

Prognostic Impact of Bone Metastases in Metastatic Colorectal Cancer: Retained Efficacy of Triplet Chemotherapy plus Bevacizumab in the TRIBE and TRIBE2 Trials

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Abstract

Colorectal cancer (CRC) is among the most frequently diagnosed malignancies, with roughly 20% of patients presenting with metastases at the time of diagnosis, and 50%-60% eventually developing metachronous metastatic lesions. Although skeletal metastases are relatively uncommon, they are often linked to increased disease burden, poorer prognosis, diminished quality of life, and substantial healthcare costs. Recently, the combination of FOLFOXIRI and bevacizumab has been established as the preferred standard of care for metastatic CRC, based on the positive outcomes of the TRIBE and TRIBE2 trials. Despite its overall efficacy, evidence regarding the performance of this regimen in patients with bone metastases is limited. We conducted a pooled analysis of the TRIBE and TRIBE2 trials, focusing specifically on individuals with bone metastases. In the overall cohort, patients with bone involvement at baseline exhibited shorter overall survival (OS; 14.0 versus 26.2 months; hazard ratio [HR] 2.04, 95% confidence interval [CI] 1.46–2.87; $P < 0.001$) and progression-free survival (PFS; 6.2 versus 11.1 months; HR 1.96, 95% CI 1.42–2.69; $P < 0.001$) compared with those without bone lesions. No significant interaction between treatment and bone involvement was observed for PFS ($P = 0.094$) or OS ($P = 0.38$). In multivariate analysis, bone metastases remained a negative prognostic factor (HR 2.24, 95% CI 1.54–3.26; $P < 0.001$). Additionally, patients whose first radiological progression involved bone (including those with pre-existing bone metastases) had reduced OS compared with those who progressed at other sites (10.4 versus 13.2 months; HR 1.48, 95% CI 1.15–1.91; $P = 0.002$). A trend toward shorter OS (7.5 versus 11 months; HR 1.50, 95% CI 0.92–2.45; $P = 0.10$) was observed in patients with baseline bone metastases compared to those who developed skeletal involvement at first progression. These results confirm that bone metastases negatively affect prognosis in CRC. Importantly, our study demonstrates for the first time that the survival benefit of triplet chemotherapy combined with bevacizumab persists in this high-risk subgroup.

Keywords: Prognosis, Triplet chemotherapy, Colorectal cancer, Bone metastases

Introduction

Colorectal cancer (CRC) is the third most common cancer globally [1]. Approximately 15%-20% of patients present with synchronous metastases [2], and 50%-60%

will develop metachronous metastatic disease [3, 4]. While the liver and lungs are the most frequent sites of distant spread [5], bone metastases are less common, occurring in around 10%-15% of patients and frequently coexisting with lesions in other organs [6]. One retrospective case series reported bone metastases in 5.5% of patients at diagnosis [7]. Though uncommon, skeletal metastases are associated with poor outcomes and reduced quality of life due to skeletal-related events (SREs), including pain, spinal cord compression, and hypercalcemia, which often necessitate hospitalization and impose significant healthcare costs [8].

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Retrospective series suggest that approximately 70% of patients with bone metastases experience SREs, with radiation therapy being the most frequently applied treatment [6]. Currently, large clinical trials provide limited prognostic or predictive data for metastatic CRC patients with bone involvement [9]. The incidence of skeletal metastases in CRC has increased in recent years, likely reflecting improvements in overall survival [6]. This highlights the urgent need to better characterize this patient population.

FOLFOXIRI combined with bevacizumab has recently been recommended as a first-line therapy for selected patients with metastatic CRC [10, 11]. The TRIBE and TRIBE2 phase III studies demonstrated that the triplet plus bevacizumab improved OS, progression-free survival (PFS), and objective response rate (ORR) compared with doublet chemotherapy (FOLFIRI/FOLFOX) plus bevacizumab [12, 13].

