RESEARCH ARTICLE

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Vitamin D3 Supplementation Modulates C-MYC/VEGF and Improves Chemotherapy Outcomes in Metastatic CRC Patients: Integrated Clinical–Mechanistic Evidence

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Abstract

Objective: Systemic chemotherapy with fluoropyrimidine regimens is the cornerstone of management for unresectable metastatic colorectal cancer (CRC). This study aimed to evaluate the clinical outcomes and potential molecular mechanisms of adding vitamin D3 supplementation to fluoropyrimidine-based chemotherapy in metastatic CRC patients. **Methods:** This study evaluated the clinical effects of vitamin D3 addition to fluoropyrimidine therapy. Serum vitamin D3 levels and expression of vascular endothelial growth factor (VEGF) and cellular myelocytomatosis (C-Myc) were determined at baseline and after two months of therapy. Clinical endpoints such as overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) were assessed. **Results:** Patients supplemented with vitamin D3 had a significant rise in the median vitamin D3 levels after two months (8 (6–14) to 13.5 (8–16.3) ng/mL; Δ +5.5 (3–8); Wilcoxon $p<0.001$), whereas those in the control group, who did not receive supplementation, experienced a decline in median vitamin D3 levels (11 (8–14.3) to 9 (8–16.3) ng/mL; Δ −2 (−4 to +1); Wilcoxon $p=0.01$). Supplementation was also associated with greater downregulation of VEGF and C-Myc expression ($p<0.05$). The overall response rate was higher in the vitamin D3 group of patients (63.3% vs. 25.8%; $p<0.01$), and median PFS was significantly prolonged (9.1 vs. 6.5 months; $p=0.028$). **Conclusion:** Our study suggests that vitamin D3 enhances fluoropyrimidine efficacy in metastatic CRC patients by modulating angiogenesis and proliferation pathways, supporting its potential as a safe, low-cost adjunct to chemotherapy.

Keywords: metastatic colorectal cancer- fluoropyrimidine- vitamin D3- VEGF- C-myc- progression-free survival

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Introduction

Colorectal cancer (CRC) is a heterogonous disease that differs according to cellular characteristics and anatomical location. CRC accounts for over 930,000 deaths globally, making it one of the top causes of mortality related to cancer [1].

Metastases are already identified in about 20% of CRC patients [2]. The mainstay of metastatic CRC chemotherapy regimens is fluoropyrimidine therapy, either alone or in combination [3].

Vitamin D is a very important fat-soluble vitamin that affects the absorption of key electrolytes such as calcium, magnesium, and phosphate from the intestine [4]. Until now, there is no sufficient evidence to recommend Vitamin D supplementation in cancer patients. Although some studies have found that low serum levels of Vitamin D may be a cause of poor prognosis in different types of malignant tumors [5], and higher Vitamin D levels in cancer patients were associated with better outcomes [6], there are also negative studies regarding these benefits in CRC [7]. Moreover, no study has investigated the molecular mechanisms of combining Vitamin D3 with fluoropyrimidine therapy and its clinical outcomes. Therefore, our study aim was to assess the clinical outcome and possible potential molecular mechanisms of addition of Vitamin D3 to fluoropyrimidine therapy in metastatic CRC patients.

Materials and Methods

This randomized phase II clinical trial was conducted at the Medical Oncology Department, South Egypt Cancer Institute, Assiut University, Egypt. Written informed

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consent was obtained from all participants prior to enrollment.

Inclusion criteria were

Adult patients (>18 years) with histologically or cytologically confirmed metastatic colorectal cancer (CRC) receiving fluoropyrimidine-based chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hepatic, renal, and hematological function.

Exclusion criteria included

Patients ≤18 years, ECOG performance status >2, severe hepatic or renal impairment, uncontrolled comorbidities, prior vitamin D supplementation before enrollment, known hypersensitivity to vitamin D preparations, malabsorption disorders affecting vitamin D metabolism, and inability to provide informed consent.

Patients were stratified according to vitamin D3 supplementation into two groups (total n = 61)

• Group A (n = 30): Newly diagnosed metastatic CRC patients treated with fluoropyrimidine therapy plus vitamin D3 supplementation (1500 IU daily for two months) [8].

• Group B (n = 31): Newly diagnosed metastatic CRC patients treated with fluoropyrimidine therapy without vitamin D3 supplementation.

