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# Nutritional Supplement Ocoxin® Combined with Oxaliplatin-Based Chemotherapy in Patients with Metastatic Colorectal Cancer

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## Abstract

**Background:** Advanced colorectal cancer (CRC) is associated with significant morbidity, which, combined with the adverse effects of cancer treatment, can further impair patient quality of life. The primary objective was to evaluate the impact of Ocoxin oral solution (OOS) in combination with oxaliplatin-based chemotherapy on quality of life. **Methods:** Forty patients participated in an exploratory, prospective, multicentre clinical trial at the "Hermanos Ameijeiras" University Hospital and the National Institute of Oncology in Havana, Cuba. Quality of life was measured using the EORTC QLQ-C30 and EORTC QLQ-C29 questionnaires. Toxicity was assessed using the NCI-CTC-AE classification, version 4.0. **Results:** Scores remained stable over time for global quality of life and functional scale criteria, while, regarding symptoms, a reduction in pain perception and loss of appetite was observed at three months. The number and severity of adverse events were lower (4.2% grade 3 - 4) than those reported with this type of chemotherapy. No adverse events (AEs) related to OOS were recorded. Biochemical and nutritional parameters remained stable during treatment. **Conclusions:** This clinical study is the first report on the use of OOS in patients with metastatic colon cancer, maintaining optimal quality of life and reducing the intensity of chemotherapy toxicity.

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**Keywords**

EORTC QLQ-C30, EORTC QLQ-C29, Ocoxin, Chemotherapy, Colorectal Cancer, Quality of Life

## 1. Introduction

Colorectal cancer (CRC) represents the third most common cancer affecting both men and women worldwide [1]. It is estimated that in 2022, there were more than 1.9 million new cases of CRC, representing 9.6% of all cancer cases, while it represented the second cause of death from malignancy worldwide, with just over 900,000 deaths (9.6%) [2]. Around 25% of patients have metastatic disease at diagnosis, and one-third of patients with initially limited disease will subsequently develop metastases, which explains the high mortality rates reported for this type of tumour [3].

In Cuba, 15.9% of the incidence and 25.2% of the mortality from cancer are attributed to malignant tumours of the digestive system, with patients with CRC constituting 47% of the incidence and 41% of the mortality in this group [4]. Unlike what occurs worldwide, the incidence and mortality rates for colon cancer are higher in women than in men, while for rectal cancer, the incidence and mortality rates in both sexes obtained in Cuba are well below the reported world average [5].

Although metastatic colorectal cancer (mCRC) remains a highly lethal disease, the management of patients with mCRC has clearly improved in recent years, with a median overall survival of 12 months in the era of 5-fluorouracil (5-FU)-based chemotherapy, compared to approximately 30 months observed in recent clinical trials or in clinical practice when combining oxaliplatin- or irinotecan-based chemotherapy with biologic agents guided by predictive biomarkers [6].

Advanced colorectal cancer is associated with significant morbidity, which, when combined with the adverse effects of cancer treatment, can further impair patient quality of life [7]. The treatment of patients with mCRC should be considered a continuum of care, with the goals of prolonging survival, improving tumour-related symptoms, and maintaining quality of life [8]. Ensuring good health-related quality of life (HRQoL) has become essential and is widely recognized as one of the main endpoints for treatment evaluation [9].

Ocoxin, in its oral solution (OOS) form, is a nutritional supplement composed of plant extracts, amino acids, vitamins, and minerals whose antioxidant capacities and biological actions have been maximized through a molecular activation process. Its antioxidant, anti-inflammatory, immunomodulatory, and antitumor effects have been confirmed in both preclinical and clinical studies [10]-[12]. A reduction in tumour cell proliferative activity has been observed in several animal models and cell line studies, both in OOS monotherapy and when combined with antineoplastic agents or targeted therapies [10] [11]. In patients with advanced

cancer who have undergone clinical trials, improvements in quality of life and therapeutic adherence have been confirmed, as well as a decrease in the toxicity of chemotherapy associated with OOS [12].

Taking this into account, the objective of this study is to evaluate the effect of OOS on the quality of life of patients with metastatic colorectal cancer when combined with oxaliplatin-based chemotherapy regimens.

