Original Study

The Impact of Surgical Resection in Early Onset Colorectal Cancer Patients With Liver Limited Disease

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Abstract

In a multicenter cohort of 1209 metastatic CRC patients, early-onset colorectal cancer (≤ 50 years) showed consistently inferior outcomes after liver metastasectomy. Among the 417 resected cases, EO-CRC had markedly shorter OS (44 vs. 64 months) and PFS (13 vs. 17 months) compared with older patients. This survival gap persisted across RAS-mutated and RAS/BRAF wild-type subgroups, suggesting a distinct and more aggressive EO-CRC phenotype.

Background: Recent studies have shown an increased incidence of early-onset CRC (EO-CRC), particularly in advanced stages and with metastatic disease. Our study aimed to evaluate the role of metastasectomies related to the clinical and molecular characteristics of EO-CRC patients with liver metastases compared to average-onset CRC (AO-CRC) patients. **Methods:** We retrospectively collected data from 1123 stage IV colorectal cancers, including 782 with liver metastases, from 5 different Italian institutions. The main objective of the study was to compare the overall survival of liver metastatic EO-CRC and AO-CRC patients who underwent metastasectomy versus those who were not resected. **Results:** Liver resected EO-CRCs patients showed a statistically significant lower mOS than liver resected AO-CRCs (44.0 vs. 64.0 months, $P < .0001$). mPFS was also statistically significant lower in EO-CRCs (13.0 vs. 17.0, $P < .0001$). Same outcomes were found in RAS mut subgroup (37.0 vs. 52.0 months, $P < .0001$) and in RAS/BRAF wild-type subgroup (50.0 vs. 81.0 months, $P < .0001$). EO-CRC patients showed a higher prevalence of TP53 alterations (56.2%) and a lower of APC mutation (29.9%). EO-CRCs presented a higher frequency of ARID1A (4.4%) and CTNNB1 (3.0%) alterations. **Conclusion:** The results indicate a worse overall prognosis for EO-CRC patients undergoing metastasectomy compared to average-onset patients. This outcome appears to occur independently of the molecular status. These observations could have a considerable impact on clinical practice and research.

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Introduction

Colorectal cancer is the third most common cancer globally, with an incidence rate of 9.6%. It ranks second in cancer mortality, accounting for 9.3% of cancer deaths.[1] At diagnosis, 25% of patients present with metastatic disease. Among all metastatic sites, the liver is the most commonly affected organ in colorectal cancer (CRC). About 15% to 25% of CRC patients present with liver metastases at initial diagnosis. Additionally, nearly 25% of patients undergoing surgical resection of the primary tumor continue to have liver metastases postoperatively.[2,3] Up to 35% of patients are diagnosed with liver metastases, and this proportion can increase to 70% by the time of death.[4,5] R0 resection of liver metastases can provide a 5-year survival benefit of 20 to 45% compared to patients who do not undergo resection.[6]

After undergoing metastasectomy, the recurrence rate in the resected organ ranges from 55% to 80%. The effectiveness of pseudo-adjuvant or perioperative chemotherapy is influenced by the resectability criteria assessed at diagnosis and key negative prognostic factors.[7,8] Many patients with liver involvement are initially considered unresectable; however, they may be re-evaluated for surgery after receiving first-line chemotherapy if they achieve a significant clinical response.[9]

The molecular profile, which includes factors like DMMR/MSI-H, RAS, and BRAF status, is crucial in selecting the most effective therapeutic strategy for patients with unresectable disease. Moreover, this profile provides prognostic information about the expected response to treatments. However, patients with BRAF-mutated disease who have undergone R0 metastasectomy do not seem to have worse outcomes compared to those with wild-type BRAF.[10]

Recent epidemiological data show an increasing incidence of colorectal cancer in patients under 50. This trend may be linked to several factors, including early exposure to diet- and lifestyle-related carcinogens, obesity, environmental agents,[11-13] and antibiotic use, which can alter the microbiota.[14,15] Our recent study revealed the clinical characteristics of patients with left-sided and rectal tumors, which have proficient MMR and exhibit a poorly differentiated or undifferentiated histological pattern. Patients with early-onset colorectal cancer (EO-CRC) also showed worse outcomes, regardless of their molecular profile.[16]

This study aims to assess outcomes in patients with early-onset colorectal cancer and liver disease, evaluating the correlation between liver metastasectomy and median overall survival.

Methods

Study Population

Data from 1123 metastatic colorectal patients, of which 782 had liver-limited disease, from 5 different Italian settings were collected. Four hundred sixty-two patients were diagnosed with EO ($\leq$ 50 years) metastatic CRC, whereas 329 are a historical cohort of patients aged $>$ 50 years. The patients included in the study had been diagnosed with metastatic colorectal cancer between 2008 and 2019. Patients had an Eastern Cooperative Oncology Group (ECOG) Performance Scale from 0 to 2. All patients had an available molecular profile, including at least KRAS, NRAS, BRAF, and dMMR/MSI-H status. Molecular profile analyses were performed on the primary tumor using polymerase chain reaction (PCR) sequencing or Next Generation Sequencing (NGS). NGS analysis was available for 252 patients (32.2%).

The main objective of the study was to compare the overall survival of liver metastatic early-onset (EO) and average-onset (AO) colorectal cancer (CRC) patients who underwent metastasectomy versus those who were not resected, also considering molecular subgroups such as RAS and BRAF. The secondary objectives were: Progression-free survival (PFS) of liver metastatic EO- and AO-CRC patients and of molecular subgroups. Finally, we performed multivariate analysis for all survival variables (ECOG-PS, CEA level, Age $\leq$ 50, first-line regimen, Fong Score, RAS/BRAF mutational status, sideness, sex) through Cox proportional hazards regression.

Patients were selected for liver metastasectomy following multidisciplinary assessment at each participating center. Selection criteria included liver-only disease, technical resectability, adequate performance status, and no contraindications to surgery. For patients initially considered unresectable, re-evaluation after systemic therapy was permitted if there was sufficient tumor response. Only patients undergoing curative-intent hepatectomy with complete (R0) resection were included in the study.

This study was performed in accordance with the study protocol, the ethical principles stated in the Declaration of Helsinki, as well as those indicated in the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP; ICH E6, 1995), and all applicable regulatory requirements.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), and categorical variables as absolute and relative frequencies. Between-group comparisons were performed using Student's t-test or Mann–Whitney U test for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables. All tests were 2-sided with statistical significance set at $P < .05$.

Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression, second malignancy, or death from any cause. Overall survival (OS) was defined as the time from metastatic diagnosis to death from any cause or last follow-up. Survival curves were estimated using the Kaplan–Meier method and compared with the log-rank test.

Associations between covariates and OS were evaluated using univariable and multivariable Cox proportional hazards regression models to appropriately account for time-to-event data and censoring. Covariates for multivariable models were selected a priori based on clinical relevance. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

To address potential baseline imbalances between early-onset (EO-CRC) and average-onset CRC (AO-CRC) groups, inverse probability weighting (IPW) based on propensity scores was applied using stabilized weights derived from a logistic regression model including pretreatment covariates. Weighted Cox models were subsequently fitted to estimate the independent prognostic impact of age group.

Interaction terms between age group and key molecular subgroups (RAS, BRAF, and MSI status) were formally tested.

Figure 1 Patients baseline characteristics.

		AO CRC		EO CRC		p-value
Median age		64.9 ± 8.2		44.2 ± 6.2		
M/F		218/101		227/235		
		Not res	Res	Not res	Res	
n.		**185**	**134**	**194**	**268**	p < 0,0001
ECOG-PS	0	110 (59.5)	116 (86.6)	136 (70.1)	215 (80.2)	
	1	69 (37.3)	17 (12.7)	55 (28.3)	51 (19.0)	p < 0,0001
	2	6 (3.2)	1 (0.7)	3 (1.6)	2 (0.8)	
Location	right	31 (16.8)	23 (17.2)	48 (24.7)	63 (23.5)	
	trasv	2 (1.1)	2 (1.5)	5 (2.6)	3 (1.1)	
	left	92 (49.7)	56 (41.8)	104 (53.6)	119 (44.4)	p = 0,0089
	rect	60 (32.4)	53 (39.5)	37 (19.1)	83 (31.0)	
Molecular profile	WT	104 (56.2)	85 (63.4)	74 (38.1)	118 (44.0)	
	KRAS	61 (32.9)	40 (29.8)	97 (50.0)	120 (44.8)	
	NRAS	8 (4.3)	5 (3.7)	13 (6.7)	17 (6.3)	
	BRAF	14 (7.6)	6 (4.5)	13 (6.7)	16 (6.0)	p = 0,0012
	MSI-H	11 (5.9)	5 (3.7)	5 (2.6)	20 (7.5)	
	Co-Exp	2 (1.1)	2 (1.5)	3 (1.5)	4 (1.5)	
Regimen	*Doublet*	23 (12.4)	19 (14.2)	16 (8.2)	22 (8.2)	
	Doublet + antiVEGF	65 (35.2)	41 (30.6)	67 (34.5)	108 (40.3)	
	Triplet + antiVEGF	12 (6.5)	4 (3.0)	58 (29.9)	51 (19.0)	
	Doublet + antiEGFR	71 (38.4)	54 (40.3)	39 (20.1)	55 (20.5)	p < 0,0001
	Triplet + antiEGFR	3 (1.6)	1 (0.7)	8 (4.2)	19 (7.1)	
	Other	11 (5.9)	15 (11.2)	6 (3.1)	13 (4.9)	

Sensitivity analyses excluding patients with confirmed hereditary syndromes and analyses adjusting for treatment era were also performed. Based on a priori power calculations from our previous study, assuming a 19% relative difference in risk, an alpha of 0.01 and beta of 0.01, the required sample size was estimated at 659 patients. Statistical analyses were performed using STATA version 17 and MedCalc version 23.1.3.