Treatment Protocol and Assessments

Routine laboratory investigations such as liver function, complete blood count, and kidney function tests, were performed before each chemotherapy cycle. Imaging studies were conducted at baseline and after 60 days determining tumor response using RECIST version 1.1 criteria [9]. In addition, all patients underwent serum vitamin D3 measurement and analysis of VEGF and C-myc genes at two time points: baseline (prior to initiation of chemotherapy) and after 60 days of treatment with or without Vitamin D3 supplementation.

Blood Sampling and Laboratory Methods

A total of 4 ml of venous blood was collected under complete aseptic conditions and divided into two tubes: an EDTA tube for molecular biology tests and a plain tube for serological testing by enzyme-linked immunosorbent assay (ELISA).

Drug Dosing and Regimen

Patients were randomized to receive fluoropyrimidine-based chemotherapy (FOLFOX-4 or CAPOX) with or without vitamin D3 supplementation until disease progression.

• FOLFOX-4 regimen consists of oxaliplatin 85 mg/m^2 intravenous infusion in 500 ml glucose 5% over 120 minutes on day 1, intravenous folinic acid 100 mg/m^2/day on days 1 and 2 before 5-FU, and 5-FU bolus 400 mg/m^2/day followed by continuous infusion 600 mg/m^2/day on days 1 and 2, repeated every 2 weeks.

• CAPOX regimen includes oxaliplatin 130 mg/m^2 Intravenous infusion in 500 ml glucose 5% over 120 minutes on the first day of the cycle and Capecitabine 1000 mg/m^2 oral twice a day for 14 day, repeated every 3 weeks.

• Targeted therapy was given according to tumor site and its molecular pattern. It included either bevacizumab, panitumumab, or cetuximab.

• Vitamin D3 tablets: Ergocalciferol 1500 IU every day for 2 months.

Protocol-specified treatment modifications were done for predefined toxic events.

ELISA measurements for vitamin D3 level

Serum 25(OH) vitamin D3 levels were determined using a commercial ELISA kit (Diametra, Italy) according to the manufacturer's instructions. Absorbance was measured using the BEST 2000 ELISA system (Biokit S.A., Spain) at a wavelength of 650 nm.

Real-Time PCR Analysis of VEGF and C-myc Expression

mRNA expression of VEGF and C-myc was quantified using qRT-PCR. Total RNA was extracted from whole blood samples with the GeneJET RNA Purification Kit (Thermo Fisher Scientific, USA), and RNA concentration was measured using a Qubit-3 fluorometer. cDNA synthesis was performed with the RevertAid First Strand cDNA Synthesis Kit (K1622, Lithuania). qRT-PCR was carried out using the Maxima SYBR Green Master Mix (Thermo Fisher Scientific, USA) on an Applied Biosystems 7500/7500 Fast Real-Time PCR System. Each 25 µl reaction contained 3 µl cDNA, 1 µl of each primer (500 nM), 12.5 µl of SYBR Green mix, 0.05 µl Rox solution, and 7.45 µl H2O. Primer sequences for VEGF, C-myc, and the housekeeping gene β-actin are shown in Supplementary Table 1 (Table S1). Cycling conditions included an initial denaturation at 95 °C for 10 min, followed by 45 cycles of 95 °C for 15 s and 60 °C for 30 s. β-actin was used as the internal reference, and relative gene expression was calculated using the 2^−ΔΔCt method method [10].

Statistical Analysis

Sample size was calculated using G*Power software (version 3.1.9.2, University of Kiel, Germany) [11]. Statistical analyses were performed with SPSS version 22 (SPSS Inc., Chicago, IL, USA) and Stata version 10. Continuous variables were expressed as mean ± SD or median (interquartile range) as appropriate. Between-group comparisons were performed using Student's t-test for normally distributed data or the Mann–Whitney U test for nonparametric data. Within-group paired comparisons (baseline vs. two months) were assessed using the paired t-test or Wilcoxon signed-rank test. Qualitative variables were compared using the chi-square test. The Kaplan–Meier method was used to estimate PFS and OS, and differences between groups were assessed with the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using stratified Cox regression models. All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant.