In the TRIBE study [12], OS was 29.8 months in the triplet plus bevacizumab arm versus 25.8 months in the FOLFIRI plus bevacizumab arm (HR 0.80, 95% CI 0.65–0.98; $P = 0.03$). PFS also improved (12.1 versus 9.7 months; HR 0.75, 95% CI 0.62–0.90; $P = 0.003$), with consistent benefits across all predefined subgroups [14]. TRIBE2 showed that frontline FOLFOXIRI plus bevacizumab followed by reintroduction at first progression outperformed the sequence of FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab (PD) [15]. However, this greater efficacy was accompanied by increased toxicity, including higher rates of neutropenia, diarrhea, and hypertension. These findings underscore the need for careful patient stratification to avoid unnecessary toxicity in patients unlikely to benefit from intensified therapy.

Notably, neither TRIBE nor TRIBE2 included a subgroup analysis specifically for patients with bone metastases; therefore, there is limited evidence regarding the effectiveness of triplet chemotherapy in this subgroup. To address this gap, we conducted a pooled analysis of TRIBE and TRIBE2 to evaluate the prognostic and predictive significance of bone metastases in patients with metastatic CRC receiving upfront chemotherapy plus bevacizumab.

Materials and Methods

Study design and procedures

The TRIBE [12] and TRIBE2 [15] trials were international, open-label, phase III randomized studies,

together enrolling 1,187 patients with metastatic colorectal cancer (mCRC) that was initially unresectable and untreated. In TRIBE, 508 patients were randomly assigned in a 1:1 ratio to receive either FOLFIRI plus bevacizumab or FOLFOXIRI plus bevacizumab. TRIBE2 randomized 679 patients 1:1 to receive FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab upon disease progression (PD), or FOLFOXIRI plus bevacizumab with reintroduction of the same regimen at PD. Treatment cycles were limited to 12 in TRIBE and 8 in TRIBE2. After completion of these cycles, all patients continued 5-fluorouracil combined with bevacizumab until PD, unacceptable toxicity, or voluntary withdrawal. Baseline CT imaging was mandatory for all patients, with follow-up scans scheduled at preplanned intervals to monitor response. PET or bone scintigraphy was optional and performed at the discretion of the investigator.

Statistical analysis

Categorical variables were compared using χ^2 or Fisher's exact tests, as appropriate. PFS and OS were estimated using Kaplan–Meier survival curves, and the log-rank test assessed differences between groups. Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs), while logistic regression provided odds ratios (ORs) and associated CIs.

The effect of baseline bone metastases on PFS and OS was initially explored using univariate analyses. Additional univariate analyses examined other potential prognostic factors, including clinical variables [Eastern Cooperative Oncology Group (ECOG) performance status (PS), age, sex, prior adjuvant therapy, time to metastasis, surgery on the primary tumor, tumor location, treatment assignment] and molecular characteristics (RAS and BRAF mutational status). Variables with $P < 0.10$ in univariate testing were entered into multivariate Cox models. All tests were two-sided, with statistical significance defined as $P \leq 0.05$. Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). Data cut-offs were 31 July 2014 for TRIBE and 30 July 2019 for TRIBE2.

Results and Discussion

Among the 1,187 patients in the intention-to-treat population, 41 (3.5%) had bone metastases at study entry (**Table 1**). No significant differences were observed in

other baseline clinical or molecular characteristics between patients with and without skeletal involvement. Fourteen patients experienced skeletal-related events (SREs) during the studies: six in TRIBE (four on FOLFOXIRI/bevacizumab, two on

FOLFIRI/bevacizumab) and eight in TRIBE2 (five on triplet therapy, three on doublet therapy). In TRIBE, five of these events required radiotherapy and one required surgery, while in TRIBE2, all SREs were managed with radiotherapy