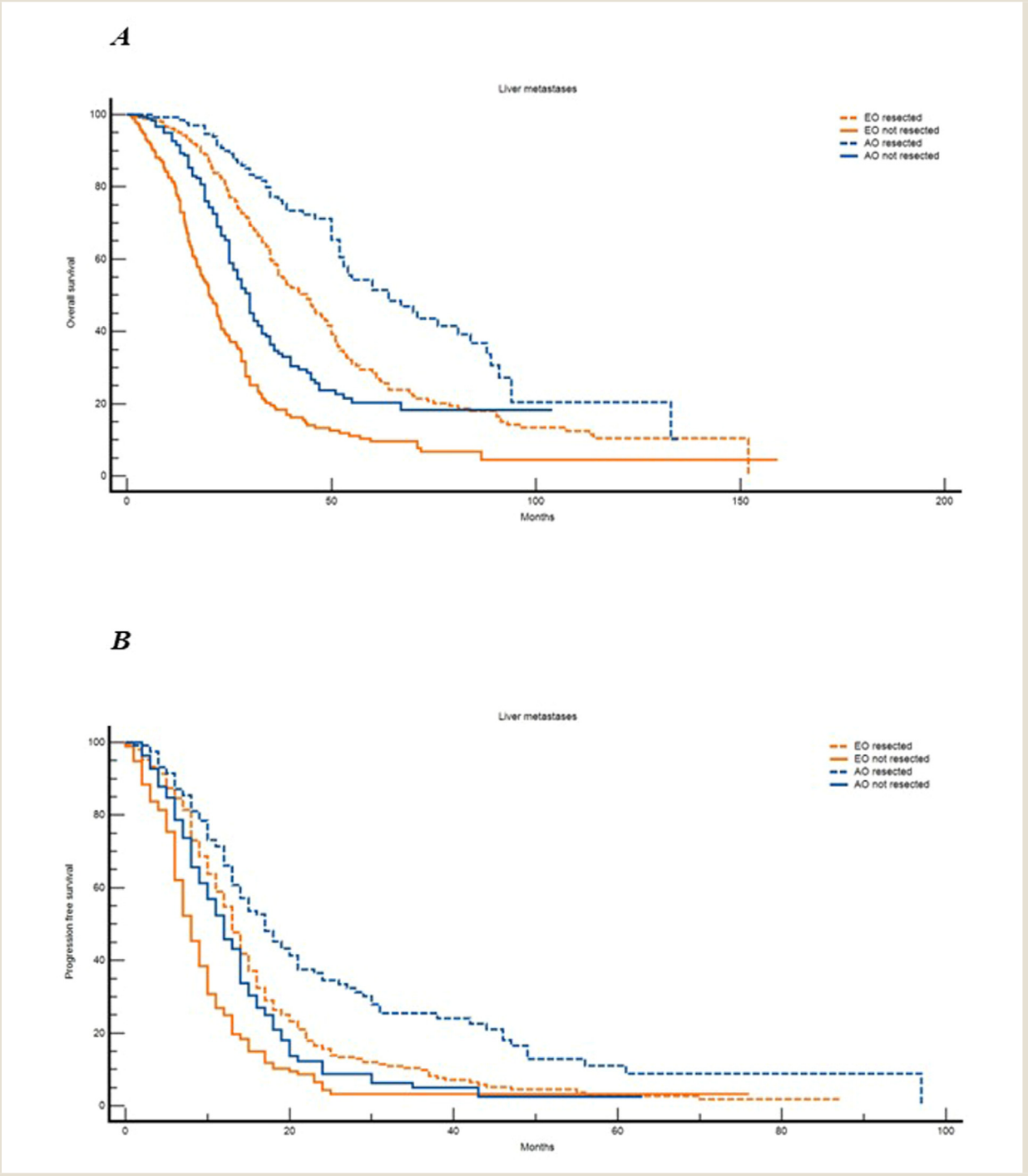
Results

Out of 782 patients with liver metastases, 462 (59%) had early-onset colorectal cancer (EO-CRC) with a median age of 44 years (± 6), while 329 (41%) had average-onset colorectal cancer (AO-CRC) with a median age of 64 years (± 8). Among EO-CRCs, there were 227 males and 235 females, while among AO-CRCs, there were 218 males and 101 females. A total of 268 out of 462 (58%) EO-CRCs underwent liver metastasectomy, while 134 out of 319 (42%) AO-CRCs underwent metastasectomy (Figure 1).

In both the EO-CRC and AO-CRC groups, patients who underwent metastasectomy had better outcomes compared to those who did not undergo resection. In the EO-CRC group, the average survival was 44.0 months for resected patients versus 20.1 months for nonresected patients, while in the AO-CRC group, it was 64.0 months compared to 30.0 months ($P < .0001$) (Figure 2).

Liver resected EO-CRC patients exhibited a statistically significant lower mOS compared to those with liver resected AO-CRC (44.0 vs. 64.0 months, $P < .0001$). Additionally, the mPFS was also significantly lower in EO-CRC patients (13.0 vs. 17.0 months, $P < .0001$) (Figure 3).

Figure 2 Overall survival and progression free survival in EO-CRC and AO-CRC patients who underwent metastasectomy.

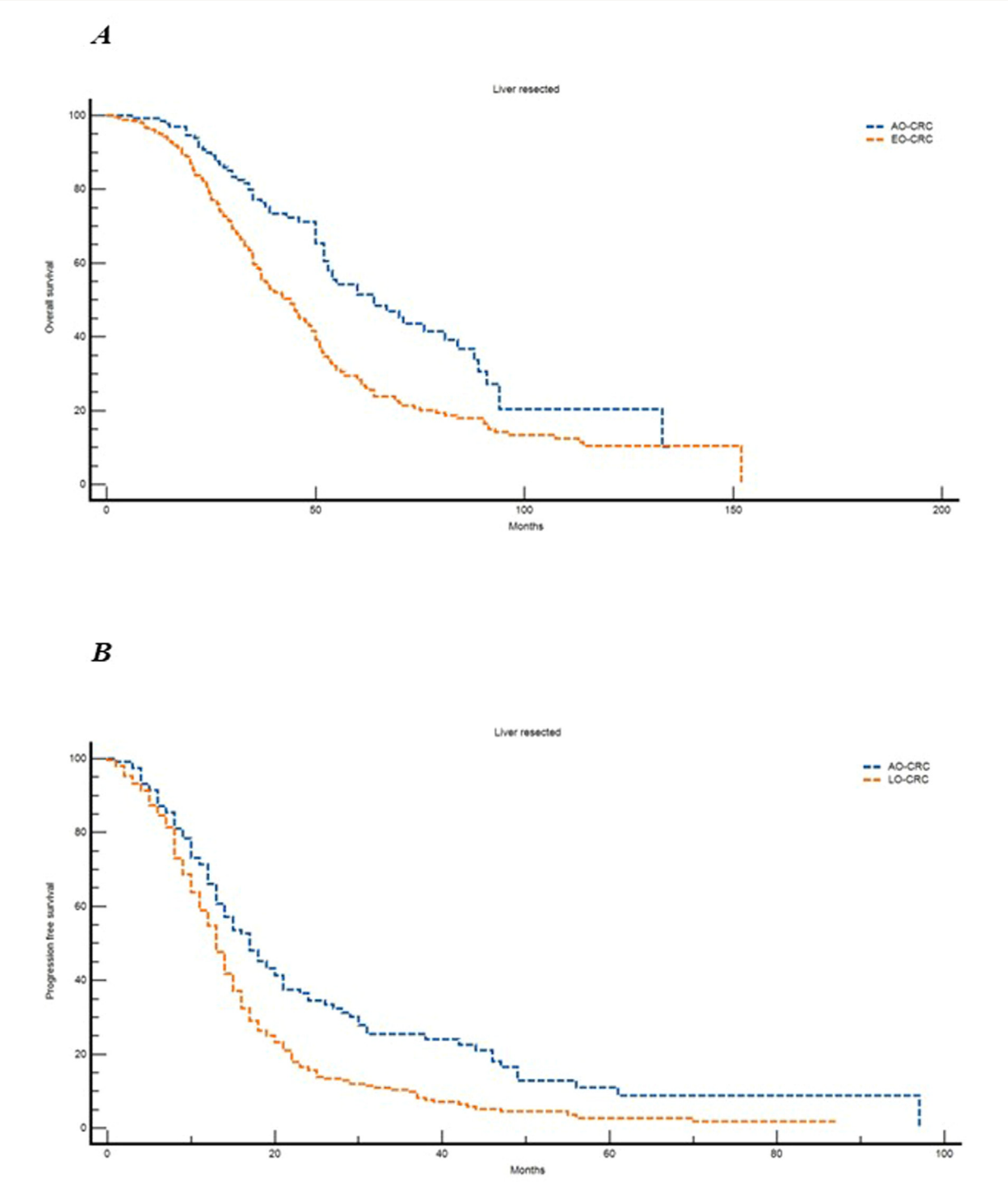


In the subgroup of patients with RAS mutations, AO-CRCs exhibited a significantly longer mOS compared to EO-CRC patients who were also resected. Specifically, the mOS for AO-CRC patients was 52.0 months, while it was only 37.0 months for EO-CRC patients ($P < .0001$). Additionally, the mPFS was significantly longer for resected AO-CRC patients at 13.0 months, compared to 11.0 months for resected EO-CRC patients ($P < .0001$) (Figure 4).