Results

Patient and Tumor Characteristics

This prospective study included 61 metastatic CRC patients treated between 2021 and 2024 with fluoropyrimidine-based chemotherapy. Baseline demographic and tumor characteristics were comparable between the two groups (Table 1). Baseline laboratory parameters were generally comparable between the two groups. However, statistically significant differences were observed in baseline creatinine (0.6 [0.2–9] vs. 0.7 [0.4–1]; p = 0.03) and AST levels (20.7 ± 10.2 vs. 25.5 ± 14.9; p = 0.03). Despite this, all values remained within acceptable clinical ranges, indicating adequate hepatic and renal function in both groups shown in Supplementary Table 2 (Table S2).

Impact of Vitamin D3 Supplementation on Serum Levels

At baseline, serum vitamin D3 levels were significantly higher in the control group compared with the supplementation group (11 [8–14.3] vs. 8 [6–14] ng/ml; p = 0.005). After two months, vitamin D3 levels increased markedly in the supplementation group (13.5 [8–16.3] ng/ml; Wilcoxon p < 0.001), while a modest decrease was observed in the control group (9 [8–16.3] ng/ml; Wilcoxon p = 0.01). The median change (Δ) differed significantly between groups, with a positive increment in the supplementation group (+5.5 [3–8]) versus a decline in the control group (–2 [–4 to +1]; p < 0.001) (Table 2).

Expression Levels of C-myc and VEGF Genes

At baseline, C-myc expression levels were comparable between the supplementation group (3.25 ± 2.39) and the control group (3.85 ± 2.03; p = 0.361). After two months, both groups showed a reduction in C-myc expression. The decrease was statistically significant within each group (Group A: p = 0.003; Group B: p = 0.029). However, although C-myc expression decreased in both groups after two months, no statistically significant differences were observed between the supplementation and control groups either at two months or in the magnitude of change from baseline (p = 0.103 and p = 0.140, respectively). Baseline VEGF levels were significantly higher in the supplementation group compared with the control group (1.42 [1.0–2.0] vs. 0.65 [0.5–0.9]; p = 0.003). After two months, VEGF levels decreased in both groups, with a significant reduction observed only in the supplementation group (p = 0.003), while no significant change was detected in the control group (p = 0.087). Between-group comparisons at two months confirmed that VEGF levels remained significantly different (p = 0.019). Similarly, the reduction in VEGF expression (ΔVEGF) was greater in the supplementation group compared to the control group (–0.46 [–0.8 to –0.2] vs. –0.07 [–0.3 to 0.1]; p = 0.021) (Table 3).

Overall Response Rate (ORR) and Disease Control Rate (DCR) after Vitamin D3 Supplementation

At the first assessment, no patients in either group achieved complete remission (CR). Partial remission (PR)

Table1. Baseline Patient and Tumor Characteristics

Characteristics		Vitamin D3 supplementation				P-value
		Yes (Group A)		No (Group B)		
		Number	%	Number	%	
Age	<50 yrs.	21	70	14	45.2	
	≥50 yrs.	9	30	17	54.8	0.071
Sex	Male	12	40	17	54.8	
	Female	18	60	14	45.2	0.309
BMI	< 30	25	83.3	29	93.5	
	≥30	5	16.7	2	6.5	0.225
Laterality	Right	9	30	9	29	
	Left	21	70	22	71	1
Type of pathology	Non-mucinous adeno carcinoma	24	80	28	90.3	0.301
	Mucinous adeno carcinoma	6	20	3	9.7	
tumor grade	Grade I II	28	93.3	27	87.1	
	Grade III	2	6.7	4	12.9	0.671
Tumor size	<T3	3	10	3	9.7	
	≥T3	27	90	28	90.3	1
Lymph nodes	N0 and N1	24	80	18	58.1	
	N2 and N3	6	20	13	41.9	0.096
No. of metastatic sites	≤2	17	56.7	11	35.5	
	>2	13	53.3	20	54.5	0.126
Route of 5 -Fu	Oral	19	63.3	17	54.8	
	Infusion	11	36.7	14	45.2	0.605

Abbreviations: yrs, years; BMI, body mass index; 5- FU, 5 –fluorouracil

Table 2. Effect of Vitamin D3 Supplementation on Serum Vitamin D3 Levels

Vitamin D3 (ng/ml)	Group A (Supplementation) Median (IQR)	Group B (Control) Median (IQR)	P-value
Baseline level	8 (6 – 14)	11 (8 – 14.3)	0.005
After 2 months	13.5 (8 – 16.3)	9 (8 – 16.3)	<0.001
Difference (Δ)	+5.5 (3 – 8)	–2 (–4 – +1)	<0.001
Within-group comparison	Wilcoxon p < 0.001	Wilcoxon p = 0.01	–

Values are presented as Median (Interquartile Range). Within-group comparisons (Baseline vs. 2 months) were assessed using the Wilcoxon Signed-Rank test. Between-group comparisons (Supplementation vs. Control) were assessed using the Mann–Whitney U test.