Table 1. Baseline characteristics of study participants

Characteristic	P-value	Bone involvement at progression	
		No (n=1106), n (%)	Yes (n=40), n (%)
Treatment arm	0.739		
Doublets + Bev		555 (50)	19 (47)
FOLFOXIRI + Bev		551 (50)	21 (53)
Sex	0.081		
Male		651 (59)	18 (45)
Female		455 (41)	22 (55)
ECOG PS	0.309		
0		972 (88)	33 (83)
1-2		134 (12)	7 (17)
Site of primary tumor	0.902		
Right		378 (34)	14 (35)
Left and rectum		704 (64)	25 (63)
Unknown		24 (2)	1 (2)
Resected primary tumor	0.058		
Yes		635 (57)	29 (73)
No		471 (43)	11 (27)
Adjuvant treatment	0.744		
Yes		73 (7)	3 (7)
No		1033 (93)	37 (93)
Age group (years)	0.186		
<70		929 (84)	37 (92)
≥70		177 (16)	3 (8)
Time to metastases	0.171		
Synchronous		944 (85)	31 (77)
Metachronous		162 (15)	9 (23)
Mutational status	0.390		
Wild type		222 (20)	6 (15)
RAS mut		623 (56)	28 (70)
BRAF mut		86 (8)	2 (5)
Unknown		175 (16)	4 (10)

BEV, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status.

Patients presenting with bone metastases at baseline had significantly shorter median PFS (6.2 vs. 11.1 months; HR 1.96, 95% CI 1.42–2.69; $P < 0.001$); (**Figure 1a**) and OS (14.0 vs. 26.2 months; HR 2.04, 95% CI 1.46–2.87; $P < 0.001$); (**Figure 1b**). In multivariate models, baseline bone involvement remained strongly associated with worse outcomes for PFS (HR 2.37, 95% CI 1.67–3.37; $P < 0.001$); (**Table 2**) and OS (HR 2.24, 95% CI 1.54–3.26;

$P < 0.001$); (**Table 3**). Additional independent predictors of OS included ECOG performance status, previous primary tumor resection, tumor sidedness, and mutation profile [14, 16, 17]. Objective response rates did not differ significantly between patients with and without skeletal metastases (46% vs. 58%; OR 0.63, 95% CI 0.33–1.17; $P = 0.14$).

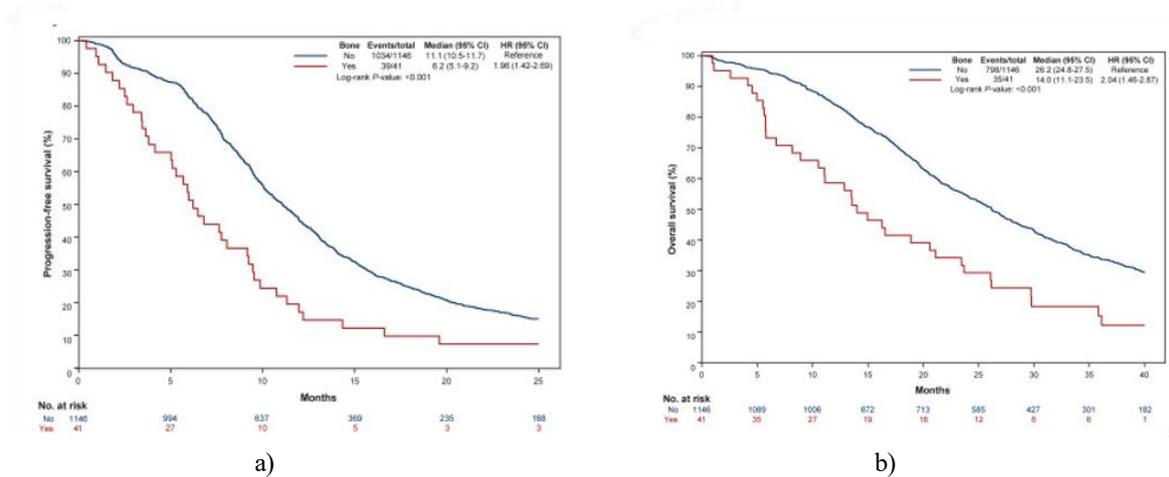


Figure 1. Kaplan–Meier survival curves comparing (a) progression-free survival and (b) overall survival according to baseline bone involvement. CI, confidence interval; HR, hazard ratio.

