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Real-World Outcomes of First-Line Capecitabine-Oxaliplatin With or Without Bevacizumab for Unresectable Metastatic Colon Cancer: Experience From Ho Chi Minh City Oncology Hospital in a Lower-Middle-Income Country

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Abstract

Background: Despite substantial advances in systemic therapy, metastatic colorectal cancer remains a leading cause of cancer-related mortality worldwide. The addition of bevacizumab to oxaliplatin-based chemotherapy has demonstrated improved clinical outcomes in randomized clinical trials. However, real-world evidence from low- and middle-income countries, where access to targeted therapies is often limited by financial constraints, remains scarce.

Objective: To evaluate the real-world effectiveness and safety of first-line CapeOX with or without bevacizumab in patients with unresectable metastatic colon cancer treated at Ho Chi Minh City Oncology Hospital.

Methods: We conducted a retrospective cohort study including 70 consecutive patients with histologically confirmed unresectable metastatic colon adenocarcinoma who received first-line CapeOX alone or CapeOX plus bevacizumab at Ho Chi Minh City Oncology Hospital between June 1, 2021, and June 30, 2023. Tumor response was assessed according to RECIST version 1.1, adverse events were graded using CTCAE version 5.0, and progression-free survival (PFS) was estimated using the Kaplan–Meier method.

Results: Among patients treated with CapeOX alone, the objective response rate (ORR) was 46.6%, the disease control rate (DCR) was 86.6%, and the median progression-free survival (mPFS) was 9.2 months (95% confidence interval [CI], 8.6–10.8). The most common treatment-related adverse events were thrombocytopenia, neutropenia, diarrhea, nausea, and vomiting, most of which were grade 1–2. In the CapeOX plus bevacizumab group, the ORR and DCR were 55.0% and 92.5%, respectively, with a median PFS of 11.5 months (95% CI, 10.2–13.0). Hypertension was the most common bevacizumab-related adverse event. Overall, toxicities were manageable, and no unexpected safety signals were observed.

Conclusions: In this real-world cohort from a tertiary oncology center in Vietnam, the addition of bevacizumab to first-line CapeOX was associated with higher response rates and longer progression-free survival compared with CapeOX alone, while maintaining an acceptable safety profile. These findings support the effectiveness and feasibility of bevacizumab-containing therapy in routine clinical practice, particularly in resource-constrained healthcare settings where access to targeted therapy remains limited.

Keywords: metastatic colon cancer; bevacizumab; CapeOX; real-world study; progression-free survival.

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains a leading cause of cancer-related mortality. According to GLOBOCAN 2022, CRC ranks third in incidence, accounting for nearly 2 million new cases annually, and second in cancer-related deaths, with approximately one million deaths each year. The global burden of CRC continues to rise, particularly in low- and middle-income countries, owing to population aging, westernization of lifestyle, obesity, physical inactivity, smoking, and dietary changes. Vietnam has also experienced a steady increase in the incidence of CRC over the past decade, making it one of the most frequently diagnosed cancers in both men and women [1].

Despite advances in screening programs, early diagnosis, and multimodal treatment strategies, a substantial proportion of patients are still diagnosed with metastatic disease at presentation, while many others eventually develop distant metastases following curative-intent treatment. Approximately 20–25% of patients present with synchronous metastatic disease, and an additional 20–30% will develop metachronous metastases during follow-up [2]. For patients with unresectable metastatic colon cancer, systemic therapy remains the cornerstone of treatment, with the primary goals of prolonging survival, controlling tumor progression, preserving quality of life, and, in selected cases, downsizing tumors to achieve secondary resectability [3].

Over the past two decades, treatment outcomes for metastatic colorectal cancer (mCRC) have improved substantially with the introduction of combination chemotherapy and molecularly targeted therapies. Oxaliplatin-based doublet chemotherapy regimens, including FOLFOX and CapeOX (capecitabine plus oxaliplatin), are widely recommended as standard first-line treatment options for patients with good performance status. Compared with infusional fluorouracil-based regimens, CapeOX offers comparable efficacy while providing greater convenience through the use of oral capecitabine, reducing the need for central venous access and

continuous infusion, and potentially improving patient satisfaction and healthcare resource utilization [3,4].