In the RAS/BRAF wild-type patients subgroup, resected AO-CRCs showed a statistically significant higher mOS than resected EO-CRCs patients (81.0 vs. 50.0 months, $P < .0001$). mPFS was also significantly longer in resected AO-CRC patients than EO-CRC (20.0 vs. 15.0 months, $P < .0001$) (Figure 5).

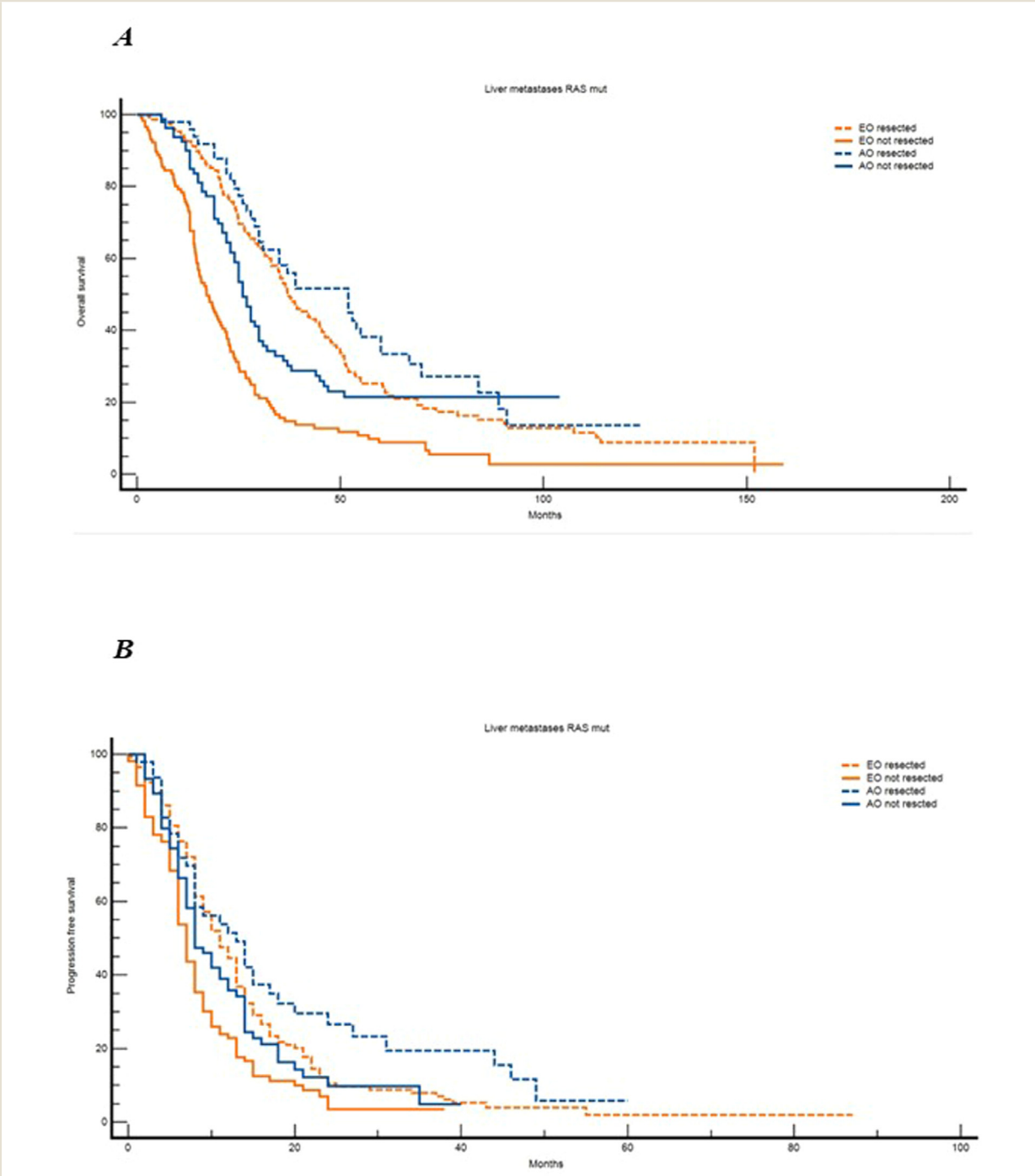
Considering BRAF-mutated patients with liver metastases, 49 patients carried the V600E mutation, of these 26 were EO-CRCs

Figure 3 Overall survival and progression free survival in liver resected EO-CRC and AO-CRC patients.



and 23 AO-CRCs. In BRAF mutated EO-CRCs, 53.8% of patients underwent liver metastasectomy, while 46.2% did not. Patients who were resected had a significantly longer mOS compared to those who were not resected, with 17.1 months versus 13.0 months for patients who did not undergo metastasectomy ($P = .047$). Among BRAF AO-CRC patients, 26.1% underwent metastasectomy, while 73.9% did not. However, those who had resection showed a comparable mOS to those who did not, with 26.0 versus 27.0 months ($P = .74$).