Table 2. Univariate and multivariate analyses for progression-free survival.

Characteristic	Category / Value	Multivariate Analysis		Univariate Analysis		n (%)
		HR (95% CI)	P-value	HR (95% CI)	P-value	
Bone involvement						
	No	1 (reference)	<0.001	1 (reference)	<0.001	1146 (97)
	Yes	2.37 (1.67-3.37)		1.96 (1.42-2.70)		41 (3)
Treatment arm						
	Doublet + Bev	1 (reference)	<0.001	1 (reference)	<0.001	596 (50)
	FOLFOXIRI + Bev	0.76 (0.66-0.87)		0.76 (0.68-0.86)		591 (50)
Age, years						
	<70	—	—	1 (reference)	0.436	1005 (85)
	≥70	—	—	1.07 (0.91-1.26)		182 (15)
ECOG Performance Status						
	0	1 (reference)	<0.001	1 (reference)	<0.001	1038 (87)
	1-2	1.72 (1.42-2.09)		1.78 (1.49-2.12)		149 (13)
Sex						
	Female	1 (reference)	0.027	1 (reference)	0.066	494 (42)
	Male	1.17 (1.02-1.34)		1.12 (0.99-1.27)		693 (58)
Previous adjuvant therapy						

	No	1 (reference)	0.512	1 (reference)	0.004	1108 (93)
	Yes	0.89 (0.62-1.27)		0.71 (0.56-0.91)		79 (7)
Time to metastases						
	Metachronous	1 (reference)	0.516	1 (reference)	0.002	179 (15)
	Synchronous	1.09 (0.85-1.39)		1.31 (1.10-1.55)		1008 (85)
Resected primary tumor						
	No	1 (reference)	0.008	1 (reference)	<0.001	499 (42)
	Yes	0.82 (0.71-0.95)		0.75 (0.66-0.84)		688 (58)
Site of primary tumor						
	Right	1 (reference)	0.645	1 (reference)	0.100	408 (34)
	Left and rectum	0.97 (0.84-1.12)		0.90 (0.79-1.02)		751 (64)
	Unknown	—	—	—	—	28 (2)
Mutational status						
	All WT (Wild type)	1 (reference)		1 (reference)		237 (20)
	RAS mut	1.22 (1.04-1.43)	0.016	1.20 (1.03-1.40)	0.022	672 (57)
	BRAF mut	1.75 (1.34-2.29)	<0.001	1.71 (1.33-2.20)	<0.001	94 (8)
	Unknown	—	—	—	—	184 (15)

Significant P-values are indicated in bold.

Table 3. Univariate and multivariate analyses for overall survival

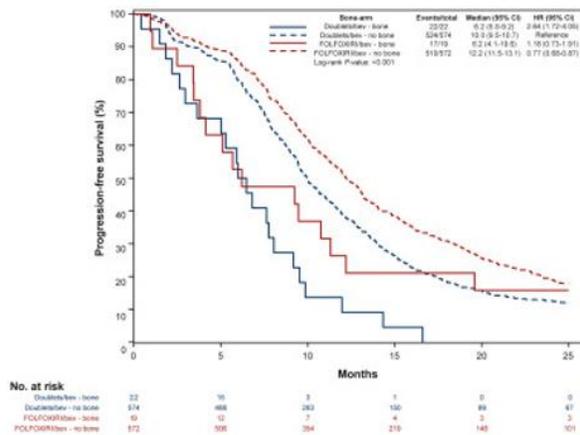
Characteristic	Category / Value	Multivariate Analysis		Univariate Analysis		n (%)
		HR (95% CI)	P-value	HR (95% CI)	P-value	
Bone involvement						
	No	1 (reference)	<0.001	1 (reference)	<0.001	1146 (97)
	Yes	2.24 (1.54-3.26)		2.04 (1.46-2.87)		41 (3)
Treatment arm						
	Doublet + Bev	1 (reference)	0.037 ^a	1 (reference)	0.007	596 (50)
	FOLFOXIRI + Bev	0.85 (0.73-0.99)		0.83 (0.72-0.95)		591 (50)
Age, years						
	<70	—	—	1 (reference)	0.107 ^a	1005 (85)
	≥70	—	—	1.16 (0.97-1.40)		182 (15)
ECOG Performance Status						
	0	1 (reference)	<0.001	1 (reference)	<0.001	1038 (87)
	1-2	2.14 (1.75-2.62)		2.24 (1.86-2.70)		149 (13)
Sex						

