (right colon, left colon, extraperitoneal rectum), sites of metastatic disease at diagnosis (liver, lung, lymph nodes, peritoneum), and first-line systemic treatment.

ECOG PS was analysed both as a three-level categorical variable (0, 1, $\geq$2) and in a prespecified dichotomised form (0 versus $\geq$1), based on clinical relevance. First-line systemic treatment was categorised according to chemotherapy backbone as triplet- or doublet-based regimens.

Genomic profiling

Comprehensive genomic profiling was performed on tumour tissue samples using a clinically validated next-generation sequencing (NGS) platform (FoundationOne® CDx or FoundationOne® Heme; Foundation Medicine, Cambridge, MA), covering more than 300 cancer-related genes. Both tissue-based assays were included, and all genomic analyses were conducted according to the manufacturer’s specifications.

Genomic alterations included short variants, copy number alterations, and rearrangements. For the purposes of this study, analyses focused on a prespecified panel of clinically relevant genes implicated in CRC biology and aggressiveness, including *KRAS*, *NRAS*, *BRAF*, *APC*, *PTEN*, and *POLE*. Alteration frequencies were compared between

Table 1. Baseline characteristics

Characteristic	Age group		P (χ^2)
	30-39 years	40-49 years	
Sex			
Male	36 (55.4%)	90 (45.2%)	0.20
Female	29 (44.6%)	109 (54.8%)	
ECOG PS			
0	57 (87.7%)	149 (74.9%)	0.046
1	8 (12.3%)	50 (25.1%)	
Metastases			
Synchronous	54 (83.1%)	154 (77.4%)	0.42
Metachronous	11 (16.9%)	45 (22.6%)	
Metastatic sites			
Liver	43 (66.2%)	138 (69.3%)	0.74
Peritoneum	21 (32.3%)	39 (19.6%)	0.051
Lung	11 (16.9%)	46 (23.1%)	0.38
Lymph nodes	15 (23.1%)	65 (32.7%)	0.19
Metastasectomy	23 (35.4%)	75 (37.7%)	0.85
Primary site			
Right	28 (43.1%)	61 (30.7%)	0.09
Left	26 (40.0%)	99 (49.7%)	0.22
Rectum	11 (16.9%)	39 (19.6%)	0.77
First-line treatment			
Triplet + biol	33 (50.8%)	77 (38.7%)	0.086
Doublet + biol	32 (49.2%)	122 (61.3%)	
TMB			
Median TMB	5.04	4.0	0.326
Mean TMB	7.53	6.43	
IQR	4.77	4.48	

Values are presented as *n* (%) unless otherwise stated.
biol, biological therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; TMB, tumour mutational burden.

age-defined subgroups. All variant calling, annotation, and quality control procedures were performed centrally by Foundation Medicine using validated, Clinical Laboratory Improvement Amendments-certified pipelines.

Outcome assessment

The primary clinical endpoint was overall survival (OS), defined as the time from diagnosis of metastatic disease to death from any cause or last follow-up. Patients alive at last follow-up were censored.

Statistical analysis

Baseline characteristics were compared between age-defined subgroups using χ^2 tests for row-by-column contingency tables and Fisher's exact tests for 2×2 comparisons, as appropriate. Continuous variables were summarised using medians and interquartile ranges.

Overall survival was estimated using the Kaplan—Meier method and compared between groups using the log-rank test. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models, with age group specified as the main covariate. The reference group was defined a priori.

Comparisons of genomic alteration frequencies between age groups were performed using odds ratios (ORs) with 95% CIs. Based on biological hypotheses prespecified before analysis, one-sided statistical tests were used to evaluate directional differences in key molecular alterations. One-sided tests were limited to a small number of prespecified hypotheses defined before data inspection. All other statistical tests were two-sided. A P value <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc (MedCalc Software Ltd, Ostend, Belgium).

RESULTS

Patient population and baseline characteristics

From a large multi-institutional cohort of patients with metastatic CRC who had undergone comprehensive genomic profiling, we identified a subset of patients diagnosed before the age of 50 years.

A total of 264 patients with metastatic EOCRC were included in the present analysis and were stratified by age at metastatic diagnosis: 30-39 years (VEOCRC; $n = 65$) and 40-49 years ($n = 199$). Baseline clinicopathological characteristics of the two groups are summarised in Table 1.