Angiogenesis plays a pivotal role in the growth and metastatic spread of colorectal cancer. Vascular endothelial growth factor (VEGF) is one of the principal mediators of tumor angiogenesis and has therefore become an important therapeutic target. Bevacizumab, a humanized monoclonal antibody directed against VEGF-A, inhibits tumor angiogenesis and has demonstrated significant clinical benefits when combined with first-line chemotherapy. Landmark randomized clinical trials have consistently shown that adding bevacizumab to fluoropyrimidine-based chemotherapy improves objective response rates, prolongs progression-free survival, and, in selected studies, extends overall survival compared with chemotherapy alone [5–7]. Consequently, current international guidelines, including those from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), recommend bevacizumab in combination with oxaliplatin- or irinotecan-based chemotherapy as a standard first-line treatment option for patients with unresectable metastatic colorectal cancer, irrespective of RAS or BRAF mutation status when anti-EGFR therapy is not indicated [3,8].

Although the efficacy of bevacizumab has been well established in randomized controlled trials, outcomes observed in routine clinical practice may differ because real-world patients are generally older, present with more comorbidities, have poorer performance status, and are managed under more heterogeneous healthcare conditions than those enrolled in clinical trials. Consequently, real-world evidence has become increasingly important for evaluating the effectiveness and safety of contemporary treatment strategies in broader patient populations and for informing clinical decision-making.

In Vietnam, the use of bevacizumab in combination with oxaliplatin-based chemotherapy has become increasingly common in routine oncology practice. However, published real-world evidence evaluating the effectiveness and safety of CapeOX with or without bevacizumab remains limited. Ho Chi Minh City Oncology Hospital is one of the largest tertiary cancer centers in Vietnam, managing a high volume of patients with colorectal cancer referred from southern provinces nationwide. Real-world data generated from this institution may therefore provide

valuable insights into treatment outcomes in routine clinical practice and complement evidence derived from randomized clinical trials.

Therefore, we conducted this retrospective study to evaluate the effectiveness and safety of first-line CapeOX with or without bevacizumab in patients with unresectable metastatic colon cancer treated at Ho Chi Minh City Oncology Hospital. The findings are expected to provide additional real-world evidence from a high-volume tertiary cancer center in Vietnam and contribute to optimizing treatment strategies for metastatic colon cancer in similar healthcare settings.

Materials and Methods

Study design, setting, and participants

This retrospective cohort study included consecutive patients with unresectable metastatic colon cancer who received first-line systemic treatment at Ho Chi Minh City Oncology Hospital, Vietnam, between June 1, 2021, and June 30, 2023. Ho Chi Minh City Oncology Hospital is one of the largest tertiary referral cancer centers in Vietnam, receiving patients from Ho Chi Minh City and the southern provinces. During the study period, all eligible patients who fulfilled the predefined inclusion criteria were consecutively enrolled to minimize selection bias.

Eligible patients were required to have histologically confirmed adenocarcinoma of the colon with either synchronous metastatic disease at initial diagnosis or recurrent metastatic disease after previous curative-intent treatment. All metastatic lesions had to be considered unresectable at initial multidisciplinary team evaluation. Additional inclusion criteria comprised an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate hematologic, hepatic, and renal function before treatment initiation, and receipt of first-line chemotherapy with either CapeOX alone or CapeOX combined with bevacizumab. Patients were also required to have at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and complete clinical records available for treatment response and safety assessment.

Patients were excluded if they had undergone major abdominal or thoracic surgery within 28 days before initiation of systemic therapy, had undergone any invasive procedure associated with a substantial risk of bleeding, had uncontrolled hypertension despite appropriate antihypertensive treatment, required high-dose

antiplatelet or anticoagulant therapy (such as aspirin >325 mg/day), had another active malignancy, or were pregnant or breastfeeding.

Data collection and study variables

Clinical information was retrospectively extracted from electronic medical records using a standardized data collection form. Baseline demographic and clinicopathological characteristics included age at treatment initiation, sex, ECOG performance status, primary tumor location, histopathological subtype, timing of metastasis (synchronous or metachronous), metastatic sites, number of metastatic organs involved, baseline carcinoembryonic antigen (CEA) concentration, complete blood count, liver function tests, renal function tests, and urinalysis for proteinuria before treatment. Treatment-related variables included the chemotherapy regimen administered, number of treatment cycles, dose modifications, treatment discontinuation, radiological response, disease progression, survival status, and treatment-related toxicities.