	Female	—	—	1 (reference)	0.180 ^a	494 (42)
	Male	—	—	1.10 (0.96-1.26)		693 (58)
Previous adjuvant therapy						
	No	1 (reference)	0.357	1 (reference)	<0.001	1108 (93)
	Yes	0.82 (0.53-1.26)		0.57 (0.42-0.77)		79 (7)
Time to metastases						
	Metachronous	1 (reference)	0.312	1 (reference)	<0.001	179 (15)
	Synchronous	1.16 (0.87-1.55)		1.53 (1.24-1.87)		1008 (85)
Resected primary tumor						
	No	1 (reference)	0.002	1 (reference)	<0.001	499 (42)
	Yes	0.77 (0.66-0.91)		0.70 (0.61-0.80)		688 (58)
Site of primary tumor						
	Right	1 (reference)	0.002	1 (reference)	<0.001	408 (34)
	Left and rectum	0.83 (0.71-0.98)		0.74 (0.64-0.85)		751 (64)
	Unknown	—	—	—	—	28 (2)
Mutational status						
	All WT (Wild type)	1 (reference)		1 (reference)		237 (20)
	RAS mut	1.64 (1.35-2.00)	<0.001 ^a	1.65 (1.37-2.00)	<0.001 ^a	672 (57)
	BRAF mut	2.85 (2.12-3.83)	<0.001 ^a	2.96 (2.24-3.92)	<0.001 ^a	94 (8)
	Unknown	—	—	—	—	184 (15)

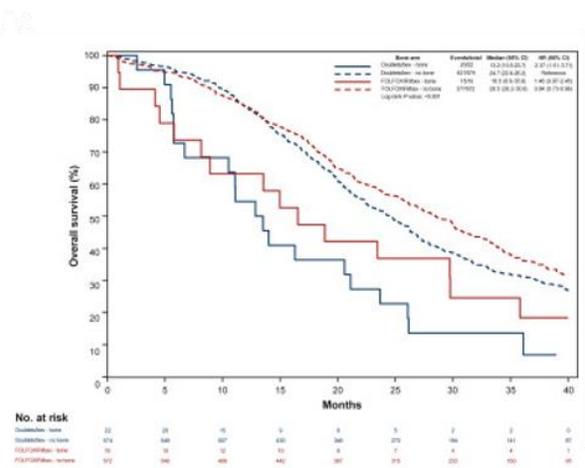
Significant P-values are highlighted in bold.

aIndicates non-significant P-values.

No statistically significant interaction was observed between the presence of bone metastases and the assigned treatment for either progression-free survival (PFS; P = 0.094); (**Figure 2a**) or overall survival (OS; P = 0.38); (**Figure 2b**).



a)



b)

Figure 2. Kaplan–Meier curves comparing (a) PFS and (b) OS stratified by the presence of bone metastases and treatment regimen. BEV, bevacizumab.

Following first disease progression, 77 out of 1,070 (7%) patients still alive exhibited bone metastases. These patients had shorter post-progression survival than those

without skeletal involvement (10.4 vs. 13.2 months; HR 1.48, 95% CI 1.15–1.91; $P = 0.002$). When comparing patients with baseline bone metastases ($n = 37$) to those who developed new bone lesions at progression ($n = 40$), a trend toward reduced survival was observed (7.5 vs. 11 months; HR 1.50, 95% CI 0.92–2.45; $P = 0.10$).