The sex distribution did not differ significantly between age groups, with female patients representing 44.6% of cases in the 30-39 age group and 54.8% in the 40-49 age group (Fisher's exact $P = 0.198$). The overall distribution of ECOG PS (0, 1, $\geq$2) was similar across groups (χ^2 $P = 0.099$). However, in a prespecified dichotomised analysis (ECOG PS 0 versus $\geq$1), patients aged 30-39 years were significantly more likely to present with ECOG PS 0 compared with those aged 40-49 years (89.1% versus 76.8%; OR 2.33, 95% CI 1.02-5.35, Fisher's exact $P = 0.0468$).

Primary tumour location (left colon, right colon, extraperitoneal rectum) did not differ significantly between age groups (χ^2 $P = 0.182$). Collapsed pairwise comparisons showed a nonsignificant trend towards a higher prevalence of right-sided primary tumours in patients aged 30-39 years compared with those aged 40-49 years (43.1% versus 30.7%; Fisher's exact $P = 0.071$), whereas no differences were observed for left-sided disease or rectal primaries.

Overall, VEOCRC patients seemed clinically fit when diagnosed with metastases, showing no signs of poorer baseline performance status or less favourable primary tumour distribution compared with older EOCRC patients.

OS differences between age-based EOCRC subgroups

OS from the time of metastatic diagnosis was considerably shorter in patients aged 30-39 years compared with those aged 40-49 years (Figure 1). Median OS was 30.0 months (95% CI 25.0-36.0) in the age 30-39 group versus 38.0 months (95% CI 31.0-46.0) in the age 40-49 group. Survival curves differed significantly according to the log-rank test ($\chi^2 = 4.90$, $P = 0.0269$).

In Cox proportional hazards regression analysis, patients aged 40-49 years showed a significantly reduced hazard of death compared with those aged 30-39 years (HR 0.67, 95% CI 0.48-0.96), confirming that very early metastatic diagnosis has an adverse prognostic impact. Notably, this survival disadvantage in the age 30-39 group was seen