Treatment

Treatment decisions were made by the treating medical oncologists according to institutional practice, international treatment guidelines, patient performance status, comorbidities, disease burden, and drug availability. The CapeOX regimen consisted of oxaliplatin administered intravenously at a dose of 130 mg/m² on Day 1 combined with oral capecitabine 1,000 mg/m² twice daily on Days 1–14 of a 21-day cycle. In the CapeOX plus bevacizumab group, bevacizumab was administered intravenously at a dose of 7.5 mg/kg on Day 1 before chemotherapy, together with oxaliplatin 130 mg/m² intravenously on Day 1 and oral capecitabine 1,000 mg/m² twice daily on Days 1–14 of each 21-day cycle. Treatment was continued until radiologically confirmed disease progression, unacceptable toxicity, patient refusal, physician decision, or conversion to potentially curative surgery when appropriate.

Outcome measures

The primary outcomes of the study were objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and treatment-related adverse events. Tumor response was assessed by contrast-enhanced computed tomography according to RECIST version 1.1. Objective response was defined as the proportion of patients achieving either complete response or partial response, whereas disease

control was defined as complete response, partial response, or stable disease. Progression-free survival was calculated from the date of initiation of first-line treatment until the first documented disease progression or death from any cause, whichever occurred first. Patients who remained alive without disease progression at the time of data analysis were censored on the date of their last clinical follow-up. Treatment-related adverse events were evaluated throughout treatment and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as means with standard deviations or medians with interquartile ranges, depending on data distribution, whereas categorical variables were presented as frequencies and percentages. Differences in categorical variables between treatment groups were analyzed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using Student's *t* test or the Mann–Whitney *U* test according to the distribution of the data. Progression-free survival was estimated using the Kaplan–Meier method with corresponding 95% confidence intervals, and survival curves were compared using the log-rank test. All statistical tests were two-sided, and a *P* value <0.05 was considered statistically significant.

Ethical considerations

The study protocol was approved by the Ethics Committee for Biomedical Research of Ho Chi Minh City Oncology Hospital, Vietnam (Approval No. **200/BVUB-HĐĐĐ**). Owing to the retrospective nature of the study and the use of anonymized medical records, the requirement for written informed consent was waived by the Ethics Committee. All patient data were de-identified prior to analysis to ensure confidentiality and were used solely for research purposes. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and relevant institutional regulations governing biomedical research involving human participants.

RESULTS

1. Study population and baseline characteristics

Between June 1, 2021 and June 30, 2023, a total of 70 eligible patients with unresectable metastatic colon cancer were included in the analysis. Overall, 42 patients (60.0%) were male and 28 (40.0%) were female. The mean age was 55.3 ± 9.5 years, with a range of 24-76 years. Most patients had an ECOG performance status of 1 (60.0%), while 22.8% had a status of 0 and 17.2% had a status of 2. De novo metastatic disease accounted for 75.7% of cases, and 57.1% of patients received CapeOX plus bevacizumab as first-line treatment. (Figure 1)

At baseline, 64.3% of patients had a CEA level >5 ng/mL, whereas 20.0% had a normal CEA level and 15.7% had no documented CEA value. Adenocarcinoma grade 2 was the predominant histologic subtype (74.3%). Left-sided primary tumors were more common than right-sided tumors (58.0% vs 42.0%). Liver metastasis was the most frequent metastatic site (57.1%), followed by peritoneal metastasis (24.3%) and lung metastasis (20.0%). (Table 1)

2. Tumor marker dynamics and radiologic response

In the CapeOX-alone group, the mean serum CEA level decreased from 15.2 ng/mL before treatment to 8.2 ng/mL after four cycles, then rose to 12.5 ng/mL after eight cycles. These changes were not statistically significant (baseline vs 4 cycles, p=0.141; 4 vs 8 cycles, p=0.241; baseline vs 8 cycles, p=0.669).

In the CapeOX plus bevacizumab group, the mean serum CEA level decreased from 23.8 ng/mL at baseline to 12.1 ng/mL after four cycles and subsequently increased slightly to 15.1 ng/mL after eight cycles. The reduction from baseline to four cycles was statistically significant (p=0.014), whereas the comparisons between four and eight cycles (p=0.584) and between baseline and eight cycles (p=0.089) were not statistically significant.

Radiologic response based on RECIST 1.1 is summarized in Table 2. After eight cycles, the overall response rate was 46.6% in the CapeOX group and 55.0% in the CapeOX plus bevacizumab group. Disease control rates were 86.6% and 92.5%, respectively. One complete response (2.5%) was observed only in the combination group. (Table 2)

3. Progression-free survival

Progression-free survival outcomes favored the combination regimen. In the CapeOX group, mean PFS was 9.7 months and median PFS was 9.2 months, with a 12-month PFS rate of 18.6%. In the CapeOX plus bevacizumab group, mean PFS was 11.6 months and median PFS was 11.5 months, with a 12-month PFS rate of 43.3%. The difference in median PFS between the two treatment groups was statistically significant (log-rank p=0.025).

