EFFECTIVENESS AND SAFETY OF CAPECITABINE WITH OR WITHOUT BEVACIZUMAB AS MAINTENANCE THERAPY IN METASTATIC COLORECTAL CANCER: REAL-WORLD EVIDENCE FROM VIETNAM

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This retrospective cohort study evaluated the effectiveness and safety of capecitabine-based maintenance therapy in 182 Vietnamese patients with recurrent or metastatic colorectal cancer who achieved disease control after first-line CAPOX plus bevacizumab. Among them, 114 received bevacizumab-capecitabine and 68 received capecitabine alone. Median progression-free survival and overall survival for the whole cohort were 7.9 and 29.6 months, respectively. Compared with capecitabine monotherapy, bevacizumab-capecitabine maintenance was associated with significantly longer progression-free survival (11.2 vs. 5.5 months) and overall survival (36.5 vs. 23.5 months). In multivariable analysis, capecitabine monotherapy was independently associated with a higher risk of progression and death, while response to first-line treatment predicted longer progression-free survival and a higher number of metastatic sites was associated with worse overall survival. Both regimens were generally well tolerated, with most adverse events being grade 1-2 and no treatment-related death. These findings suggest that bevacizumab plus capecitabine is an effective and tolerable maintenance strategy for appropriately selected patients with metastatic colorectal cancer in routine Vietnamese clinical practice.

Keywords: Metastatic colorectal cancer, capecitabine, bevacizumab, maintenance therapy, Vietnam, real-world study.

I. INTRODUCTION

Colorectal cancer (CRC) remains a major global health burden and is among the leading causes of cancer-related morbidity and mortality. According to GLOBOCAN 2022, CRC ranks third in incidence and second in mortality worldwide. In Vietnam, CRC also represents a significant public health challenge, with 16,835 new cases and approximately 8,454 deaths annually.[1] Despite advances in screening and treatment, a substantial proportion of patients are diagnosed at or progress to metastatic disease, which is associated with a poor prognosis and five-year survival rates below 20%.[2] Over the past two decades, survival outcomes in metastatic CRC (mCRC) have improved markedly, with median overall survival reaching over 30 months in contemporary practice.[3]

This progress is largely driven by the use of combination chemotherapy regimens such as FOLFOX, FOLFIRI, or CAPOX, often combined with targeted agents like bevacizumab. These induction therapies can achieve high disease control rates; however, prolonged use is

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limited by cumulative toxicities that negatively impact treatment adherence and quality of life.[4] However, prolonged administration of full-intensity combination chemotherapy is often limited by cumulative toxicities, including peripheral neuropathy, myelosuppression, gastrointestinal adverse events, and fatigue, which may adversely affect treatment adherence and quality of life.[5]

To address this challenge, maintenance therapy has emerged as a strategy to sustain disease control while reducing treatment-related toxicity. This approach involves de-escalation to less intensive regimens after initial response or stabilization. Capecitabine, alone or combined with bevacizumab, is commonly used due to its efficacy, tolerability, and convenience.[6,7] Evidence from randomized trials such as CAIRO3 and OPTIMOX2 supports the role of maintenance therapy in prolonging progression-free survival and reducing severe adverse events, although its impact on overall survival remains inconsistent.[8-10]

In real-world settings, particularly in low- and middle-income countries like Vietnam, treatment decisions are further influenced by patient characteristics and resource availability. Capecitabine monotherapy is often used when biologic agents are not feasible, while combination therapy may be reserved for selected patients. However, comparative real-world data on these strategies remain limited in the Vietnamese population. Therefore, this study aimed to evaluate the effectiveness and safety of maintenance therapy with capecitabine with or without bevacizumab in patients with recurrent or metastatic CRC in Vietnam.

II. MATERIALS AND METHODS

1. Study design and setting

A retrospective cohort study was conducted at K Hospital, Vietnam, between March and May 2025. Medical records of patients treated between January 2018 and May 2025 were reviewed. Data collection was performed between March and May 2025.

Patient eligibility

Eligible patients were adults aged 18 years or older with histologically confirmed metastatic colorectal adenocarcinoma who were not candidates for curative surgical resection. All patients had achieved disease control, defined as complete response, partial response or stable disease, after first-line induction chemotherapy with the CAPOX (capecitabine and oxaliplatin) regimen in combination with bevacizumab. Additional inclusion criteria comprised an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, adequate hepatic, renal, and bone marrow function permitting continuation of systemic therapy, and receipt of capecitabine-based maintenance therapy-either alone or combined with bevacizumab-for a minimum of three cycles.