## 2. Methods

### 2.1. Study Design

A multicentre, prospective, exploratory clinical trial was conducted, including 40 patients (26 patients from the Hermanos Ameijeiras University Hospital and 14 patients from the National Institute of Oncology, both centres located in Havana, Cuba). The study was conducted by the National Clinical Trials Coordinating Centre (CENCEC). The primary objective was to evaluate the effect of OOS in combination with oxaliplatin-based chemotherapy regimens on the quality of life of patients with metastatic colorectal cancer. The secondary objective was to evaluate changes in clinical parameters, nutritional status, and toxicity.

### 2.2. Study Population

Patients were required to be ≥18 years of age with a histological diagnosis of colon and/or rectal adenocarcinoma; stage IV; general health status according to a Karnofsky score ≥ 70%; life expectancy equal to or greater than 3 months; eligibility for chemotherapy with oxaliplatin-based regimens; hematologic parameters that did not contraindicate chemotherapy; total bilirubin values ≤ 1.5 times and ALT/AST ≤ 2.5 times the upper limit of the normal range established at the institution, and creatinine values within the normal limits of the institution; and signed informed consent.

Patients were excluded if they were receiving another investigational product; had a known hypersensitivity to 5-fluorouracil, folinic acid, or oxaliplatin; had chronic or decompensated intercurrent illnesses; or had any other special condition that, in the physician's judgment, could jeopardize their health and life during the study or their participation in the trial. Pregnant or breastfeeding women, those with mental disorders that could limit compliance with clinical trial requirements and hinder data collection, treatment, or follow-up, and patients with brain metastases were excluded. Patients with an ostomy were excluded.

### 2.3. Diagnostic and Clinical Extension Procedures

Extension, staging, and confirmatory diagnostic testing were performed according to the approved protocol for this neoplastic disease. All patients underwent clinical examinations, haematological and blood chemistry analyses, abdominopelvic ultrasound, chest X-ray, colonoscopy, and computed axial tomography (CT) of the chest, abdomen, and pelvis (plain and contrast-enhanced). Histopathological confirmation was performed in all cases, with or without ultrasound

and CT guidance.

## 2.4. Treatment Plan

Patients were evaluated in the multidisciplinary digestive tumour clinic at each centre participating in the clinical trial. Evaluation was based on the following factors: general condition, vital organ function, associated diseases, potential adherence to the proposed treatment, patient preferences, and tolerability. Once the patient was considered a candidate for chemotherapy, they were offered participation in the clinical trial. The oxaliplatin-based chemotherapy regimens allowed were FOLFOX or XELOX. The FOLFOX regimen (4 or 6) consists of oxaliplatin, 5-fluorouracil administered as a bolus and continuous infusion, modulated by folinic acid every 14 days for 12 cycles, or XELOX every 21 days for eight cycles (oral capecitabine and intravenous oxaliplatin).

The OOS nutritional supplement was administered at a rate of 60 ml daily (one 30 ml vial twice daily), preferably after breakfast and lunch. It was started two weeks before the start of the selected chemotherapy, throughout the entire treatment until three weeks after its completion, or after treatment discontinuation for any reason. Continued administration of OOS was permitted during periods of chemotherapy discontinuation due to toxicities attributable to the specific oncotherapy. The composition of OOS per 30 mL vial is: glucosamine sulphate, potassium chloride 600 mg, L-glycine 600 mg, malic acid 360 mg, L-arginine 192 mg, L-cysteine 61.2 mg, liquorice extract (Glycyrrhiza glabra L.) 60 mg, vitamin C (L-ascorbic acid) 36 mg, sodium benzoate 30 mg, potassium sorbate 30 mg, zinc sulphate 24 mg, passion fruit flavour 15 mg, green tea extract (Camellia sinensis (L.) Kuntze) 7.5 mg, sucralose 7.2 mg, pantothenic acid (calcium D-pantothenate) 3.6 mg, manganese sulphate 1.2 mg, vitamin B6 (pyridoxine hydrochloride) 1.2 mg, cinnamon extract (Cinnamomum verum J. Presl.) 0.9 mg, folic acid (pteroylmonoglutamic acid) 120 μg, vitamin B12 (cyanocobalamin) 0.6 μg and water q.s. 30 mL.