The Kaplan–Meier curves for progression-free survival comparing CapeOX and CapeOX plus bevacizumab are shown in Figure 2, and the corresponding survival estimates are summarized in Table 3.

4. Safety

Treatment-related toxicities were generally manageable in both groups. Hematologic toxicity was dominated by grade 1-2 neutropenia, occurring in 33.3% of patients treated with CapeOX and 37.5% of those treated with CapeOX plus bevacizumab. Grade 3 thrombocytopenia was recorded in one patient (2.5%) in the combination group, whereas no grade 3-4 neutropenia was reported.

Among non-hematologic toxicities, peripheral neuropathy, nausea/vomiting, diarrhea, and transaminase elevation were the most frequent events. Peripheral neuropathy occurred in 43.3% of the CapeOX group and 55.0% of the combination group. Hand-foot syndrome was mostly mild, although grade 3 events occurred in 3.3% and 5.0% of the two groups, respectively. Bevacizumab-related hypertension was observed in 12.5% of patients and all events were grade 1-2. Bleeding occurred in 7.5% of patients receiving bevacizumab, and no gastrointestinal perforation, thrombosis, or proteinuria was observed. (Table 4)

5. Subgroup analyses

5.1 Factors associated with radiologic response

Across the available subgroup comparisons, most clinicopathologic variables were not significantly associated with response. In the CapeOX group, response rates did not differ significantly according to age, sex, baseline CEA level, histologic grade, or peritoneal metastasis status. In the CapeOX plus bevacizumab group, the only statistically significant association identified in the extracted source tables was a

lower response rate among patients with peritoneal metastasis after four cycles (16.7% vs 67.6% in those without peritoneal metastasis, p=0.029). (Table 5)

5.2 Factors associated with progression-free survival

Exploratory subgroup analyses suggested that, within the CapeOX-alone group, PFS was not significantly associated with baseline CEA, histologic grade, number of metastatic organs, liver metastasis, or peritoneal metastasis. In contrast, in the CapeOX plus bevacizumab group, lower baseline CEA (<=5 ng/mL) and lower-grade histology (grade 1-2) were associated with longer PFS. In both treatment groups, best tumor response after eight cycles was strongly associated with PFS, with the longest PFS observed among patients who achieved an objective response.

These findings support the clinical relevance of early tumor response and suggest that baseline tumor burden biology, particularly CEA level and histologic grade, may influence the durability of benefit from bevacizumab-containing therapy. (Table 6)

Discussion

The present study evaluated the real-world effectiveness and safety of first-line CapeOX with or without bevacizumab in patients with unresectable metastatic colon cancer treated at Ho Chi Minh City Oncology Hospital, one of the largest tertiary oncology centers in Vietnam. Our findings demonstrated that the addition of bevacizumab to CapeOX resulted in numerically higher objective response and disease control rates together with a longer median progression-free survival, while maintaining an acceptable safety profile. These results provide important real-world evidence supporting the use of bevacizumab-containing therapy in a resource-limited healthcare setting where access to biologic agents remains constrained by financial considerations.

Combination chemotherapy with fluoropyrimidine and oxaliplatin remains a cornerstone of first-line treatment for metastatic colorectal cancer. The NO16966 trial established CapeOX as an effective alternative to FOLFOX, demonstrating comparable efficacy with the additional convenience of oral capecitabine, thereby reducing the need for continuous intravenous infusion and central venous access. This regimen has subsequently become one of the recommended first-line treatment options in international guidelines. Our study further confirms that CapeOX remains an effective backbone chemotherapy regimen in Vietnamese patients, achieving an

objective response rate of 46.6% and a median progression-free survival of 9.2 months, findings that are generally consistent with previous randomized trials and contemporary international guidelines **[3–5]**.

The incorporation of bevacizumab into first-line chemotherapy has substantially improved treatment outcomes in metastatic colorectal cancer through inhibition of vascular endothelial growth factor (VEGF)-mediated angiogenesis. In the pivotal AVF2107g study, bevacizumab significantly prolonged both progression-free and overall survival when combined with irinotecan-based chemotherapy, thereby establishing anti-angiogenic therapy as an integral component of first-line treatment **[6]**. Subsequently, the NO16966 trial demonstrated that the addition of bevacizumab to oxaliplatin-based chemotherapy improved progression-free survival, although the magnitude of benefit was more modest than initially anticipated **[5]**. In the present study, patients receiving CapeOX plus bevacizumab achieved a median progression-free survival of 11.5 months compared with 9.2 months in the CapeOX group. Although the study was not powered to detect small between-group differences, the observed improvement is clinically meaningful and closely resembles outcomes reported in large international trials.