Patients were excluded if they had documented disease progression following induction therapy, underwent surgical resection of metastatic lesions during chemotherapy, had a concurrent or prior diagnosis of another malignancy, presented with central nervous system metastases, were pregnant or breastfeeding at the time of treatment, had active infections requiring systemic therapy, or had incomplete clinical documentation relevant to treatment exposure or disease status.

2. Methods

Treatment protocol

All participants were initially treated with up to eight cycles of first-line induction chemotherapy using the CAPOX plus bevacizumab regimen, with the goal of achieving maximal tumor

response prior to transition to maintenance therapy. Capecitabine was administered orally at 1,000 mg/m² twice daily on days 1-14 of each 21-day cycle, oxaliplatin was administered intravenously at 130 mg/m² on day 1, and bevacizumab was given as an intravenous infusion at 7.5 mg/kg on day 1 of each cycle.

Patients who achieved partial response or stable disease after induction were subsequently transitioned to maintenance therapy. Maintenance regimens consisted of either capecitabine monotherapy (1,000 mg/m² orally twice daily on days 1-14 every 3 weeks) or capecitabine combined with bevacizumab (capecitabine at the same dose and schedule plus bevacizumab 7.5 mg/kg intravenously on day 1 every 3 weeks). The choice of maintenance regimen was determined by the treating physician based on patient tolerability, convenience, and financial considerations.

Maintenance treatment was continued until documented disease progression, unacceptable toxicity, or patient withdrawal. Supportive care included routine monitoring, patient education regarding potential adverse effects, and symptomatic management as clinically indicated. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not routinely administered but was permitted as secondary prophylaxis in cases of severe or febrile neutropenia.

Assessments and follow-up

Baseline assessments included a comprehensive medical history, physical examination, ECOG performance status evaluation, and assessment of metastatic burden. Measurable metastatic lesions were identified using contrast-enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis, with a maximum of five target lesions per organ site, each measuring at least 10 mm in the longest diameter. Metastatic disease was diagnosed according to the AJCC 2010 criteria, based on clinical evaluation, CT imaging, and, where applicable, histopathology or positron emission tomography/computed tomography (PET/CT). Serum carcinoembryonic antigen (CEA) levels were measured as a tumor marker at baseline.

During the maintenance phase, patients were clinically evaluated before each treatment cycle. Routine evaluations included physical examination, ECOG performance status assessment, documentation of treatment-related adverse events, and laboratory investigations, including complete blood count and liver and renal function tests. Radiologic assessments with CT scans of the abdomen and pelvis, and chest imaging when clinically indicated, were repeated every two months to evaluate disease status. Serum CEA levels were reassessed every two months.

Maintenance therapy was continued until documented disease progression, unacceptable toxicity, patient withdrawal, death, or loss to follow-up. Patients who discontinued maintenance therapy for reasons other than disease progression continued to be followed every three months until documented progression, death, or last contact. For patients who discontinued maintenance therapy because of disease progression, subsequent systemic treatments and survival status were recorded during follow-up.

Study endpoints

The primary endpoints of the study were progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from initiation of maintenance therapy to the first documented disease progression or death from any cause, whichever occurred first. Disease progression was defined according

to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, including: (1) an increase of at least 20% and a minimum of 5 mm in the sum of the longest diameters of target lesions compared with baseline; (2) progression of non-target lesions; and/or (3) the appearance of one or more new lesions. OS was defined as the time from initiation of maintenance therapy to death from any cause, administrative censoring, or the last date the patient was known to be alive.[11]

The secondary endpoint was the safety profile of maintenance therapy. Adverse events (AEs) were evaluated and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Prespecified toxicities of interest during the maintenance phase included hemorrhage, hypertension, thromboembolic events, gastrointestinal perforation, hand-foot syndrome, diarrhea, peripheral neuropathy, anemia (hemoglobin <8.0 g/dL or requiring transfusion), neutropenia (absolute neutrophil count <2,000/μL), elevated liver transaminases (AST or ALT >100 U/L), and hyperbilirubinemia (total bilirubin >1.5 times the upper limit of normal).[12]

Sample size and sampling

The sample size was estimated based on an expected 1-year PFS rate of 35% among patients receiving maintenance therapy, as reported in the CAIRO3 trial.[8] Assuming a 10% margin of error and a 95% confidence level, the minimum required sample size was calculated to be 87 patients. To account for an anticipated loss to follow-up of approximately 20%, the target sample size was set at 109 patients.

Consecutive sampling was employed. All patients who met the eligibility criteria during the study period were consecutively screened and included in the analysis.