## 2.5. Evaluated Parameters

For the measurement of health-related quality of life (HRQoL), the QLQ-C-30 and QLQ-CR-29 questionnaires were used. The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) is a 30-item instrument, validated in Spanish, that measures global QL and 5 functional areas (physical function, autonomy, emotional well-being, cognitive function, and social function) and 9 symptoms (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, and economic impact), while the EORTC QLQ-CR-29 questionnaire includes 29 specific questions that have functional scales (body image, sexual function, and prospects for the future), and symptom scales (urinary problems, gastrointestinal symptoms, adverse effects of chemotherapy, sexual problems, problems defecating, and weight loss). Both questionnaires are administered together, with a response scale

of 1 to 4, with the following structure: 1 = Not at all; 2 = A little; 3 = Quite a bit; 4 = A lot. All scores are transformed to a measurement scale of 0 to 100, using a linear transformation process, where a high score on the functional scale represents a high level of health function or quality of life, and a high score on the symptom scale represents, in turn, a high level of problems. To evaluate the strength of clinically significant differences, we used the evidence-based guidelines for the interpretation of EORTC QLQ-C30 probability scores developed by Cocks *et al.* [13].

Toxicity was assessed using the NCI-CTC-AE classification version 4.0 [US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0]. For the assessment of toxicity, the highest degree of toxicity and complication recorded for each patient was obtained, and the duration, intensity (mild, moderate, severe, life-threatening, death related to the adverse event (AE)), severity (severe/serious, not severe/not serious), attitude to study treatment (unchanged, dose modification, temporary discontinuation, definitive discontinuation), outcome of AE (recovered, improved, persists, sequelae), and causality (very likely/certain, likely, possible, unlikely, unrelated, not evaluable/unclassifiable) were considered.

Nutritional status was assessed using body mass index (BMI), haematological parameters (haemoglobin, platelets, neutrophils, and lymphocytes), and blood chemistry (albumin, blood glucose, ALT/AST, total bilirubin, and creatinine). Three indices of systemic inflammation were calculated: the neutrophil-lymphocyte ratio (NLR), the prognostic nutritional index (PNI), and the prognostic immune nutritional index (PINI). The NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count in the complete blood count, while the PNI and PINI were calculated using the formulas:

$$\text{PNI} = (10 \times \text{serum albumin [g/dL]}) \times (0.005 \times \text{Lymphocytes}/\mu\text{L})$$

$$\text{PINI} = (0.09 \times \text{serum albumin [g/dL]}) \times (0.0007 \times \text{Monocytes}/\mu\text{L})$$

Measurements were made for all parameters at three time points: baseline, month 3, and month 6 (at the end of chemotherapy treatment).

## 2.6. Statistical Analysis

The data analysis was descriptive. Qualitative variables were described using absolute and relative percentage frequencies. Pearson's chi-squared ($X^2$) statistical test was used as a method of analysis to assess the association between qualitative variables, and the non-parametric Wilcoxon test was used to compare quantitative variables. A significance level of 0.05 with a 95% confidence interval (CI) was set for all tests. The data were analyzed using SPSS statistical software, version 28.0.

## 2.7. Ethical Aspects

The protocol was reviewed and approved by the Ethics Committees of the National Institute of Oncology (05.10.2018) and the "Hermanos Ameijeiras" University Hospital (18.10.2018). The study was conducted in accordance with the Dec-

laration of Helsinki. Written informed consent was obtained from all participants before the start of the study. National data protection legislation was applied. Documents containing patients' personal information were encrypted; only authorized personnel had access to them.

**Trial registration**: in the Cuban Clinical Trials Register (RPC). Code: RPCEC00000276. ClinicalTrials.gov ID (NCT03559543).

## 3. Results

The median age of the patients studied was 61.0 years (min.: 28; max.: 81), and the body mass index (BMI) was 23.7 kg/m2 (min.: 21.1; max.: 27.3). Most patients presented with a moderately differentiated histological type of adenocarcinoma of unspecified origin, with involvement of a single metastatic site. At the start of treatment, more than 80% of patients had normal serum albumin levels as well as absolute lymphocyte and platelet counts (Table 1). The most common symptoms and signs at inclusion in the clinical trial were abdominal pain, altered bowel habits, and weight loss in 35.0%, 32.5%, and 20.0% of patients, respectively. All patients had an ECOG classification between 0 and 1.