Our findings are also consistent with those from large prospective observational studies evaluating bevacizumab under routine clinical practice. The BEAT study and the BRiTE registry demonstrated progression-free survival of approximately 10–11 months with acceptable tolerability in heterogeneous patient populations outside randomized clinical trials **[11,12]**. Likewise, our cohort comprised consecutive patients treated at a high-volume tertiary referral center, thereby reflecting treatment effectiveness in routine oncology practice rather than the highly selected populations enrolled in clinical trials.

An important strength of the present study is its relevance to cancer care in low- and middle-income countries. Although current international guidelines recommend biomarker-guided treatment selection based on RAS, BRAF, HER2, and mismatch repair status **[3,8]**, implementation of precision oncology remains challenging in many developing countries because of limited availability and reimbursement of molecular testing. During the study period, comprehensive molecular profiling was not routinely available for every patient at our institution, and treatment decisions were frequently influenced by economic considerations in addition to clinical

factors. Consequently, bevacizumab was frequently selected because it can be administered irrespective of RAS mutation status and was generally more accessible than anti-EGFR therapy. Therefore, our findings reflect authentic clinical decision-making within the Vietnamese healthcare system.

Financial toxicity has emerged as an increasingly recognized determinant of treatment access and clinical outcomes in oncology. Although bevacizumab has become more widely available in Vietnam, substantial out-of-pocket expenditure remains a major barrier for many patients because reimbursement is incomplete. Consequently, treatment selection is frequently influenced by affordability rather than solely by clinical indications. This situation is common across many low- and middle-income countries and highlights the importance of generating local real-world evidence to support reimbursement policies and improve equitable access to effective targeted therapies **[13,14]**.

The toxicity profile observed in our study was comparable to previous reports. Most hematologic and gastrointestinal toxicities were grade 1–2 and were manageable with standard supportive care. Hypertension represented the most frequent bevacizumab-related adverse event, whereas severe bleeding, gastrointestinal perforation, and treatment-related mortality were uncommon. These findings are consistent with published meta-analyses and previous studies demonstrating that bevacizumab has a predictable and manageable safety profile when appropriate patient selection and monitoring are applied **[15,16]**.

Several limitations should be acknowledged. First, the retrospective design introduces the possibility of selection bias and residual confounding. Second, the relatively small sample size limits statistical power for subgroup analyses. Third, comprehensive molecular profiling was unavailable for many patients because these tests were not routinely performed during the study period. Finally, overall survival data remain immature owing to the limited duration of follow-up. Nevertheless, the strengths of this study include standardized RECIST 1.1 response assessment, CTCAE toxicity grading, and the use of consecutive real-world data from one of the largest tertiary oncology centers in Vietnam.

In conclusion, first-line CapeOX plus bevacizumab demonstrated favorable effectiveness and acceptable tolerability in Vietnamese patients with unresectable metastatic colon cancer. Beyond confirming findings from pivotal randomized trials,

our study provides valuable real-world evidence from a resource-constrained healthcare setting where access to biologic therapy remains influenced by financial considerations. Future multicenter prospective studies incorporating comprehensive molecular profiling, health economic evaluation, and longer follow-up are warranted to optimize personalized treatment strategies and improve equitable access to targeted therapy.

Declarations

Abbreviations

CEA: Carcinoembryonic antigen

CI: Confidence interval

CTCAE: Common Terminology Criteria for Adverse Events

DCR: Disease control rate

ECOG: Eastern Cooperative Oncology Group

mCRC: Metastatic colorectal cancer

mPFS: Median progression-free survival

ORR: Objective response rate

PFS: Progression-free survival

RECIST: Response Evaluation Criteria in Solid Tumors

VEGF: Vascular endothelial growth factor

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee for Biomedical Research of Ho Chi Minh City Oncology Hospital, Ho Chi Minh City, Vietnam (Approval No. 200/BVUB-HĐĐĐ). Owing to the retrospective nature of the study and the use of anonymized medical records, the requirement for written informed consent was waived by the Ethics Committee. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain patient information protected under institutional and ethical regulations but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NHQ: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing—original draft, Writing—review & editing, Supervision. NTT: Investigation, Data curation, Validation, Writing—review & editing. PTHD: Conceptualization, Supervision, Validation, Writing—review & editing. All authors read and approved the final manuscript.