Statistical analysis

Categorical variables were summarized as frequencies and percentages and compared between treatment groups using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were presented as means with standard deviations. Progression-free survival and overall survival were estimated using the Kaplan-Meier method, and differences between treatment groups were assessed using the log-rank test. Median survival times were reported. Cox proportional hazards regression models were constructed to identify factors associated with survival outcomes. Candidate variables were selected a priori based on clinical relevance and evidence from the literature. Hazard ratios (HRs) with 95% CIs were reported.

Adverse events during maintenance therapy were summarized descriptively by treatment group and severity according to CTCAE v5.0. All statistical analyses were performed using R language, version 4.2.3. A two-sided p-value of less than 0.05 was considered statistically significant.

3. Ethical consideration

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Hanoi Medical University under decision No. 1766 dated February 4th 2025. Given the retrospective nature of the study and the use of anonymized medical records, the requirement for individual informed consent was waived by the review board.

III. RESULTS

A total of 182 patients were included in the analysis. Overall, the study population was predominantly male (58.2%), with more than half of patients aged <60 years old (53.3%) and the majority presenting with good performance status

(ECOG PS 0, 64.8%). Rectal cancer was the most common primary tumor site (43.4%), followed by left-sided (35.7%) and right-sided colon cancers (20.9%). Liver metastasis was the most frequent metastatic site, observed in 74.2% of patients, while 64.8% of patients had a single metastatic site. Most patients presented with synchronous metastases (76.4%). Partial response to first-line therapy was achieved in 72.5% of patients, while 22.5% had stable disease and 4.9% achieved complete response. The mean number of first-line treatment cycles was 8.0 ± 1.7.

Baseline demographic and clinical characteristics were generally well balanced between the bevacizumab-capecitabine and capecitabine groups, with no significant difference in age, sex, ECOG performance status, baseline CEA level, primary tumor location, prior primary tumor resection, adjuvant chemotherapy, timing of metastasis, number of first-line treatment cycles, or response to first-line therapy (all $p > 0.05$). However, several clinically relevant imbalances were observed. Mucinous adenocarcinoma was more frequent in the capecitabine group than in the bevacizumab-capecitabine group (17.6% vs. 4.4%, $p = 0.003$). Peritoneal metastasis occurred significantly more often in patients receiving capecitabine-monotherapy compared with those receiving bevacizumab-capecitabine combination (42.6% vs. 14.9%, $p < 0.001$). In addition, patients in the capecitabine group more commonly had multiple metastatic sites (≥2 sites: 45.6% vs. 29.0%), whereas a single metastatic site was more frequently observed in the bevacizumab-capecitabine group (71.1% vs. 54.4%, $p = 0.04$). (Table 1)

Table 1. Baseline characteristics (n=182)

Characteristic	Overall (N = 182)	Bevacizumab Capecitabine (N = 114)	Capecitabine (N = 68)	P
Age group, n (%)				0.200
< 60 years old	97 (53.3)	57 (50.0)	40 (58.8)	
≥ 60 years old	85 (46.7)	57 (50.0)	28 (41.2)	
Sex, n (%)				0.200
Male	106 (58.2)	71 (62.3)	35 (51.5)	
Female	76 (41.8)	43 (37.7)	33 (48.5)	
ECOG PS, n (%)				0.500
PS = 0	118 (64.8)	76 (66.7)	42 (61.8)	
PS = 1	64 (35.2)	38 (33.3)	26 (38.2)	
CEA level, n (%)				0.200
< 5 ng/mL	97 (53.3)	65 (57.0)	32 (47.1)	
≥ 5 ng/mL	85 (46.7)	49 (43.0)	36 (52.9)	

Characteristic	Overall (N = 182)	Bevacizumab Capecitabine (N = 114)	Capecitabine (N = 68)	P
Primary tumor location, n (%)				0.120
Right colon	38 (20.9)	25 (21.9)	13 (19.1)	
Left colon	65 (35.7)	46 (40.4)	19 (27.9)	
Rectum	79 (43.4)	43 (37.7)	36 (52.9)	
Histopathology, n (%)				0.003
Adenocarcinoma	165 (90.7)	109 (95.6)	56 (82.4)	
Mucinous adenocarcinoma	17 (9.3)	5 (4.4)	12 (17.6)	
Primary tumor resection, n (%)				0.600
Yes	146 (80.2)	90 (78.9)	56 (82.4)	
No	36 (19.8)	24 (21.1)	12 (17.6)	
Adjuvant chemotherapy, n (%)				0.900
None	147 (80.8)	90 (78.9)	57 (83.8)	
CAPOX	22 (12.1)	15 (13.2)	7 (10.3)	
Capecitabine	8 (4.4)	5 (4.4)	3 (4.4)	
FOLFOX	5 (2.7)	4 (3.5)	1 (1.5)	
Liver metastasis, n (%)	135 (74.2)	86 (75.4)	49 (72.1)	0.600
Lung metastasis, n (%)	43 (23.6)	29 (25.4)	14 (20.6)	0.500
Peritoneal metastasis, n (%)	46 (25.3)	17 (14.9)	29 (42.6)	< 0.001
Bone metastasis, n (%)	13 (7.1)	8 (7.0)	5 (7.4)	> 0.90
Lymph node metastasis, n (%)	14 (7.7)	9 (7.9)	5 (7.4)	0.900
Ovarian metastasis, n (%)	1 (0.5)	0 (0.0)	1 (1.5)	0.400
Number of metastatic sites, n (%)				0.040
1 site	118 (64.8)	81 (71.0)	37 (54.4)	
2 sites	58 (31.9)	31 (27.2)	27 (39.7)	
≥ 3 sites	6 (3.3)	2 (1.8)	4 (5.9)	
Timing of metastasis, n (%)				0.500
Synchronous metastasis	139 (76.4)	85 (74.6)	54 (79.4)	
Metachronous metastasis	43 (23.6)	29 (25.4)	14 (20.6)	