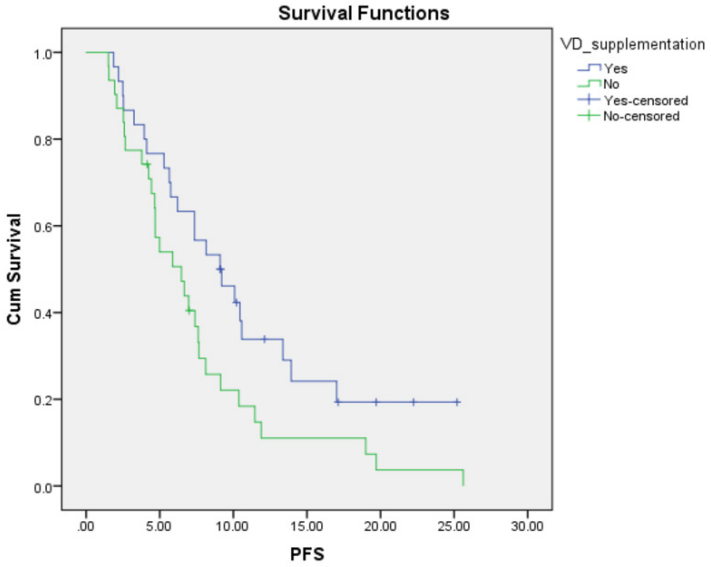

Figure 1. Kaplan–Meier Test of Progression-Free Survival Comparing Vitamin D3-Supplemented and Non-Supplemented Patient Groups.

was observed in 19 patients (63.3%) of Group A and 8 patients (25.8%) of Group B. Stable disease (SD) was reported in 6 patients (20.0%) of Group A and 16 patients (51.6%) of Group B, while progressive disease (PD) occurred in 5 patients (16.7%) of Group A and 7 patients (22.6%) of Group B. Overall, Group A demonstrated a significantly higher ORR (63.3%, P = 0.005), whereas no statistically significant difference was observed between the groups in terms of DCR.

Progression-Free Survival (PFS) and Vitamin D3 Supplementation

Patients in Group A who received vitamin D3 supplementation had a significantly longer median PFS compared with Group B who did not receive supplementation. The median PFS was 9.1 months (95% CI, 5.7–12.5) in Group A versus 6.5 months (95% CI, 3.9–9.1) in Group B (P = 0.045), as illustrated in Figure 1.

Prognostic Value of Vitamin D3 Supplementation

To evaluate the independent prognostic significance of vitamin D3 supplementation, both univariate and multivariate analyses were performed as shown in supplementary Table 2 (Table S2). Vitamin D3 supplementation emerged as an independent favorable prognostic factor for progression-free survival (PFS).

Table3. Expression Levels of C-myc and VEGF Genes in Both Study Groups

Vitamin D	Group (A): Mean ± SD / Median (IQR)	Group (B): Mean ± SD / Median (IQR)	P-value
Baseline level of C-myc	3.25 ± 2.39	3.85 ± 2.03	0.361
After 2 months C-myc	2.56 ± 2.19	3.55 ± 2.02	0.103
Difference in C-myc	+0.69 ± 1.07	+0.31 ± 0.59	0.140
Within-group p-value	0.003	0.029	–
Baseline level of VEGF	1.42 (1.0 – 2.0)	0.65 (0.5 – 0.9)	0.003
After 2 months VEGF	0.96 (0.6 – 1.3)	0.58 (0.5 – 0.7)	0.019
Difference in VEGF	–0.46 (–0.8 – –0.2)	–0.07 (–0.3 – 0.1)	0.021
Within-group p-value	0.003	0.087	–

C-myc values are presented as Mean ± SD and analysed with paired/independent t-tests. VEGF values are presented as Median (IQR) and analysed with Wilcoxon Signed-Rank and Mann–Whitney U tests.

Cox regression analysis showed that vitamin D3 supplementation was associated with a 48.4% reduction in the risk of progression (HR = 0.516; 95% CI, 0.286–0.931; P = 0.028).