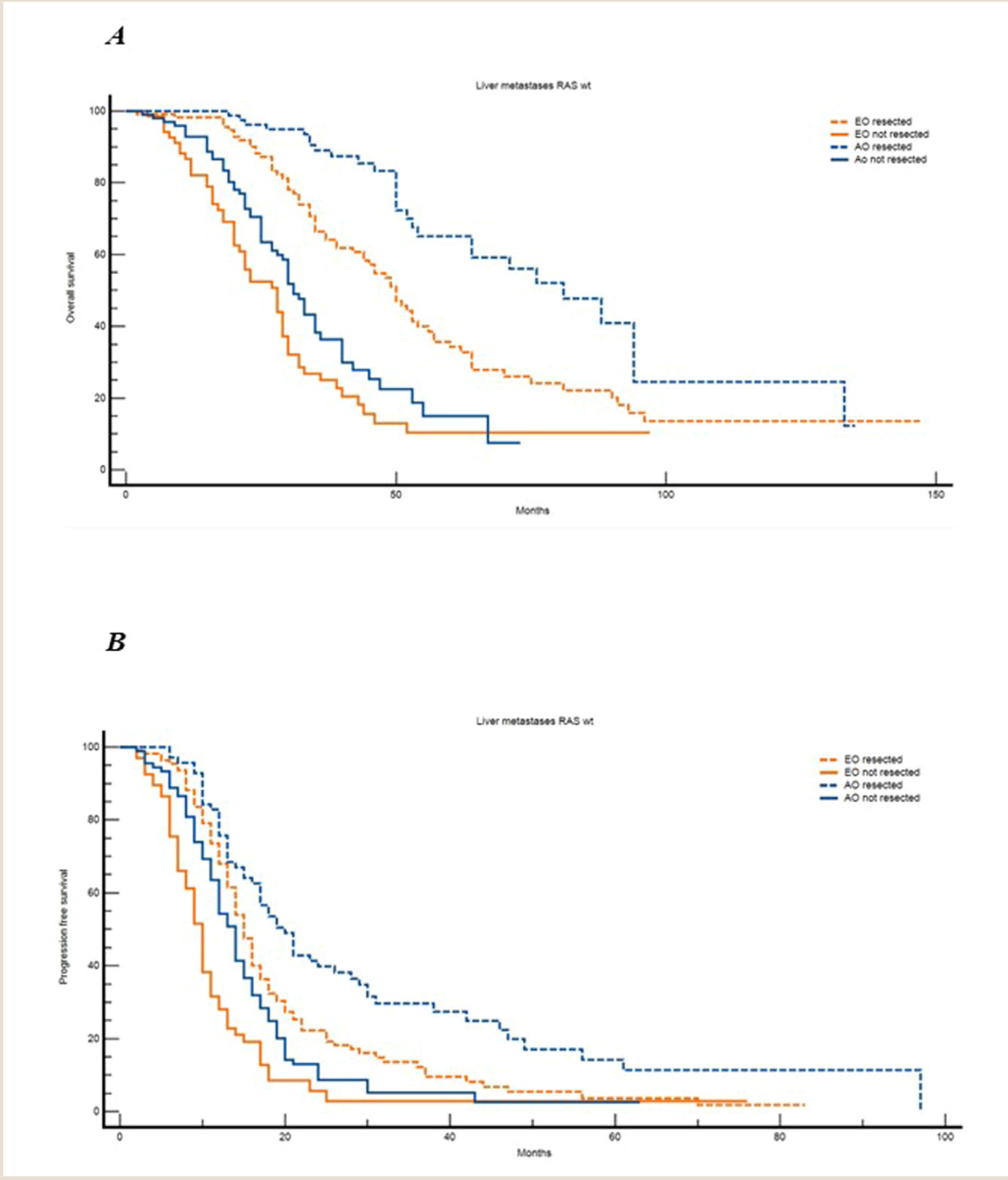
Figure 4 Overall survival and progression free survival in KRAS mutated, liver resected EO-CRC and AO-CRC patients.



In comparing the mOS of resected patients with EO-CRCs and AO-CRCs, patients with AO-CRCs demonstrated a higher mOS with 27.1 versus 17.1 months. However, this difference was not statistically significant ($P = .9$).

In multivariable Cox analysis adjusting for clinical and tumor-related factors, early-onset CRC remained independently associated with worse overall survival (adjusted HR 1.62, 95% CI, 1.33-1.98). To address potential selection bias, inverse probability weighting was applied to balance baseline characteristics between age groups. The negative prognostic impact of early-onset disease remained consistent in weighted analyses (IPW marginal HR 1.42, 95% CI, 1.18-1.70; doubly robust HR 1.38, 95% CI, 1.14-1.67).

Figure 5 Overall survival and progression free survival in RAS-BRAF wild type, liver resected EO-CRC and AO-CRC patients.



Interaction analyses did not show significant effect modification between age group and RAS ($P = .81$) or BRAF status ($P = .23$), although a borderline interaction was observed for MSI status ($P = .084$). Sensitivity analyses excluding patients with confirmed Lynch syndrome showed consistent results, with early-onset disease still independently linked to worse overall survival (HR 1.68, 95% CI, 1.38-2.05; $P = 3.3 \times 10^{-7}$).

Sensitivity analyses considering treatment era (defined by the median year of metastatic diagnosis) confirmed consistent results. In multivariable Cox models adjusted for Fong score, treatment era,

Table 1 Multivariate Analysis

	Standard Error	*P* Value	Exp(b)	95% CI, Exp(b)
ECOG-PS	0.4621	.0310	2.7098	1.0954-6.7035
CEA	0.0002	.4526	1.0002	0.9997-1.0007
Age ≤ 50 y	0.4901	.0244	3.0136	1.1531-7.8756
First line regimen	0.2368	.4526	1.1947	0.7511-1.9002
Fong score	0.2498	.3698	1.2511	0.7668-2.0414
All RAS/BRAF mut	0.3551	.7264	0.8832	0.4404-1.7712
Sideness	0.2844	.3623	1.2957	0.7421-2.2623
Sex	0.4193	.9655	0.9820	0.4318-2.2336

and an EO × era interaction term, early-onset disease remained independently associated with poorer overall survival (HR 1.52, 95% CI, 1.12-2.05; $P = .007$). The treatment era itself was not associated with the outcome ($P = .89$), and no significant interaction between age group and era was observed ($P = .52$), indicating that the prognostic impact of early-onset CRC remained consistent over time.

NGS found at least 1 mutation in 115 AO-CRC and 137 EO-CRC. EO-CRC patients showed a higher prevalence of TP53 alterations (56.2%) and a lower of APC mutation (29.9%); conversely, AO-CRC patients exhibited a higher prevalence of APC alterations (54.0%) and a lower prevalence of TP53 mutations (46.9%). AO-CRCs also showed a higher frequency of SMAD4 (13.0%) and FBXW7 (6.1%) mutations. Instead, EO-CRCs presented a higher frequency of ARID1A (4.4%) and CTNNB1 (3.0%) alterations (Figure 6).

Patients with early-onset colorectal cancer (EO-CRC) were more frequently treated with a triplet regimen plus anti-VEGF therapy compared to those with late-onset colorectal cancer (AO-CRC). Specifically, 29.9% of nonresected EO-CRC patients and 19.0% of resected EO-CRC patients received this treatment. In both groups, the most commonly used regimen was the doublet regimen combined with anti-VEGF, which accounted for 30.6% to 40.3% of treatments. Detailed systemic treatment patterns, including chemotherapy backbone, use of targeted agents, and number of treatment lines, are summarized in Figure 7.