Characteristic	Overall (N = 182)	Bevacizumab Capecitabine (N = 114)	Capecitabine (N = 68)	P
Number of first-line treatment cycles	8.0 ± 1.7	8.2 ± 2.0	7.8 ± 1.1	0.300
Response to first-line treatment, n (%)				0.900
Partial response	132 (72.5)	81 (71.1)	51 (75.0)	
Stable disease	41 (22.5)	27 (23.7)	14 (20.6)	
Complete response	9 (4.9)	6 (5.3)	3 (4.4)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; CAPOX, capecitabine plus oxaliplatin; FOLFOX, fluorouracil, leucovorin, and oxaliplatin.

The median follow-up time was 31.4 months (IQR, 22.6-39.8 months). The median PFS and OS for the entire cohort was 7.9 months and 29.6 months, respectively. When stratified by treatment group, patients receiving maintenance therapy with bevacizumab plus capecitabine achieved a longer median PFS and OS of 11.2 months and 36.5 months compared to 5.5 months and 23.5 months in those receiving capecitabine alone. This difference was statistically significant (log-rank $p < 0.05$) (Figure 1).

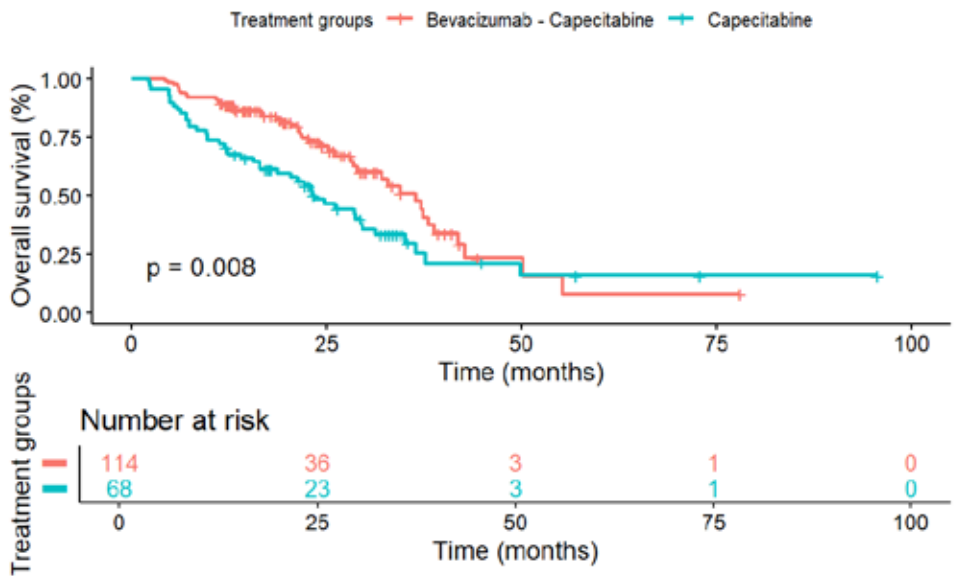

Figure 1. Progression-free and overall survival by maintenance treatment regimen (n = 182)