Overall Survival (OS) and Vitamin D3 Supplementation

Vitamin D3 supplementation did not result in a significant difference in OS between the two groups. The median OS was 14.7 months (95% CI, 3.3–26.2) in Group A and 22.9 months (95% CI, 10.6–35.3) in Group B (P = 0.361).

Safety

With respect to gastrointestinal toxicity after two months of chemotherapy, vomiting was reported in 4 patients (13.3%) in Group A and 9 patients (29.0%) in Group B, showing a significant difference (P = 0.029). Diarrhea occurred in 0 patients (0.0%) in Group A versus 6 patients (19.4%) in Group B, and gastritis in 0 patients (0.0%) in Group A versus 5 patients (16.1%) in Group B. One patient in each group had oral mucositis.

Regarding neurotoxicity, no patients in Group A and 4 patients (12.9%) in Group B were affected, with no significant difference (P = 0.113). No hepatic or renal toxicities were reported. Importantly, no adverse effects were attributed to vitamin D3 supplementation.

Discussion

Metastatic CRC is primarily managed with systemic chemotherapy, often combined with targeted or biological agents to prolong survival while maintaining quality of life. Beyond conventional therapy, interest has grown in the effect of vitamin D status in modulating CRC outcomes [12]. These inconsistencies highlight the need for clinical studies that not only evaluate survival outcomes but also integrate molecular markers, as we aimed to do in the present trial

In our study, patients supplemented with vitamin D3 had a significant rise in median of vitamin D3 levels after two months (8 (6-14) to 13.5 (8-16.3) ng/ml; Δ +5.5 (3-8); Wilcoxon p<0.001), whereas those in the control group, who did not receive supplementation, experienced a decline in median of vitamin D3 levels (11 (8-14.3) to 9 (8-16.3) ng/ml; Δ –2 (-4-+1); Wilcoxon p=0.01), suggesting that chemotherapy may contribute to vitamin D depletion. This is consistent with Fakih et al., who reported that CRC patients undergoing chemotherapy had a three-fold higher risk of vitamin D insufficiency compared with those not receiving treatment [13]. Also, Isenring et al ., observed a deficiency in vitamin D levels in cancer patients who received chemotherapy for cancer [14].

After two months of chemotherapy, the two groups had no significant difference in disease control rate. However, the overall response rate was markedly higher in the vitamin D3 group (63.3% vs. 25.8%). This supports the hypothesis that vitamin D3 may synergize with 5-FU through pathways involving DNA damage, differentiation, proliferation, and angiogenesis [15].

To explore the potential of this synergy, we examined the effects of vitamin D3 supplementation on VEGF and C-myc expression in patients. C-myc expression decreased significantly in both groups after two months of fluoropyrimidine-based therapy, with a more pronounced reduction in the vitamin D3 group (p=0.009 vs. p=0.026). As C-myc is a key proto-oncogene and a downstream target of vitamin D3, these findings suggest that vitamin D3 may exert an additional anti-proliferative effect in treated patients. Previous molecular studies have demonstrated that treatment with fluoropyrimidines such as 5-fluorouracil is associated with down-regulation of c-Myc and other proliferation-related genes in cancer cells, supporting the observation that chemotherapy itself contributes to C-myc suppression [16]. However, the numerically greater decline in the vitamin D3 group suggests a possible additive biological contribution of vitamin D3 that did not reach statistical significance in this relatively small cohort.

Vitamin D3 inhibits C-myc expression in CRC cells by many indirect mechanisms, the most relevant of which is antagonism of Wnt/b-catenin signaling [17].

Lastly, we measured VEGF as a marker of angiogenesis and found a more significant reduction in the vitamin D3 group than in controls. VEGF is a critical driver of tumor angiogenesis and metastasis, and vitamin D3 has been shown to suppress its expression by inhibiting HIF-1α, thereby enhancing the therapeutic outcome of 5-FU [18]. In contrast, other study has reported that 1,25(OH)2D3 stimulated VEGF expression in colon carcinoma and other cell types [19], suggesting context-dependent effects. This may explain the greater VEGF down-regulation observed in our vitamin D3 group and its association with the improved response rate and prolonged PFS.