A subgroup analysis was performed on patients who developed bone metastases at the time of first radiological progression, excluding those with bone involvement at baseline. Of 1,146 patients, 40 (3%) experienced new skeletal lesions, while 1,106 (97%) never developed bone metastases. Baseline characteristics were comparable between these two groups (**Table 1**).

The objective response rate (ORR) did not differ significantly (60% vs. 57%; OR 1.088, 95% CI 0.571–2.070; $P = 0.798$). Median PFS showed a non-significant trend toward shorter duration in patients with bone progression at first radiological assessment (9.0 vs. 11.1 months; HR 1.35, 95% CI 0.98–1.85; $P = 0.06$) compared with those progressing at other sites.

Evidence regarding the prognostic and predictive impact of bone metastases in colorectal cancer (CRC) is limited, with most data derived from retrospective studies [9, 18]. Previous reports indicate that skeletal involvement is associated with reduced survival [6], though its influence on treatment response is not well defined. To address this gap, we conducted a pooled analysis of the TRIBE [12] and TRIBE2 [15] trials, evaluating the prognostic and predictive relevance of bone metastases in patients receiving doublet or triplet chemotherapy plus bevacizumab.

In our cohort, patients with baseline bone lesions had significantly worse PFS and OS than those without skeletal involvement. Multivariate analyses confirmed baseline bone metastases as an independent negative prognostic factor for both OS and PFS, alongside established predictors such as ECOG performance status, tumor sidedness, previous primary resection, and mutation profile [16, 17]. Additionally, patients who developed skeletal metastases at first radiological progression exhibited inferior OS compared with those progressing at other sites. Subgroup analyses of patients developing new bone lesions at progression (excluding baseline cases) showed no differences in baseline features or ORR compared with patients without skeletal involvement.

Although not statistically significant, this subgroup demonstrated a trend toward shorter PFS, consistent with

the notion that bone-involving CRC displays more aggressive clinical behavior. Nevertheless, similar ORR between groups suggests that the efficacy of chemotherapy is maintained even in patients with bone metastases.

Patients with bone involvement at baseline exhibited a non-significant tendency toward worse OS compared with those developing skeletal lesions at first progression, likely reflecting higher disease burden in synchronous bone metastases. Importantly, no interaction between skeletal involvement and chemotherapy intensity was observed for either PFS or OS, indicating that the survival benefit of FOLFOXIRI plus bevacizumab persists in this high-risk population.

Our findings, based on a large prospective cohort, provide important prognostic and predictive insights for mCRC patients with skeletal metastases. Limitations include the retrospective nature of bone-specific analyses, lack of data on antiresorptive therapies, and the low number of SREs, which precluded treatment arm comparisons.

Conclusion

In conclusion, bone metastases confer a negative prognostic impact in CRC. The triplet regimen with bevacizumab retains its survival benefit in this subgroup, supporting its use in patients with poor prognosis due to skeletal involvement. Future prospective studies are needed to clarify which patients benefit most from intensive treatment and to better understand the biology and clinical trajectory of bone metastases in CRC.

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Conflict of Interest: CC reports consulting or advisory role for Roche, Bayer, Amgen, MSD, and Pierre Fabre; is on the speakers bureau for SERVIER and Merck; honoraria from Roche, Amgen, Bayer, SERVIER, MSD, Merck, Pierre Fabre, and Organon; research funding from Merck, Bayer, Roche, and SERVIER. DR is on the speakers bureau for MSD Oncology. SL received consulting or advisory role from Amgen, Merck Serono, Lilly, AstraZeneca, Incyte, Daiichi-Sankyo, Bristol-Myers Squibb, Servier, and MSD; is on the speakers bureau for Roche, Lilly, Bristol-Myers Squibb, Servier, Merck Serono, Pierre-Fabre, GSK, and Amgen; research funding from Amgen, Merck Serono, Bayer, Roche, Lilly, Astra Zeneca, and Bristol-Myers Squibb. AZ is on

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