In the univariate analyses, the maintenance regimen was significantly associated with both progression-free survival and overall survival. Compared with bevacizumab-capecitabine, capecitabine monotherapy was associated with a higher risk of disease progression (HR 2.37, 95% CI 1.70-3.30) and death (HR 1.75, 95% CI 1.15-2.68). Response to first-line treatment was associated with improved PFS (HR 0.61, 95% CI 0.41-0.90) but not OS. In addition, peritoneal metastasis was associated with shorter PFS, while a higher metastatic burden was associated with worse OS in the univariate analysis. Primary tumor resection was not associated with PFS but was significantly associated with improved OS (HR 0.60, 95% CI 0.37-0.98). After multivariable adjustment, capecitabine monotherapy was independently associated with an increased risk of progression (HR 2.22, 95% CI 1.52-3.25) and death (HR 2.15, 95% CI 1.30-3.54) compared with bevacizumab-capecitabine. Response to first-line treatment remained an independent predictor of longer PFS (HR 0.52, 95% CI 0.35-0.80), whereas a higher number of metastatic sites was independently associated with worse OS (HR 2.32, 95% CI 1.02-5.26). Primary tumor resection remained independently associated with improved OS after adjustment (HR 0.54, 95% CI 0.31-0.93). Other clinicopathologic variables were not independently associated with survival outcomes. (Table 2)

Table 2. Univariate and multivariable analysis of factors associated with progression-free survival and overall survival among the study participants (n=182)

Variables	Progression-free survival		Overall survival	
	Univariate HR (95% CI)	Multivariable HR (95% CI)	Univariate HR (95% CI)	Multivariable HR (95% CI)
Clinicopathologic factors				
Age (≥ 60 vs. < 60 years old)	0.96 (0.69-1.33)	1.11 (0.78-1.57)	0.85 (0.55-1.30)	1.10 (0.68-1.79)
Sex (female vs. male)	1.35 (0.97-1.87)	1.34 (0.94-1.90)	1.44 (0.94-2.21)	1.22 (0.75-1.98)
ECOG performance status (PS 0 vs. PS 1)	0.91 (0.65-1.28)	0.76 (0.52-1.11)	0.99 (0.63-1.54)	1.01 (0.61-1.65)
Preoperative CEA (<5 vs. ≥ 5 ng/mL)	1.20 (0.86-1.66)	1.10 (0.77-1.57)	1.44 (0.94-2.20)	1.29 (0.83-2.01)
Primary tumor location (rectum vs. colon)	1.31 (0.94-1.82)	1.17 (0.81-1.69)	0.83 (0.54-1.27)	0.87 (0.54-1.41)
Primary tumor resection (yes vs. no)	0.94 (0.63-1.40)	0.86 (0.56-1.31)	0.60 (0.37-0.98)	0.54 (0.31-0.93)
Histopathology (mucinous adenocarcinoma vs. adenocarcinoma)	1.50 (0.88-2.57)	1.06 (0.59-1.91)	1.26 (0.63-2.52)	0.87 (0.41-1.88)

Variables	Progression-free survival		Overall survival	
	Univariate HR (95% CI)	Multivariable HR (95% CI)	Univariate HR (95% CI)	Multivariable HR (95% CI)
Metastatic characteristics				
Liver metastasis (yes vs. no)	1.05 (0.73-1.52)	1.41 (0.85-2.35)	0.81 (0.33-7.80)	0.70 (0.33-1.48)
Lung metastasis (yes vs. no)	0.95 (0.65-1.40)	1.03 (0.60-1.78)	0.99 (0.61-1.62)	1.21 (0.58-2.55)
Peritoneal metastasis (yes vs. no)	1.58 (1.10-2.26)	1.45 (0.79-2.65)	1.30 (0.83-2.06)	1.36 (0.58-3.15)
Number of metastatic sites (≥ 2 vs. < 2 sites)	1.34 (0.95-1.87)	1.00 (0.57-1.74)	**1.61 (1.00-2.56)**	**2.32 (1.02-5.26)**
Timing of metastasis (metachronous vs. synchronous)	1.01 (0.68-1.49)	1.08 (0.72-1.62)	0.99 (0.59-1.66)	1.00 (0.58-1.73)
Treatment-related factors				
Response to first-line treatment (yes vs. no)	**0.61 (0.41-0.90)**	**0.52 (0.35-0.80)**	0.85 (0.50-1.42)	0.99 (0.57-1.74)
Maintenance regimen (Capecitabine vs. Bevacizumab-Capecitabine)	2.37 (1.70-3.30)	2.22 (1.52-3.25)	1.75 (1.15-2.68)	2.15 (1.30-3.54)

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; PFS, progression-free survival; OS, overall survival.

Variables in bold were statistically significant.