Table 1. Patient characteristics.

| Characteristic | n | % |
|---|---|---|
| **Gender** | | |
| Male | 20 | 50.0 |
| Female | 20 | 50.0 |
| **Age** | | |
| <60 years | 16 | 40.0 |
| ≥60 years | 24 | 60.0 |
| **Primary Tumour Location*** | | |
| Ascending colon | 7 | 17.5 |
| Descending colon | 7 | 17.5 |
| Sigmoid colon | 15 | 37.5 |
| Transverse colon | 4 | 10.0 |
| Rectum | 7 | 17.5 |
| **Histological differentiation** | | |
| Well differentiated | 3 | 7.5 |
| Moderately differentiated | 29 | 72.5 |
| Poorly differentiated | 5 | 12.5 |
| Not available | 3 | 7.5 |
| **Number of metastatic sites** | | |
| 1 | 30 | 75.0 |
| ≥2 | 10 | 25.0 |
| **Metastatic sites (n = 54)** | | |

**Continued**

| | | |
|---|---|---|
| Liver | 40 | 74.1 |
| Lungs | 7 | 13.0 |
| Lymph nodes | 3 | 5.5 |
| Omentum | 3 | 5.5 |
| Ovary | 1 | 1.9 |
| **Body Mass Index (BMI)** (kg/m$^2$) | | |
| <18.5 | 1 | 2.5 |
| 18.5 - 24.9 | 28 | 70.0 |
| ≥25 | 11 | 27.5 |
| **Serum albumin** | | |
| ≤35 g/L | 6 | 15.0 |
| >35 g/L | 34 | 85.0 |
| **Absolute leukocyte count**** | | |
| ≤5.0 × 10$^9$ | 17 | 42.5 |
| >5.0 × 10$^9$ | 23 | 57.5 |
| **Absolute lymphocyte count** | | |
| ≤1.0 × 10$^9$ | 7 | 17.5 |
| >1.0 × 10$^9$ | 33 | 82.5 |
| **Absolute platelet count***** | | |
| ≤150 × 10$^9$ | 1 | 2.5 |
| 150 - 350 × 10$^9$ | 32 | 80.0 |
| >350 × 10$^9$ | 7 | 17.5 |

At diagnosis; Absolute leukocyte count (normal range: 5.0 - 10.0 × 10$^9$) Absolute platelet count (normal range: 150 - 350 × 10$^9$).

Table 2 presents the biochemical and laboratory parameters observed during treatment. A significant reduction was observed in the absolute neutrophil and platelet counts. In contrast, the absolute lymphocyte counts initially increased at three months before decreasing to levels below baseline. In addition, an upward trend was observed in the body mass index (BMI). While the decrease in albumin levels was not statistically significant, the Prognostic Nutritional Index (PNI) increased at three months before decreasing in the medium term. The neutrophil-lymphocyte ratio (NLR) showed a downward trend, which was more pronounced in the short term, while the Prognostic Immune Nutritional Index (PINI) maintained a downward trend at both three and six months. Throughout treatment, haemoglobin, blood glucose, and creatinine levels remained stable.

**Table 2.** Analytical parameters.

| Parameters | **Baseline** (± SD) | **3 months** (± SD) | **p*** | **6 months** (± SD) | **p**** |
|---|---|---|---|---|---|
| BMI (kg/m$^2$) | 24.4 (±4.7) | 25.0 (±4.3) | 0.22 | 24.9 (±4.4) | 0.54 |
| Neutrophil count (×10$^6$) | 5561.3 (±1100.0) | 3564.8 (±1552.5) | **0.03** | 3969.0 (±1312.2) | **0.04** |
| Lymphocyte count (×10$^6$) | 1759.6 (±353.1) | 2072.4 (±847.3) | **0.04** | 1694.7 (±525.8) | 0.200 |
| Monocytes count (×10$^6$) | 701.4 (±25.3) | 773.9 (±54.2) | 0.23 | 666.5 (±54.1) | 0.12 |
| Platelet count (×10$^9$) | 332.2 (±10.6) | 237.0 (±11.4) | **0.02** | 235.4 (±10.1) | **0.01** |
| Total protein (g/L) | 76.2 (±6.3) | 72.5 (±5.4) | 0.113 | 75.6 (±8.2) | 0.542 |
| Albumin (g/L) | 43.1 (±4.0) | 41.3 (±6.0) | 0.215 | 39.2 (±9.0) | 0.133 |
| Haemoglobin (g/L) | 11.2 (±1.4) | 11.0 (±1.6) | 0.345 | 10.8 (±1.5) | 0.128 |
| Glycaemia (mmol/L) | 5.4 (±1.1) | 5.6 (±1.3) | 0.358 | 5.7 (±1.6) | 0.369 |
| Creatinine (mmol/L) | 71.1 (±3.7) | 72.7 (±4.3) | 0.255 | 74.8 (±6.5) | 0.166 |
| PNI | 38.0 (±9.1) | 42.8 (±6.8) | 0.06 | 33.2 (±10.3) | 0.345 |
| PINI | 3.39 (±1.1) | 3.18 (±1.1) | 0.22 | 3.06 (±1.0) | 0.18 |
| NLR | 3.17 (±1.2) | 1.72 (±1.1) | **0.03** | 2.34 (±1.2) | 0.07 |