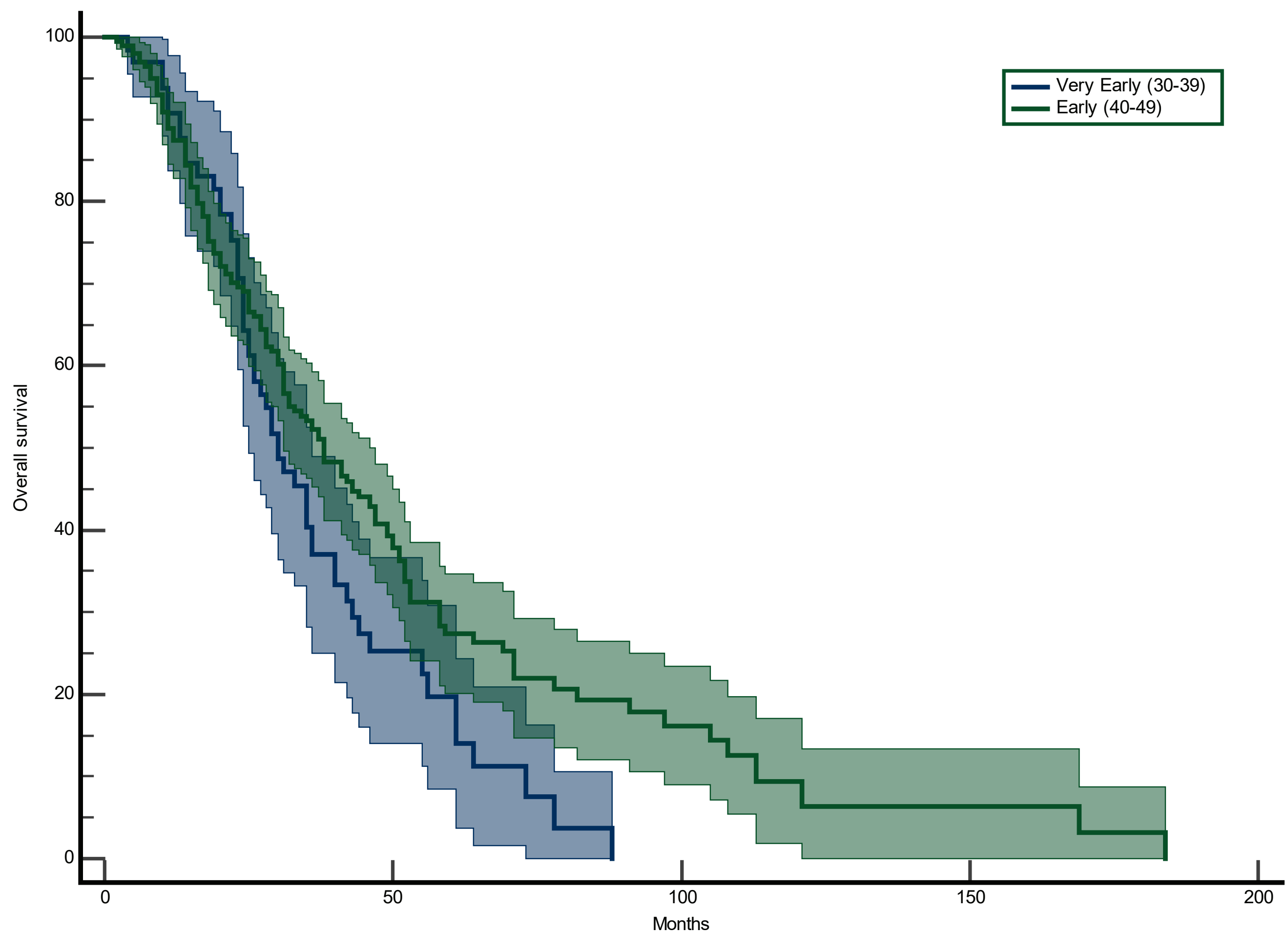

Figure 1. Overall survival by early-onset age clusters (30-39 versus 40-49 years).

despite a higher prevalence of ECOG PS 0 at baseline, suggesting that the differences in outcomes are unlikely to be solely due to baseline clinical fitness and may instead indicate underlying biological heterogeneity within EOCRC.

Distinct genomic landscape in metastatic VEOCRC

Comprehensive genomic profiling was available for most patients in both age-defined subgroups and allowed a comparative analysis of key oncogenic drivers and tumour suppressor alterations (Figure 2). Within the prespecified gene panel, patients aged 30-39 years showed a distinct genomic profile compared with those aged 40-49 years.

KRAS alterations occurred more frequently in the 30-39 age group, affecting 55.4% of patients (36 of 65), compared with 42.0% (84 of 199) in the 40-49 age group (OR 1.71, 95% CI 0.98-3.01, one-sided $P = 0.041$, in the prespecified direction). Conversely, alterations in the *APC* tumour suppressor gene were significantly less common in patients aged 30-39 years than in those aged 40-49 years (69.2% versus 82.0%; OR 0.49, 95% CI 0.26-0.94, one-sided $P = 0.024$).

Alterations in other clinically relevant genes, including *NRAS*, *BRAF*, *PTEN*, and *POLE*, were more frequently observed in the 30-39 age group and aligned with a more aggressive tumour biology. However, due to limited event counts, these differences did not achieve statistical significance. The overall pattern across the analysed genes indicates an enrichment of oncogenic signalling pathways alongside a relative reduction in canonical tumour suppressor alterations in very early-onset disease. Tumour mutational burden did not differ between patients aged 30-39 and 40-49 years, indicating that the observed clinicogenomic differences are unlikely to be driven by global mutational load.

Taken together, these findings suggest that patients diagnosed with metastatic CRC aged 30-39 years have a molecular landscape that differs from that of older EOCRC patients, characterised by increased *KRAS*-driven oncogenic signalling and reduced involvement of APC-mediated tumour suppressor pathways. This age-related genomic divergence offers a potential biological explanation for the adverse clinical outcomes observed in this subgroup.

Clinical correlates of aggressive disease: metastatic patterns at diagnosis

To explore whether the adverse prognosis observed in VEOCRC was associated with distinct patterns of disease dissemination, we compared the prevalence of metastatic sites at baseline between patients aged 30-39 and 40-49 years (Figure 3).