Overall, both maintenance regimens were generally well tolerated, with the majority of adverse events being grade 1-2. Gastrointestinal toxicities were the most frequently observed clinical AEs in both groups, including diarrhea, stomatitis, and hand-foot syndrome. Diarrhea and hand-foot syndrome occurred at comparable rates between the bevacizumab-capecitabine and capecitabine groups, with low incidences of grade 3-4 events. Hematological AEs were generally mild and infrequent. Anemia was the most common hematologic toxicity in both groups, while grade 3-4 leukopenia and neutropenia were rare and occurred at similar rates between treatment arms. Hepatic and renal toxicities were uncommon and limited to grade 1-2 elevations in liver enzymes or creatinine, with no grade 3-4 hepatic or renal AEs observed in either group. Hypertension was the most common bevacizumab-associated toxicity, including a small prevalence of grade 3-4 events. Serious bevacizumab-related complications, such as venous thromboembolism and gastrointestinal perforation, were rare, and no treatment-related death was reported. (Table 3)

Table 3. Adverse events according to treatment regimen

Adverse event	Bevacizumab - Capecitabine (n = 114)		Capecitabine (n = 68)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Clinical AEs				
Nausea	12 (10.5%)	0	5 (7.4%)	0
Stomatitis	13 (11.4%)	0	6 (8.8%)	0
Diarrhea	14 (12.3%)	4 (3.5%)	10 (14.7%)	3 (4.4%)
Hand-foot syndrome	28 (24.6%)	6 (5.3%)	17 (25%)	5 (7.4%)
Peripheral neuropathy	18 (15.8%)	2 (1.8%)	10 (14.7%)	2 (2.9%)
Hematological AEs				
Anemia	15 (13.2%)	0	8 (11.8%)	0
Thrombocytopenia	9 (7.9%)	0	6 (8.8%)	0
Leukopenia	10 (8.8%)	2 (1.8%)	5 (7.4%)	2 (2.9%)
Neutropenia	9 (7.9%)	1 (0.9%)	6 (8.8%)	1 (1.5%)
Hepatic and renal AEs				
AST elevation	15 (13.2%)	0	6 (8.8%)	0
ALT elevation	12 (10.5%)	0	5 (7.4%)	0
Hyperbilirubinemia	7 (6.1%)	0	5 (7.4%)	0
Creatinine elevation	3 (2.6%)	0	1 (1.5%)	0
Bevacizumab-related AEs				
Bleeding	2 (1.8%)		-	
Hypertension	19 (16.7%)	7 (6.1%)	-	
Venous thromboembolism	1 (0.9%)	1 (0.9%)	-	
GI perforation	1 (0.9%)		-	

Abbreviations: AEs, adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GI, gastrointestinal.

The median duration of maintenance therapy in the overall cohort was 5.8 months, corresponding to 8 cycles. Most patients completed the planned induction therapy with XELOX plus bevacizumab, with 85.2% receiving all eight cycles. Treatment discontinuation during the induction phase due to toxicity occurred in 14.8% of patients, and dose reductions were required in approximately one quarter of cases (25.3%). During the maintenance phase, treatment modifications were relatively infrequent. Capecitabine dose

reduction was required in 8.2% of patients, while discontinuation of bevacizumab due to adverse events or patient preference occurred in 3.3% and 3.8% of patients, respectively. Following disease progression, 118 patients received subsequent systemic therapy. Irinotecan-based regimens were the most commonly administered second-line treatments (75.4%), followed by oxaliplatin-based regimens (16.9%). Bevacizumab was continued beyond progression in nearly two thirds of patients (64.4%). Cetuximab-based therapy was used in a minority of cases (12.7%), while 8.5% of patients discontinued systemic treatment after progression. (Table 4)

Table 4. Treatment characteristics and subsequent therapies

Treatment characteristics	N	Results
Induction therapy	182	
Completed all 8 cycles of XELOX + bevacizumab		155 (85.2%)
Discontinued after 6-7 cycles due to toxicity		27 (14.8%)
Dose reduction required during induction phase		46 (25.3%)
Maintenance therapy	182	
Number of maintenance cycles, median (IQR)		8 (5-12)
Median duration (months), median (IQR)		5.8 (3.5-8.5)
Capecitabine dose reduction		15 (8.2%)
Discontinuation of bevacizumab due to adverse events		6 (3.3%)
Discontinuation of bevacizumab due to patient preference		7 (3.8%)
Systemic therapy after disease progression	118	
Irinotecan-based regimens		89 (75.4%)
Oxaliplatin-based regimens		20 (16.9%)
Continuation of bevacizumab beyond progression		76 (64.4%)
Cetuximab-based therapy		15 (12.7%)
Discontinuation of systemic treatment		10 (8.5%)

Abbreviations: XELOX, capecitabine plus oxaliplatin.