SD: standard deviation; $p < 0.05$; BMI: body mass index; *(3 months vs. baseline); *(6 months vs. baseline); PNI: prognostic nutritional index; PINI: prognostic immune nutritional index; NLR: neutrophil-lymphocyte ratio.

The adverse events (AEs) reported by investigators were conclusively determined to be unrelated to the investigational product. Gastrointestinal toxicities were the most common, accounting for 36.4% of all reported events. The main adverse events included elevated liver enzymes (17.2%), elevated glucose levels (14.2%), and anaemia (14.2%). Notably, only 4.2% of reported toxicities were classified as grade 3/4, while the vast majority (84.3%) were classified as grade 1 (See Table 3).

**Table 3.** Adverse events according to NCI-CTC-AE (National Cancer Institute—Common Terminology Criteria for Adverse Events) by severity.

| **Adverse events** | **Grade 1** | **Grade 2** | **Grade 3 - 4** | **Total** |
|---|---|---|---|---|
| **Haematological Alterations** | | | | |
| Reduced haemoglobin | 28 | 7 | 2 | 37 |
| Increased leukocytes | 0 | 3 | 0 | 3 |
| Reduced leukocytes | 3 | 2 | 0 | 5 |
| Increased platelets | 2 | 0 | 0 | 2 |
| Reduced platelets | 9 | 0 | 0 | 9 |
| **Digestive disorders** | | | | |
| Anorexia | 5 | 0 | 0 | 5 |
| Increased liver enzymes | 44 | 1 | 0 | 45 |
| Nausea | 9 | 1 | 0 | 10 |

**Continued**

| | | | | |
|---|---|---|---|---|
| Vomiting | 8 | 0 | 0 | 8 |
| Diarrhoea | 16 | 2 | 0 | 18 |
| Decreased albumin | 9 | 0 | 0 | 9 |
| **Neurological/Cardiovascular/Renal/Endocrine disorders** | | | | |
| Neuropathy | 4 | 3 | 2 | 9 |
| Headache | 3 | 0 | 0 | 3 |
| Increased blood pressure | 3 | 1 | 1 | 5 |
| Increased creatinine | 4 | 2 | 1 | 7 |
| Increased blood glucose | 25 | 7 | 5 | 37 |
| **General** | | | | |
| Asthenia | 7 | 0 | 0 | 7 |
| Weight loss | 3 | 0 | 0 | 3 |
| Increased lactic dehydrogenase | 5 | 0 | 0 | 5 |
| Pain | 16 | 1 | 0 | 17 |
| **Others** | | | | |
| Others* | 17 | 0 | 0 | 17 |
| **Total** | **220** | **30** | **11** | **261** |

Incidence of a case per symptom or sign that is not serious or unexpected.

The EORTC QLQ-C30 and QLQ-BR29 questionnaires (see Table 4 and Table 5) were administered to patients at baseline, as well as at 3 and 6 months after enrolment. These assessments were designed to comprehensively evaluate global quality of life (Table 4) and colorectal cancer-specific quality of life (Table 5).