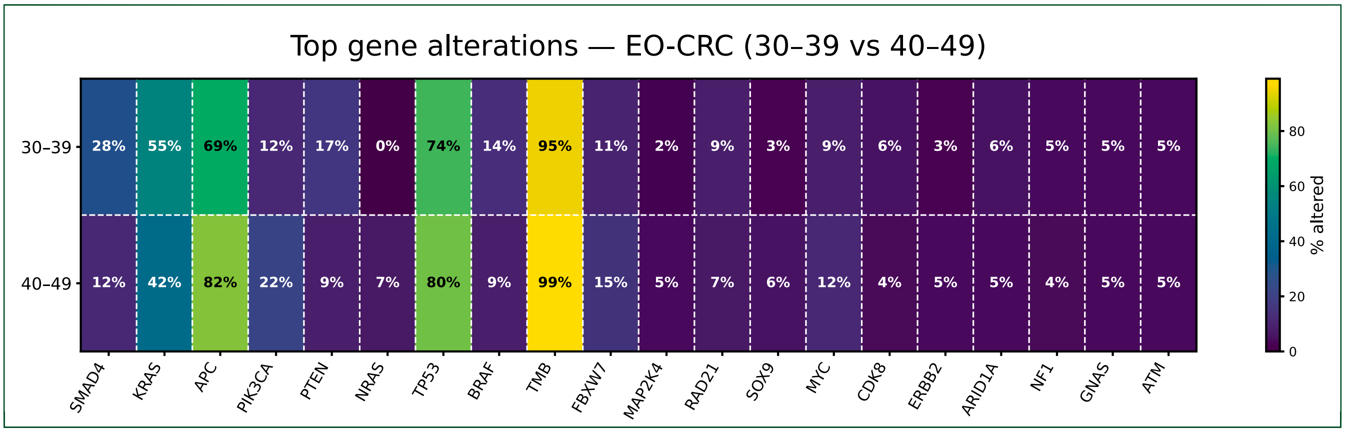

Figure 2. Heatmap of gene alteration rates in early-onset colorectal cancer (EOCRC): 30-39 versus 40-49 years.

Peritoneal metastases were significantly more common in patients aged 30-39 years than in those aged 40-49 years, occurring in 32.3% (21 of 65) versus 19.6% (39 of 199) of cases, respectively (OR 1.96, 95% CI 1.05-3.65, Fisher's exact $P = 0.041$). In contrast, no significant differences were noted for other common metastatic sites, including liver (66.2% versus 69.3%; $P = 0.646$), lung (16.9% versus 23.1%; $P = 0.385$), or lymph node involvement (23.1% versus 32.7%; $P = 0.164$).

These findings indicate that metastatic VEOCRC is characterised by a tendency for peritoneal dissemination rather than an overall increased metastatic burden. The targeted presence of peritoneal metastases in patients aged 30-39 years offers a clinically relevant link to the distinct genomic profile seen in this subgroup and aligns with a more aggressive disease biology.

Notably, the higher rate of peritoneal involvement was observed despite similar baseline performance status and comparable patterns of systemic disease at other metastatic sites, further supporting the hypothesis that tumour-intrinsic biological factors, rather than clinical presentation alone, contribute to the unfavourable outcomes associated with VEOCRC.

Systemic treatment intensity at metastatic diagnosis

To assess whether differences in first-line systemic treatment could have contributed to the observed survival disparities between age-defined EOCRC subgroups, we compared first-line systemic treatment strategies at the time of metastatic diagnosis between patients aged 30-39 and 40-49 years (Figure 4).

The distribution of first-line systemic treatment did not significantly differ between the two age groups. Patients aged 30-39 years were numerically more likely to receive triplet-based regimens compared with those aged 40-49 years (50.8% versus 38.7%), although this difference did not reach statistical significance ($P = 0.086$). Similarly, rates of metastasectomy were comparable between groups (35.4% versus 37.7%; $P = 0.85$; Table 1). Accordingly, no evidence of undertreatment or less intensive systemic or surgical therapeutic approaches were observed in the very early-onset subgroup.

These findings suggest that the lower OS observed in patients aged 30-39 years is unlikely to be attributable to differences in initial systemic treatment intensity. Instead, the persistence of outcome disparities despite comparable first-line treatment strategies supports the hypothesis that intrinsic tumour biology plays a major role in driving prognosis in metastatic VEOCRC.