In our study, we performed a multivariate analysis of patients who underwent resection, focusing on several variables: ECOG performance status (ECOG-PS), sex, baseline carcinoembryonic antigen (CEA) levels, age under 50, first-line treatment regimen, Fong Score, mutational status, and tumor side. Our findings indicated that ECOG-PS and being under 50 years of age were significant and independent prognostic factors (Table 1).

Discussion

In this large multicenter real-world cohort of patients with liver-limited metastatic CRC undergoing curative-intent strategies, early-onset disease consistently emerged as an independent adverse prognostic factor despite higher resection rates and more intensive systemic treatment.

Colorectal cancer patients with liver metastases typically have a poorer prognosis compared to those with metastases in other sites, such as the lungs. However, our findings indicate that metastasectomy can have a positive prognostic effect on patients with colorectal cancer and liver disease, applicable to both early-onset colorectal cancer and average-onset colorectal cancer. This aligns with existing literature. In multivariate analyses, the Fong score was not an independent prognostic factor. However, the Fong criteria are fundamental for therapeutic choices, similar to the Meta-Lung score, which is applicable for patients with metastatic lung disease.[17]

EO-CRC patients who underwent liver metastasectomy experienced worse outcomes compared to AO-CRC who received the same treatment, both in terms of median overall survival and median progression-free survival.

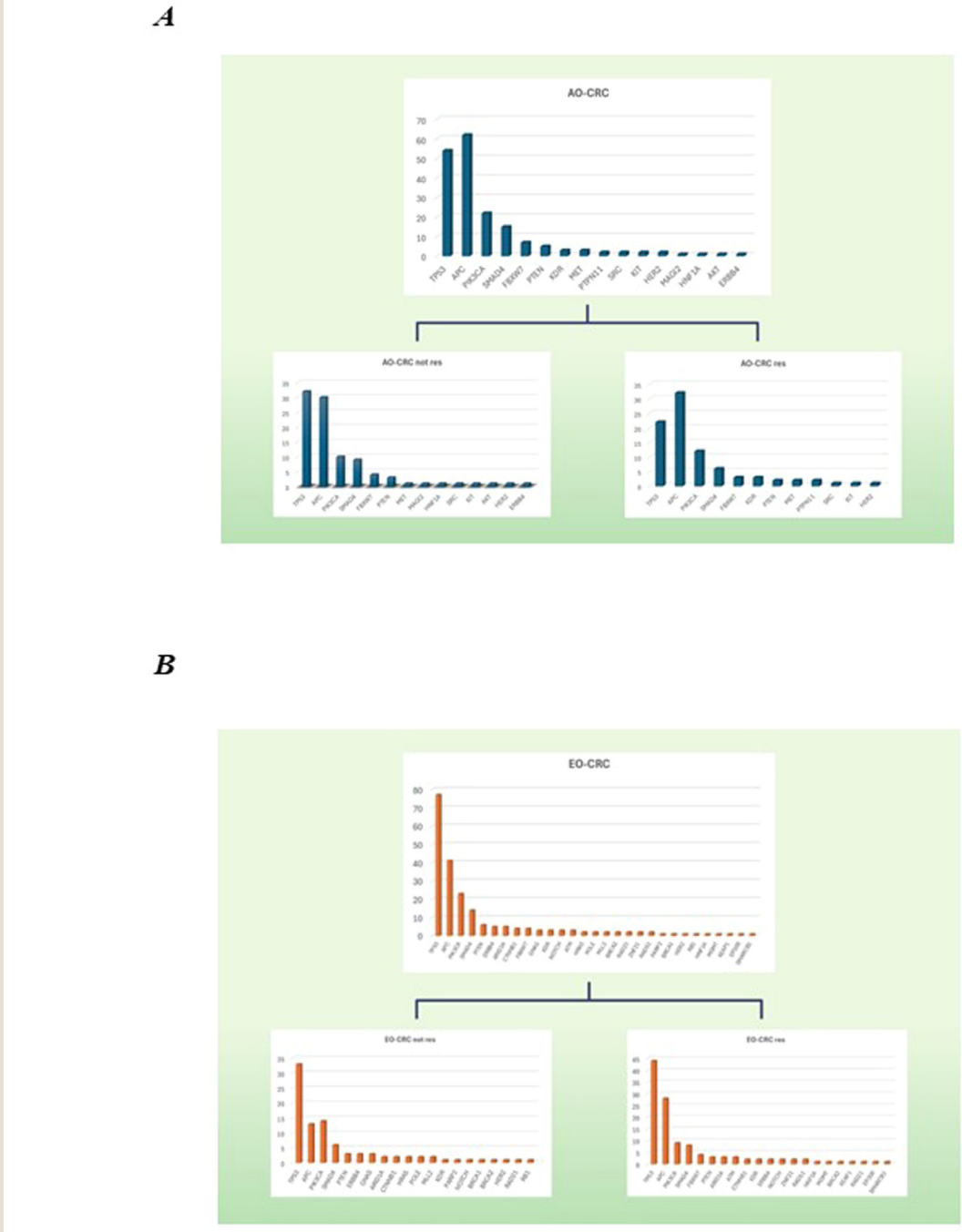
These findings should be interpreted in the context of prior surgical series, such as the study by Tsilimigras et al.[18] who described comparable long-term outcomes between early-onset and late-onset patients undergoing curative-intent hepatectomy for colorectal liver metastases. However, this apparent discrepancy is probably due to significant differences in study design, patient selection, and analytical perspective.

In the study by Tsilimigras et al.[18] the analysis was limited to a highly selected group of patients who successfully underwent liver resection, thus representing a favorable prognostic subgroup where surgical candidacy itself acts as a significant selection criterion. Conversely, our cohort reflects a real-world population, including both resected and nonresected patients with liver-limited disease, enabling us to assess the overall prognostic impact of early-onset disease beyond surgical selection alone.

Importantly, although Tsilimigras et al.[18] reported similar genomic profiles between early- and late-onset disease using large public genomic datasets, our next-generation sequencing analysis on treated patients revealed a higher prevalence of alterations linked to aggressive tumor biology in early-onset CRC, including TP53, ARID1A, and CTNNB1 mutations. These biological differences may contribute to the poorer outcomes seen in early-onset patients despite higher resection rates and more intensive systemic treatment.