Regarding clinical outcomes, our study found that median PFS was significantly longer in patients receiving vitamin D3 supplementation compared with controls (9.1 months; 95% CI, 5.7–12.5 vs. 6.5 months; 95% CI, 3.9–9.1; p=0.045). Multivariate Cox regression confirmed vitamin D3 as an independent prognostic factor with a 48.4% reduction in risk of progression (HR 0.516; 95% CI, 0.286–0.931; stratified p=0.028). These findings are consistent with Nimeiri et al. [20] who demonstrated improved PFS with high-dose vitamin D (HR 0.66; p=0.02), and with a 2021 trial showing that daily 4000 IU supplementation increased serum vitamin D and prolonged PFS from 11.0 to 13.0 months in stage IV CRC (HR 0.64) [21]. In contrast, a study of 71 metastatic CRC patients treated for 24 months with high-dose vitamin D found no significant difference in PFS [7].

In our cohort, OS did not differ significantly between groups (14.7 vs. 22.9 months; p=0.361). An apparent discrepancy was observed between the significant effect of vitamin D3 supplementation on PFS in Cox regression analysis and the absence of a statistically significant improvement in overall survival (OS). This finding is consistent with evidence from oncology trials indicating that OS is heavily influenced by post-progression survival, subsequent lines of therapy, and supportive care, which may dilute the measurable impact of early treatment effects on survival outcomes. In contrast, PFS more directly reflects the immediate biological interaction between therapy and tumor behaviour. Therefore,

improvements in PFS may not necessarily translate into measurable OS differences within the follow-up period, particularly in metastatic colorectal cancer where multiple active post-progression treatments are available [22, 23]. While other observational studies suggested that higher dietary or supplemental vitamin D intake was associated with improved survival [24].

Regarding toxicity, patients in the vitamin D3 group experienced fewer gastrointestinal adverse events, including vomiting, diarrhea, gastritis, and oral mucositis, but these differences were without statistical significance (vomiting: p=0.361). While in cisplatin-induced intestinal injury models, vitamin D3 supplementation preserved barrier integrity and reduced cytokine release [25]. Calcitriol has also been shown to maintain gut health by regulating epithelial tight junction proteins [26].

We also observed a lower, though non-significant, incidence of chemotherapy-induced neuropathy in the vitamin D3 group. Zhang et al. reported that vitamin D deficiency induced paclitaxel-induced neuropathy, suggesting that higher vitamin D levels may protect against oxidative stress and neuropathic pain [27].

This study has some limitations that should be acknowledged. First, the relatively small sample size may have limited the statistical power to detect subtle molecular and survival differences, particularly regarding C-myc expression and overall survival outcomes. Second, the vitamin D3 supplementation dose (1500 IU/day) and the short duration of administration (two months) may not have been sufficient to achieve optimal biological modulation, as higher doses and longer durations have been used in other trials demonstrating more pronounced effects. Third, although a significant improvement in progression-free survival and overall response rate was observed, no significant difference in OS was detected, which may be attributed to the limited follow-up period, post-progression treatments, and multifactorial determinants of survival in metastatic CRC. Therefore, our findings should be interpreted as exploratory and hypothesis-generating rather than definitive evidence for clinical guideline incorporation. Larger randomized trials with optimized dosing strategies and longer follow-up are required to validate these observations.

In conclusion, our study demonstrates that vitamin D3 supplementation was associated with increased serum vitamin D levels, improved ORR, and prolonged PFS in metastatic CRC patients receiving fluoropyrimidine-based chemotherapy. These clinical observations were supported by mechanistic findings suggesting modulation of proliferation and angiogenesis pathways.

Author Contribution Statement

AR: Conceptualization, Funding acquisition, Methodology, Investigation, Visualization, Formal Analysis Writing – Original Draft. MSH: Formal Analysis, Writing – Review & Editing. NH: Conceptualization, Software, Formal Analysis, Data Curation. NG: Conceptualization, Methodology, Formal Analysis, Writing – Review & Editing. MO: Conceptualization, Methodology, Software, Validation, Formal Analysis. SS: Supervision, Data Curation, Validation, Formal Analysis, Writing – Review & Editing. SK: Data Curation, Methodology, Validation, Formal Analysis, Writing – Review & Editing.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the South Egypt Cancer Institute, Assiut University (IRB No. 528, approved on 28/02/2021).

Study Registration

This clinical study was not registered in a public clinical trial registry.

Conflicts of Interest

The authors declare that they have no conflicts of interest to report regarding this study.

Thesis Statement

This work is part of the approved MD thesis of Aya Mahmoud Abdel Rahman.

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