IV. DISCUSSION

The primary objective of this study was to evaluate the efficacy of maintenance therapy with bevacizumab plus capecitabine compared with capecitabine alone in patients with metastatic colorectal cancer who had achieved disease control after first-line chemotherapy. The findings showed that bevacizumab-capecitabine maintenance was associated with prolonged progression-free survival and a favorable overall survival benefit, suggesting more sustained disease control than capecitabine alone. These results are consistent

with previous evidences supporting the role of maintenance therapy in mCRC. The phase III CAIRO3 trial established the clinical benefit of bevacizumab-capecitabine maintenance following CAPOX-B induction, reporting significant prolongation in both PFS and OS.[8] Likewise, the randomized study by Luo et al. in a Chinese cohort demonstrated the benefit of capecitabine monotherapy maintenance over observation, underscoring the feasibility of a de-escalation strategy in resource-limited settings.[13] Clinical trials such as ML18147 and BEBYP demonstrated significant overall survival benefits with the continuation or reintroduction of bevacizumab beyond disease progression, supporting the concept that sustained VEGF inhibition may translate into survival advantages in mCRC.[14,15] Further supporting this strategy, a meta-analysis by Stein et al. pooling data from CAIRO3, SAKK 41/06, and AIO KRK 0207 demonstrated that bevacizumab-based maintenance after bevacizumab-containing induction significantly improved progression-free survival compared with observation (HR 0.57; 95% CI, 0.43-0.75), with a consistent trend toward overall survival benefit (HR 0.89; 95% CI, 0.78-1.02), and showed superior PFS with combination maintenance using bevacizumab plus a fluoropyrimidine over bevacizumab alone.[16] The observed benefit in our study may be attributed to the sustained anti-angiogenic activity of bevacizumab, which suppresses tumor regrowth following cytoreductive induction therapy. Additionally, continuous exposure to capecitabine may maintain cytotoxic pressure on residual tumor clones, delaying disease progression. The additive or synergistic effect of combining anti-VEGF therapy with a fluoropyrimidine backbone has been demonstrated across multiple settings and is biologically plausible given the vascular dependency of metastatic lesions. Clinically, these findings support the incorporation of bevacizumab-capecitabine as a rational maintenance approach in mCRC patients with good performance status and no contraindications to anti-angiogenic therapy.

In our study, the combination of bevacizumab and capecitabine was generally well tolerated, with no treatment-related deaths and a low incidence of grade 3-4 toxicities. The rates of hypertension, diarrhea, and hand-foot syndrome were within the expected range and did not significantly compromise treatment adherence or quality of life. These findings align with those from the phase III CAIRO3 trial, which demonstrated that maintenance therapy with capecitabine-bevacizumab significantly prolonged both PFS1 and PFS2 compared to observation, while maintaining an acceptable safety profile. Grade 3-4 adverse events-including diarrhea, hypertension, and hand-foot syndrome-occurred in 23% of patients, without significant deterioration in quality of life.[8] Comparable tolerability was reported in the phase III study by Luo et al. (2016), in which capecitabine monotherapy extended median PFS compared to observation, though with a higher incidence of grade 3-4 toxicities (41.9%), primarily neutropenia, hand-foot syndrome, and mucositis.[13] Despite a higher toxicity burden than in our cohort, the adverse events remained manageable and clinically acceptable, particularly in real-world settings where access to biologics may be limited. A retrospective analysis by Huang et al. (2022) showed that adding bevacizumab to capecitabine did not lead to increased severe toxicity or treatment-related mortality in RAS-mutant mCRC patients.[17] Additional evidence from a comprehensive meta-analysis by Ma et al. (2019), which included nine phase III trials and 3,121 patients, further supports the favorable safety profile of bevacizumab-based

maintenance strategies. The study found that patients receiving maintenance therapy with bevacizumab had a significantly lower risk of experiencing grade 3-4 adverse events compared to those continuing full-intensity chemotherapy (pooled OR = 0.57; 95% CI: 0.43-0.76; p < 0.0001). Notably, the incidence of fatigue, neutropenic fever, hand-foot syndrome, nausea/vomiting, and diarrhea was significantly reduced in the maintenance group, whereas hypertension and sensory neuropathy rates were similar between arms.[18] These findings suggest that bevacizumab-based maintenance regimens can effectively mitigate cumulative toxicity while preserving efficacy-an important consideration in long-term disease management.

The outcomes of this study demonstrate that the real-world efficacy and tolerability of maintenance therapy with capecitabine ± bevacizumab in Vietnamese patients are consistent with results from pivotal clinical trials, confirming the feasibility of this treatment approach under local resource constraints. In addition, these findings reinforce current recommendations from the NCCN and ESMO guidelines,[19,20] as well as the Vietnamese Ministry of Health's national colorectal cancer guideline,[21] which prioritize bevacizumab-based first-line regimens and support the continuation of maintenance therapy with capecitabine ± bevacizumab in patients who achieve good disease control and tolerate treatment adequately.