Differences in systemic treatment strategies might better explain the diverging results. In surgical series such as that of Tsilimigras et al.[18] systemic therapy mainly acts as a selection tool, as only patients with adequate disease control proceed to curative-intent resection. Conversely, in our real-world cohort, early-onset patients more frequently received intensified initial regimens and multiple lines of systemic therapy, indicating a higher baseline disease aggressiveness. In this context, treatment intensity may serve as a surro-

Figure 6 Main genes altered in the 2 subgroups of AO-CRC (A) and EO-CRC (B) patients.

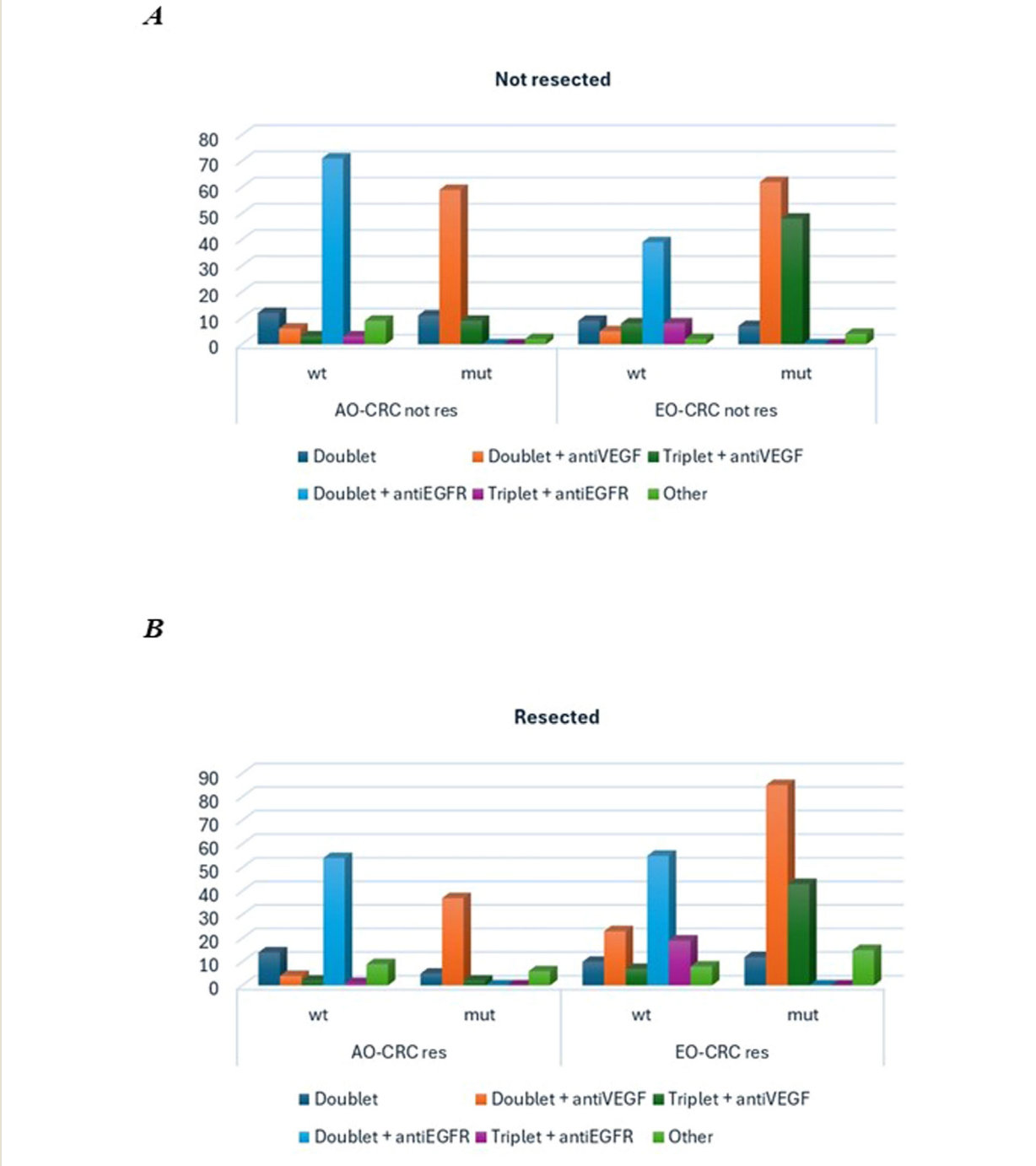


gate marker of unfavorable tumor biology rather than a factor that improves outcomes.

Taken together, these considerations suggest that the poorer survival observed in early-onset CRC in our study does not contradict previous surgical series but instead highlights how variations in patient selection, treatment timing, and biological context may influence outcomes in this population.

Importantly, these findings remained consistent across multiple sensitivity analyses, including propensity score–weighted models, interaction testing with major molecular subgroups, and exclu-

Figure 7 Main therapeutic regimens used in the 2 subgroups of EO-CRC and AO-CRC patients.



sion of hereditary syndromes, which supports the robustness of the observed association between early-onset disease and survival.

Furthermore, when analyzing the molecular subgroups, EO-CRC patients showed worse outcomes, regardless of whether they were wild-type or had RAS mutations. Patients with a BRAF mutation typically have a poorer prognosis compared to other subgroups.[18,19] However, those with EO-CRC who underwent metastasectomy demonstrated improved overall survival (OS) compared to those who did not have the surgery. This finding aligns with existing literature and major clinical guidelines.[10] In BRAF-mutated AO-CRC patients, those who underwent metastasectomy had a median overall survival comparable to those who did not have the

surgery. This finding is noteworthy because it indicates that metastasectomy provides no advantage for patients over 50. This data warrants further investigation. EO-CRC patients, despite undergoing a higher percentage of resections and more intensive chemotherapy, still experienced poorer outcomes.

The prognostic effect of early-onset CRC was largely consistent across major molecular subgroups, with no significant interactions observed for RAS or BRAF mutations. A borderline interaction with MSI status was noted, although this finding should be interpreted cautiously due to limited sample size and missing data.

Patients with early-onset cancer, given their optimal clinical condition and younger age at diagnosis, more often initiate intensive treatment with triplet chemotherapy combined with anti-VEGF. This therapeutic approach aims to maximize the chances of a favorable response, potentially leading to a reduction in tumor size and subsequent reevaluation for surgical operability.[19-22] Despite the more intense treatment regimen, our work showed that the prognosis for early-onset patients is worse compared to that of AO-CRC patients.