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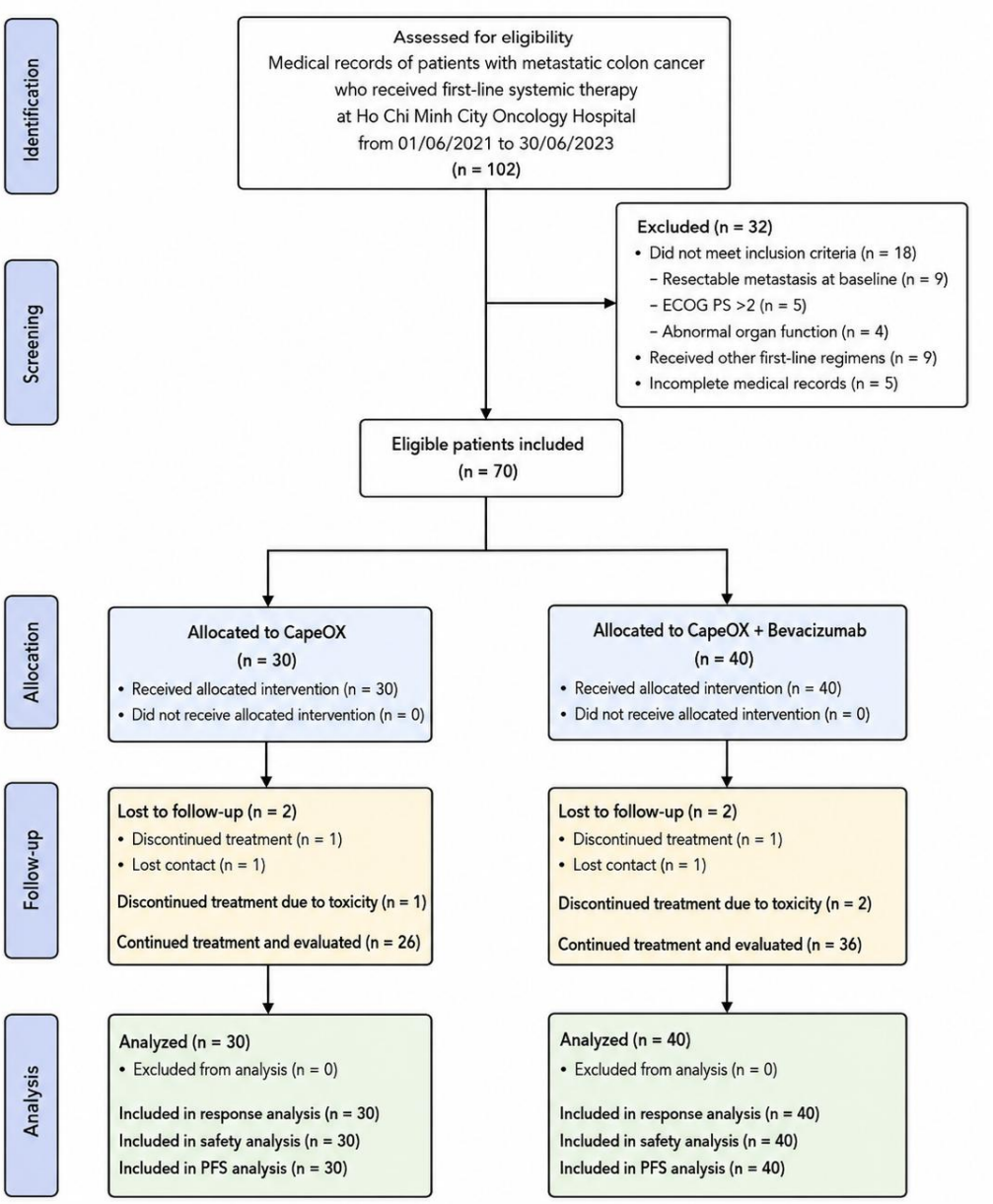

Figure 1. Study flow diagram (STROBE flow chart)