The depth of response following induction therapy emerged as a clinically relevant predictor of maintenance benefit. Patients achieving complete or partial response had significantly improved outcomes compared to those with stable disease, with a hazard ratio of 0.52 (95% CI: 0.35-0.80). These findings align with a pooled analysis of three randomized trials-CAIRO3, AIO 0207, and NCT02027363-encompassing 1,301 patients, which demonstrated that CR/PR status conferred a greater benefit from maintenance therapy, especially when bevacizumab was part of the regimen (HR = 1.79 for CR/PR vs. HR = 1.63 for SD).[18] In our study, this association was observed for progression-free survival but not for overall survival. This pattern may reflect that early tumor response primarily captures initial chemosensitivity and disease control during the maintenance phase, thereby translating into prolonged PFS. In contrast, overall survival is influenced by multiple downstream factors, including subsequent lines of therapy, tumor heterogeneity, and post-progression management, which may attenuate the impact of initial response status. Although overall survival did not significantly differ between subgroups, the differential effect on PFS suggests that early tumor shrinkage may serve as a surrogate marker for maintenance sensitivity and guide treatment stratification.

Additionally, in our study, a higher number of metastatic sites was independently associated with significantly worse overall survival. This finding is well supported by previous clinical evidence. A 2021 retrospective cohort study including more than 3,000 patients with metastatic colorectal cancer demonstrated that patients with involvement of multiple metastatic sites had substantially shorter median overall survival compared with those with single-site disease (approximately 19 vs. 31 months; p < 0.001), and the number of metastatic sites remained an independent prognostic factor in multivariable analysis.[22] Consistent results were also reported in a recent retrospective study including 999 mCRC patients treated at Taipei Veterans General Hospital from 2013 to 2019, in which patients with ≥2 metastatic sites exhibited significantly higher mortality risk

than those with limited metastatic disease.[23] Together, these data highlight the importance of individualized patient selection for maintenance therapy, incorporating both biological (VEGF pathway sensitivity) and clinical (depth of response, metastatic pattern) parameters. Such stratification may enhance treatment efficacy while minimizing unnecessary exposure to prolonged therapy in patients unlikely to derive meaningful benefit. Lastly, the observed survival benefit associated with primary tumor resection is consistent with previous studies suggesting that removal of the primary lesion may reduce tumor burden and systemic inflammatory effects, thereby contributing to improved survival in selected patients with metastatic colorectal cancer.

This study has several limitations that warrant consideration. First, its retrospective design inherently introduces the risk of selection bias and unmeasured confounders. Treatment allocation between capecitabine alone and bevacizumab-capecitabine may have been influenced by factors such as drug affordability, patient preference, and physician judgment in routine clinical practice, rather than randomization. Second, the treatment groups were not randomized, limiting causal inference regarding the comparative efficacy and safety of bevacizumab-containing maintenance regimens. Third, molecular characteristics such as KRAS (Kirsten rat sarcoma viral oncogene homolog), NRAS (neuroblastoma RAS viral oncogene homolog), BRAF (B-Raf proto-oncogene, serine/threonine kinase), and microsatellite instability (MSI) status were not routinely available or analyzed in this retrospective dataset. These biomarkers are known to influence treatment response and prognosis in metastatic colorectal cancer and should be considered in future studies. Lastly, the relatively small sample size and single-center nature of the study may constrain the generalizability of the findings. These limitations underscore the need for prospective, multi-center trials to validate and extend our observations.

IV. CONCLUSIONS

To our knowledge, this is the first real-world study conducted in a resource-limited setting like Vietnam to evaluate the effectiveness and safety of maintenance therapy in metastatic colorectal cancer. Our findings demonstrate that maintenance treatment with bevacizumab plus capecitabine significantly prolongs both progression-free survival and overall survival compared to capecitabine monotherapy, without increasing the risk of severe toxicities or treatment-related mortality. The combination regimen was well tolerated, and multivariate analysis highlighted the prognostic significance of the metastactic burden and the post-induction tumor response. These results underscore the clinical relevance of incorporating bevacizumab into maintenance strategies, particularly among patients who achieve a favorable response to first-line therapy. Further randomized, multi-center prospective trials are warranted to validate these observations and guide optimal patient selection in similar low-resource healthcare settings.

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DECLARATION OF INTEREST STATEMENT

Consent to participate

Not applicable. This was a retrospective

study using existing medical records, and no direct contact with patients occurred. The requirement for informed consent to participate was waived by the Institutional Review Board.

Consent for publication

Not applicable. The study did not involve any individual patient data (including images or identifiable personal information) that would require consent for publication.

Conflict of interest declaration

The authors declare no competing interests in preparing this article.

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Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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