DISCUSSION

EOCRC is increasingly recognised as a distinct and growing clinical problem, with rising incidence in adults younger than 50 years and frequent presentation with advanced disease.[6,10] Within EOCRC, VEOCRC, commonly defined as diagnosis before age 40 years, has been associated with clinicopathologic and molecular heterogeneity that may not be captured by broader age cut-offs.[17-19] In this context, our age-stratified analysis within metastatic EOCRC suggests that the youngest subgroup (30-39 years) represents a clinically relevant subset with less favourable outcomes than those of patients aged 40-49 years.[17-19]

A key interpretive finding is that the survival disadvantage in the 30-39 group was not mirrored by worse baseline clinical fitness or by an apparent reduction in upfront treatment intensity, which makes purely 'host-related' or 'undertreatment' explanations less compelling.[17,18,22] This pattern is consistent with prior clinicogenomic EOCRC studies indicating that age-related outcome differences can reflect tumour-intrinsic biology, metastatic behaviour, and therapy-defining molecular profiles rather than traditional clinical variables alone.[17-19] At the same time, the retrospective nature of real-world cohorts means that unmeasured differences in treatment sequencing, access to specialised care, and temporal changes in standards of care may still contribute to outcome variability and should be addressed in prospective validation.[19-22]

Clinically, our data point towards a distinct metastatic phenotype in the youngest patients, characterised by a higher burden of peritoneal involvement at presentation compared with the age 40-49 subgroup.[23,24] Peritoneal metastases are consistently associated with inferior prognosis in metastatic CRC and remain a type for which systemic therapies have comparatively limited effectiveness, and radiographic ascertainment may be challenging, particularly when disease is

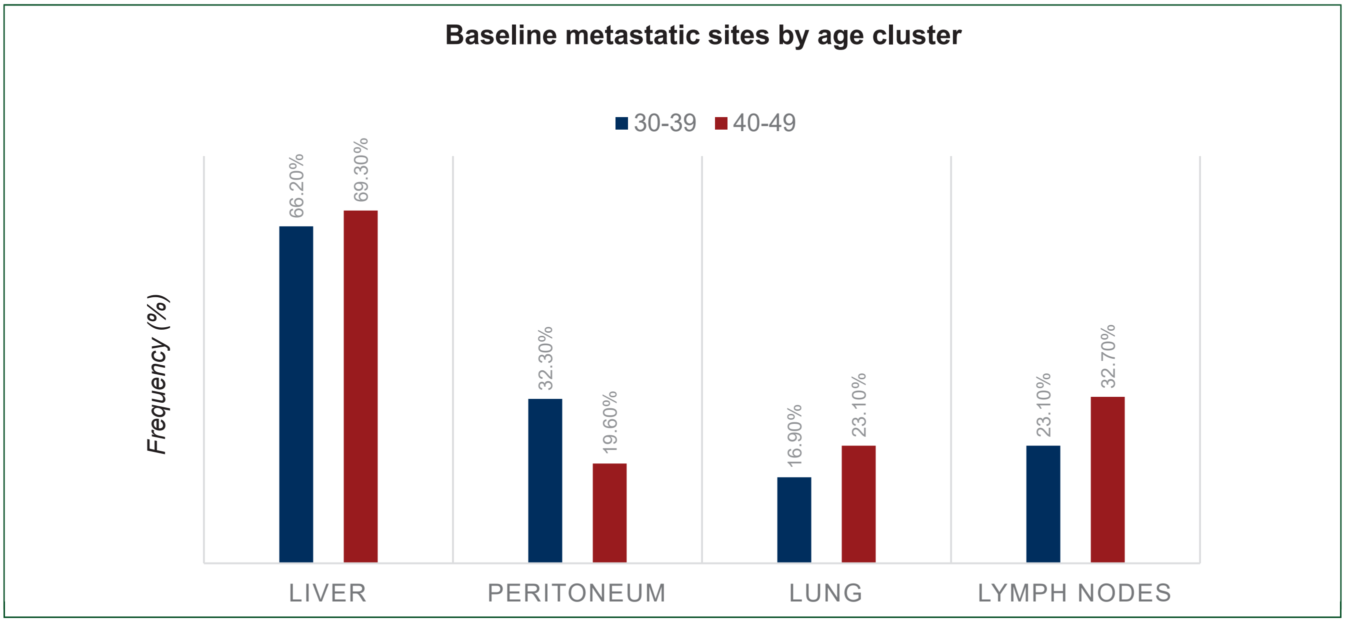

Figure 3. Baseline metastatic patterns according to age-defined early-onset colorectal cancer subgroups.
FDR, false discovery rate.