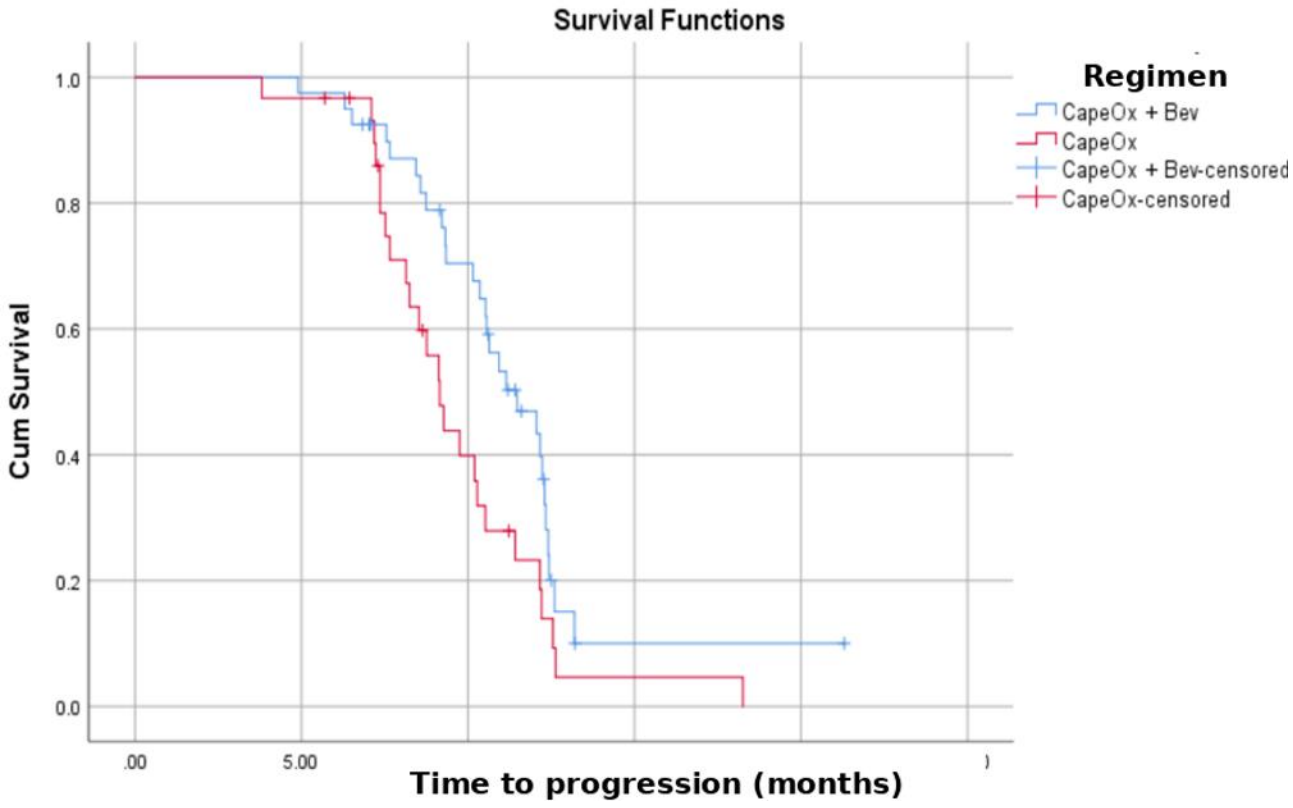

Figure 2. Kaplan-Meier curves of progression-free survival according to treatment regimen (CapeOX vs CapeOX plus bevacizumab).

Table 1. Baseline clinicopathological characteristics of the study population (N = 70).

Characteristic	**n**	**%**
Male sex	42	60.0
Female sex	28	40.0
Age, years, mean ± SD (range)	55.3 ± 9.5 (24-76)	—
ECOG performance status 0	16	22.8
ECOG performance status 1	42	60.0
ECOG performance status 2	12	17.2
De novo metastatic disease	53	75.7
Recurrent metastatic disease	17	24.3
CapeOX	30	42.9
CapeOX plus bevacizumab	40	57.1
CEA ≤ 5 ng/mL	14	20.0
CEA > 5 ng/mL	45	64.3
CEA not available	11	15.7
Adenocarcinoma, grade 1	3	4.3
Adenocarcinoma, grade 2	52	74.3
Adenocarcinoma, grade 3	9	12.8

Mucinous adenocarcinoma	6	8.6
Right-sided primary tumor	29	42.0
Left-sided primary tumor	41	58.0
One metastatic organ	43	61.4
Two or more metastatic organs	27	38.6
Liver metastasis	40	57.1
Lung metastasis	14	20.0
Abdominal lymph node metastasis	11	15.7
Peritoneal metastasis	17	24.3
Peripheral lymph node metastasis	15	21.4
Ovarian metastasis	7	10.0
Other metastatic sites	5	7.1

Table 2. Tumor response according to RECIST 1.1.