NGS data showed a higher mutational burden in EO-CRC patients. In particular, our study highlighted a higher frequency of TP53, ARID1A, and CTNNB1 mutations. The TP53 gene is a tumor suppressor and plays a crucial role in regulating cell growth, DNA repair, and apoptosis. Mutations or deletions of the TP53 gene are found in nearly 50% of human cancers, leading to a loss of its tumor-suppressing capabilities.[22] Tumors with a TP53 mutation show genomic instability and have a poor prognosis.[23-25] Furthermore, p53 overexpression is linked to resistance against 5-FU-based chemotherapy and anti-EGFR monoclonal antibody treatments.[26]

ARID1A mutations are commonly observed in colorectal carcinomas, resulting in truncation and loss of protein expression. The function of ARID1A is closely linked to the activity of mismatch repair proteins, such as MSH2, which is activated during the mismatch repair process that occurs during neoplastic cell replication. ARID1A mutations are frequently found alongside mutations in several other genes, including TP53, KRAS, APC, FBXW9, and PIK3CA. These mutations lead to an increased level of neoantigens, which is associated with higher tumor mutational burden (TMB) and frameshift mutations. This mechanism presents an opportunity to utilize immune checkpoint inhibitors, either as a standalone treatment or in combination with other therapies in this context.[27,28]

CTNNB1 acts as a coactivator in the Wnt/β-catenin pathway, which enhances cell signaling by interacting with E-cadherin and actin to facilitate cell-cell adhesion. Mutations in CTNNB1 disrupt the transcription of genes related to the Wnt/β-catenin signaling pathway, thereby promoting carcinogenesis.[29] Mutations in the CTNNB1 gene are linked to poorer prognosis and outcomes in cancer patients. Additionally, CTNNB1 seems to affect tumor immune infiltration by influencing the behavior of tumor-infiltrating lymphocytes and cancer-associated fibroblasts. Lastly, CTNNB1 is involved in various cell signalling processes, including the Wnt and Hippo signalling pathways.[30]

The main limitations of our study are its retrospective nature and the recruitment of an unselected population, with different clinical approaches in the participating centers. Additionally, adherence to screening programs in AO-CRC patients may have contributed to the early diagnosis of metastatic disease, thereby partially impacting differences in survival rates. Finally, it should be noted that the analysis was conducted from 2008 to 2019, before the availability of several therapies, which at the time were not approved, were pending approval, or were not widely used, such as encorafenib, tucatinib, and pembrolizumab.

Another aspect to consider is the availability of NGS tests during the time frame considered. Over the years, NGS panels have improved in performance and in the number of genes that can be evaluated with a single test. Therefore, with modern panels, more mutations can be detected.

The highly selective nature of the study population represents a significant limitation. Our findings are specifically relevant to patients with liver-limited metastatic colorectal cancer who were considered suitable for curative-intent hepatectomy and should not be extrapolated to the broader metastatic CRC population, which includes patients with extrahepatic disease or unresectable tumors. Nonetheless, this targeted approach enables a clinically meaningful assessment of outcomes in a subgroup where aggressive multimodal strategies are often employed and where prognostic differences between early-onset and typical-onset disease may have the most significant therapeutic implications.

In the dataset, there were a total of 41 patients with dMMR or MSI-H. Out of these, 11 were treated with immune checkpoint inhibitors (7 EO patients and 4 LO patients). However, due to the low numbers, it is difficult to draw statistically significant differences. In this subgroup of patients, 3 cases of Lynch syndrome were diagnosed. It should be noted that in the time frame indicated, the MSI-H test was not yet universally performed and therefore was not available for some patients. It is also important to investigate the role of targeted therapies for the KRAS G12C mutation and the potential impact they could have on differences in prognosis.[31-33]

In conclusion, EO-CRC shows peculiar clinical and biological features, with a more aggressive and advanced disease at the time of diagnosis. Outcomes are not better, reflecting different biology or a greater tumor burden at presentation. An approach that could provide a survival advantage in this group of patients could involve liver transplantation. The recent TransMet study has shown that in a well-selected population of patients with unresectable liver metastases, a combined chemotherapy and liver transplant approach yielded excellent results in terms of 5-year OS compared to patients treated with chemotherapy alone (56.6% vs. 12.6%).[34,35] Further research should focus on translational studies to assess differences in treatment resistance and early metastasis.

Ethics Approval and Consent to Participate

Ethics Committee approval was obtained for the study (Protocol number 2020/10912 – code: EMIBIOCCOR) from Cagliari Indipendent Ethics Committee and written informed consent was obtained from all participants for their tissues to be utilized for this work. This study was performed in accordance with the study protocol, the ethical principles stated in the Declaration of Helsinki as well as those indicated in the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP; ICH E6, 1995), and all applicable regulatory requirements.

Data Availability

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

Disclosure

The authors declare no competing interests.

CRediT authorship contribution statement

Andrea Pretta: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Pina Ziranu:** Writing – review & editing, Investigation, Data curation. **Francesca Bergamo:** Investigation, Data curation. **Andrea Bottelli:** Investigation, Data curation. **Federica Marmorino:** Investigation, Data curation. **Mariapaola Masiello:** Investigation, Data curation. **Stefano Mariani:** Investigation, Data curation. **Krisida Cerma:** Investigation, Data curation. **Filippo Ghelardi:** Investigation, Data curation. **Paolo Ciracì:** Investigation, Data curation. **Alessia Lancianese:** Investigation, Data curation. **Valeria Pusceddu:** Investigation, Data curation. **Eleonora Perissinotto:** Investigation, Data curation. **Alberto Giovanni Leone:** Investigation, Data curation. **Ada Taravella:** Investigation, Data curation. **Erika Cimbro:** Investigation, Data curation. **Gianluca Pretta:** Writing – review & editing. **Riccardo Cerantola:** Investigation, Data curation. **Luca Papini:** Investigation, Data curation. **Clelia Donisi:** Investigation, Data curation. **Gianmarco Ricagno:** Investigation, Data curation. **Raffaele Squitieri:** Investigation, Data curation. **Riccardo Giampieri:** Writing – review & editing, Visualization, Investigation, Data curation. **Chiara Cremolini:** Writing – review & editing, Visualization. **Sara Lonardi:** Writing – review & editing, Visualization. **Filippo Pietrantonio:** Writing – review & editing, Visualization. **Mario Scartozzi:** Writing – review & editing, Validation, Supervision, Funding acquisition.

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