diffuse or low-volume.[24] These considerations provide a biologically and clinically plausible pathway by which an age-enriched peritoneal pattern could contribute to worse survival in very early-onset metastatic disease.[23,24] Importantly, the early-onset setting has prompted calls for standardised reporting of colorectal peritoneal metastases to reduce heterogeneity in definitions and capture, and our findings reinforce the relevance of that agenda for age-stratified EOCRC research.[23]

Our genomic results add further context to this phenotype. Importantly, all patients in our cohort were pMMR/MSS, ensuring biological homogeneity with respect to mismatch repair status and avoiding potential confounding related to the distinct prognosis and treatment paradigms associated with microsatellite instability-high (MSI-H) disease. Using tumour tissue-based broad NGS profiling and focusing on prespecified CRC-relevant drivers, we observed an enrichment of *KRAS* alterations and a relative depletion of *APC* alterations in the age 30-39 subgroup compared with patients aged 40-49 years.[17,18] These patterns align with large clinicogenomic datasets showing that, although EOCRC broadly shares canonical drivers with later-onset CRC, the distribution

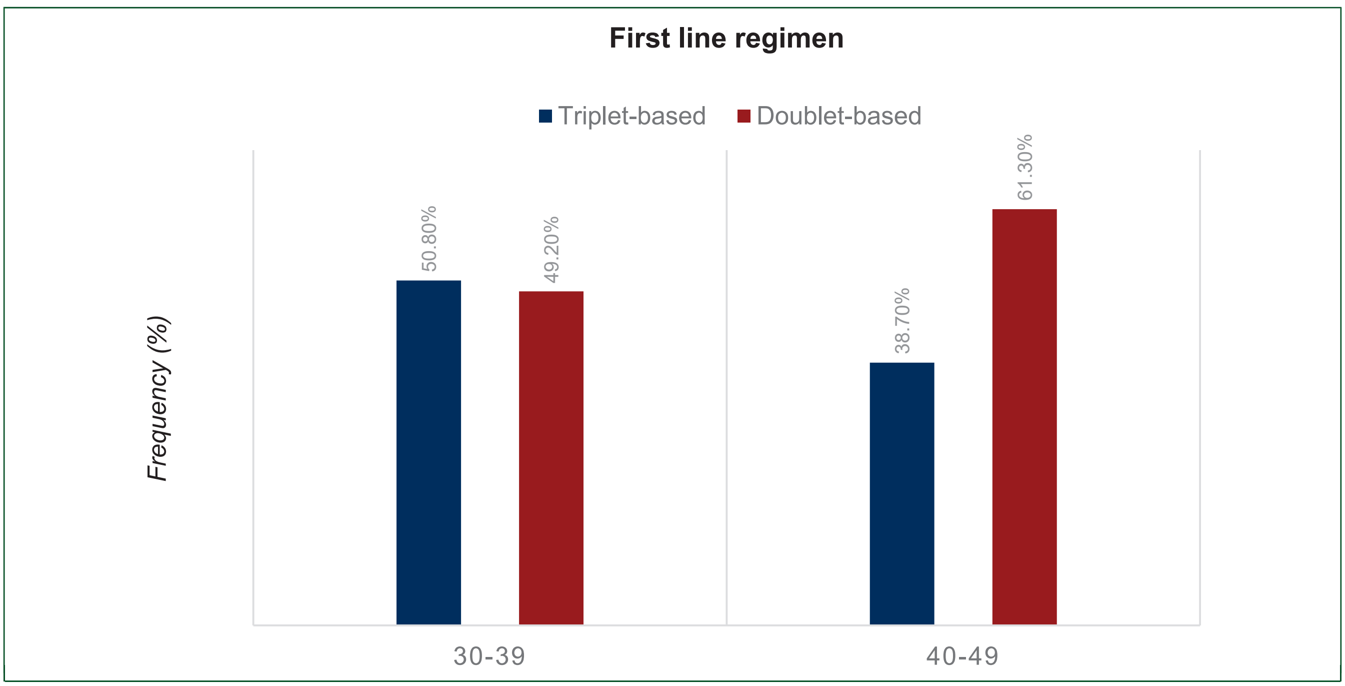

Figure 4. First-line systemic chemotherapy backbone according to age-defined early-onset colorectal cancer subgroups.