Response category	**CapeOX**	**CapeOX**	**CapeOX + bevacizumab**	**CapeOX + bevacizumab**
	After 4 cycles (n = 30)	**After 8 cycles (n = 30)**	**After 4 cycles (n = 40)**	**After 8 cycles (n = 40)**
Complete response	0	0	1 (2.5%)	1 (2.5%)
Partial response	16 (53.3%)	14 (46.6%)	23 (57.5%)	21 (52.5%)
Stable disease	13 (43.3%)	12 (40.0%)	15 (37.5%)	15 (37.5%)
Progressive disease	1 (3.4%)	4 (13.4%)	1 (2.5%)	3 (7.5%)
Overall response rate	53.3%	46.6%	60.0%	55.0%
Disease control rate	96.6%	86.6%	97.5%	92.5%

Table 3. Progression-free survival outcomes.

Regimen	Mean PFS, months	Median PFS, months	Minimum	Maximum	12-month PFS, %	Log-rank p
CapeOX	9.7	9.2	3.8	18.3	18.6	0.025
CapeOX + bevacizumab	11.6	11.5	4.9	21.3	43.3	0.025

Table 4. Treatment-related adverse events.

Adverse event	**CapeOX**	**CapeOX**	**CapeOX + bevacizumab**	**CapeOX + bevacizumab**
	Grade 1-2	**Grade 3-4**	**Grade 1-2**	**Grade 3-4**
Neutropenia	10 (33.3%)	0	15 (37.5%)	0
Thrombocytopenia	7 (23.3%)	0	9 (22.5%)	1 (2.5%)
Nausea/vomiting	11 (36.7%)	0	17 (42.5%)	0
Diarrhea	8 (26.6%)	0	13 (30.0%)	0
Peripheral neuropathy	13 (43.3%)	0	22 (55.0%)	0
Hand-foot syndrome	3 (10.0%)	1 (3.3%)	5 (12.5%)	2 (5.0%)
AST/ALT elevation	14 (46.6%)	0	15 (37.5%)	0
Creatinine elevation	2 (6.7%)	0	5 (12.5%)	0
Hypertension*	—	—	5 (12.5%)	0
Bleeding*	—	—	3 (7.5%)	0
Gastrointestinal perforation*	—	—	0	0
Thrombosis*	—	—	0	0
Proteinuria*	—	—	0	0

Abbreviations: CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; DCR, disease control rate; PFS,

progression-free survival. *Bevacizumab-specific adverse events were reported only for the combination group in the source document.

Table 5. Factors associated with radiologic response

Factor / comparison	**CapeOX**	**p**	**CapeOX + bevacizumab**	**p**
Age (<=60 vs >60 years)	50.0% vs 40.0%	0.709	50.0% vs 70.0%	0.454
Sex (male vs female)	53.8% vs 57.1%	0.400	53.8% vs 57.1%	0.400
Baseline CEA (<=5 vs >5 ng/mL)	22.2% vs 57.1%	0.118	42.9% vs 60.0%	0.437
Histologic grade after 8 cycles (grade 1-2 vs grade 3/mucinous)	48.0% vs 40.0%	1.000	58.8% vs 33.3%	0.381
Peritoneal metastasis after 4 cycles (absent vs present)	54.5% vs 50.0%	1.000	67.6% vs 16.7%	0.029

Table 6. Subgroup analyses for progression-free survival (PFS).

Factor / subgroup	CapeOX PFS, months	p	CapeOX + bevacizumab PFS, months	p
Sex (male vs female)	NR in subgroup table	NR	12.2 vs 10.4	0.149
Baseline CEA (>5 vs <=5 ng/mL)	9.9 vs 8.9	0.321	11.0 vs 12.1	0.018
Histologic grade (grade 1-2 vs grade 3/mucinous)	9.8 vs 9.1	0.605	11.9 vs 8.8	0.045
Number of metastatic organs (<2 vs >=2)	9.9 vs 9.3	0.434	12.37 vs 10.35	0.374
Liver metastasis (present vs absent)	10.0 vs 9.0	0.308	11.9 vs 10.3	0.603
Peritoneal metastasis (present vs absent)	8.7 vs 10.1	0.179	10.5 vs 11.5	0.857
Best response after 8 cycles (response / stable disease / progression)	10.8 / 9.1 / 6.6	<0.001	12.5 / 10.9 / 7.6	0.002

NR, not reported; PFS, progression-free survival.