of key alterations can vary by age strata and cohort composition.[17,18] From a management standpoint, higher *KRAS* mutation prevalence in the youngest metastatic patients is directly relevant because *KRAS* alterations are established negative predictive biomarkers for anti-epidermal growth factor receptor (EGFR) therapy benefit and strongly influence first-line biologic selection.[22,25] In parallel, primary tumour sidedness remains a major biological and predictive axis in metastatic CRC, and even in *RAS* wild-type disease, right-sided primaries derive less benefit from EGFR antibody strategies than left-sided tumours, underscoring the importance of integrating anatomy and genomics when interpreting outcomes in EOCRC.[22,26]

Biologically, a lower frequency of *APC* alterations in the youngest subgroup raises the possibility that a proportion of metastatic VEOCRC may arise through APC-independent mechanisms of WNT pathway activation, rather than the classic APC-driven adenoma-carcinoma sequence.[27,28] *RSPO* fusions are a well-described APC-independent route to WNT activation in CRC and can define ligand-dependent biology that is mechanistically distinct from *APC* truncation.[27] Alterations in negative regulators such as *RNF43* have also been linked to serrated-pathway CRC and WNT ligand dependency, offering additional mechanistic routes through which 'APC-low' tumours may still be WNT-driven.[28] Although our study was not designed to resolve the full WNT architecture (including comprehensive fusion detection, epigenetic phenotypes, or transcriptomic subtypes), these established mechanisms provide a coherent biological framework to interpret our APC signal and motivate deeper pathway-level interrogation in very early-onset metastatic disease, particularly in relation to metastatic tropism such as peritoneal spread.[17,18,27,28]

Beyond driver distributions, emerging whole-genome evidence suggests that EOCRC, especially disease arising before 40 years of age, may reflect distinct mutational processes linked to early-life exposures, including colibactin-associated signatures.[21] This body of work supports an integrative etiologic model in which host—microbiome interactions and early exposures influence tumour evolution and may shape clinically observable phenotypes in VEOCRC.[18,21] Accordingly, future confirmatory studies should consider coupling driver-level analysis with MSI/MMR status, germline testing, and mutational process inference to better distinguish hereditary subsets from sporadic, exposure-linked pathways.[6,17-19,21]

Our findings also reinforce the need for scalable biomarkers that can capture tumour biology longitudinally in EOCRC. Liquid biopsy approaches in CRC are rapidly evolving for monitoring and stratification and may be particularly valuable in very early-onset metastatic disease where baseline 'fitness' measures may not anticipate aggressive trajectories.[29] In parallel, proof-of-concept work on NGS-enabled miRNA detection in alternative biofluids, such as exhaled breath condensate, highlights the broader trajectory towards minimally invasive nucleic acid platforms that could inform future translational programmes, even if CRC applications remain earlier in development.[30,31] Within metastatic CRC, clinically implementable risk models illustrate how pragmatic phenotypic stratification can complement biomarker-driven assessment and inform subgroup-focused trial design.[32]

Several limitations should be acknowledged. This study is retrospective and may be influenced by selection for comprehensive genomic profiling, centre-level differences in diagnostic pathways (including detection of peritoneal disease), and heterogeneity in treatment sequencing across time and institutions.[33] The relatively small age 30-39 years subgroup limits inference for rare alterations and subtle clinicopathologic signals and reinforces the need for external validation in larger, harmonised datasets.[33] Finally, the absence of systematic integration of MSI/MMR, germline testing, centralised pathology review, and mutational signatures constrains biologic attribution and should be prioritised in subsequent studies aimed at mechanism and clinical translation.[6,17-19,21,33]

In summary, our results support the concept that metastatic EOCRC contains clinically meaningful heterogeneity by age, with the age 30-39 year subgroup showing an adverse clinical course accompanied by distinctive metastatic behaviour and a non-random distribution of key genomic drivers.[17-19] These findings provide a rationale for age-refined EOCRC classification, standardised peritoneal metastasis reporting, and integrated translational efforts combining pathway-level genomics with minimally invasive biomarker strategies to better understand, and ultimately mitigate, the aggressive phenotype observed in very young metastatic CRC.[6,21,22,29]

DATA AVAILABILITY

Datasets generated during and/or analysed during the present study are available from the corresponding author on reasonable request.

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DISCLOSURE

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