The results revealed an encouraging mean global health-related quality of life (HRQoL) score of 72.1 out of a maximum of 100 points before treatment. This score improved significantly to 77.7 points at three months, followed by a slight decrease to 75.9 points at the end of the six-month treatment period. Importantly, the stability observed in global quality of life measures and functional scales over time underscores the positive impact of the treatment. Regarding symptom assessment, a significant reduction was observed in the mean scores for pain, dyspnoea, insomnia, and loss of appetite between month 0 and month 6. Notably, this decrease was statistically significant in the short term (at three months) for both pain and loss of appetite. While fatigue, nausea, and vomiting showed a decrease after three months, it is important to highlight that these symptoms reappeared at the six-month assessment.

An increase in the mean score for future projects was observed from month 0 to month 6. Furthermore, concern about weight loss decreased over time, even though the mean score for the effects of chemotherapy increased. Other parameters remained stable during this period (see Table 5).

**Table 4.** QLQ-C30 quality of life (QoL) scales.

| | **Baseline** (±SD) | **3 months** (±SD) | p* | **6 months** (±SD) | p** |
|---|---|---|---|---|---|
| **Overall Quality of life (QoL)** | 72.1 (±2.9) | 77.7 (±3.0) | **0.03** | 75.9 (±4.4) | 0.55 |
| **Functional scale** | | | | | |
| Physical function | 75.8 (±3.5) | 79.1 (±3.6) | 0.29 | 76.7 (±5.0) | 0.40 |
| Daily activity | 63.3 (±5.3) | 74.0 (±5.8) | **0.02** | 69.3 (±7.6) | 0.57 |
| Emotional well-being | 53.8 (±4.8) | 64.4 (±5.0) | **0.01** | 64.7 (±6.9) | 0.28 |
| Cognitive function | 90.0 (±3.6) | 90.4 (±4.4) | 0.59 | 88.7 (±4.7) | 0.30 |
| Social function | 82.5 (±4.4) | 83.3 (±5.5) | 1.0 | 81.3 (±6.6) | 0.76 |
| **Symptoms** | | | | | |
| Fatigue | 35.8 (±4.9) | 31.7 (±5.1) | 0.40 | 34.2 (±6.2) | 0.53 |
| Nausea | 11.3 (±3.3) | 7.8 (±3.0) | 0.49 | 10.7 (±4.6) | 0.64 |
| Pain | 32.5 (±5.1) | 22.1 (±4.8) | **0.02** | 26.0 (±6.5) | 0.11 |
| Dyspnoea | 5.0 (±2.2) | 1.0 (±1.0) | 0.5 | 1.3 (±1.3) | 0.5 |
| Insomnia | 35.0 (±6.0) | 27.5 (±5.9) | 0.53 | 26.7 (±6.7) | 0.28 |
| Anorexia | 37.5 (±6.2) | 19.6 (±5.6) | **0.01** | 24.0 (±8.3) | 0.82 |
| Constipation | 14.0 (±4.5) | 7.8 (±4.0) | 0.54 | 13.3 (±5.4) | 1.0 |
| Diarrhoea | 23.9 (±5.6) | 22.5 (±5.7) | 1.00 | 16.7 (±5.7) | 1.00 |
| Economic impact | 20.0 (±5.2) | 17.2 (±5.5) | 0.94 | 21.3 (±6.3) | 0.55 |

p< 0.05; SD: standard deviation. *(3 months vs. baseline) **(6 months vs. baseline).

**Table 5.** QLQ-CR29 quality of life (QoL) scales.

| | **Baseline** (±SD) | **3 months** (±SD) | p* | **6 months** (±SD) | p** |
|---|---|---|---|---|---|
| **Functional scale** | | | | | |
| Body image | 82.9 (±3.3) | 82.8 (±4.8) | 0.63 | 82.7 (±4.9) | 0.32 |
| Sexual Function | 92.5 (±3.3) | 90.2 (±4.6) | 1.0 | 89.3 (±5.0) | 0.25 |
| Prospects for the future | 40.8 (±4.7) | 49.0 (±5.8) | 0.45 | 46.7 (±6.9) | 0.90 |
| **Symptoms** | | | | | |
| Urinary problems | 17.1 (±1.8) | 15.0 (±1.9) | 0.87 | 15.3 (±2.0) | 0.26 |
| Gastrointestinal symptoms | 14.2 (±1.7) | 12.9 (±1.9) | 0.23 | 13.8 (±2.9) | 0.84 |
| Adverse effects of chemotherapy | 2.5 (±1.8) | 9.8 (±3.9) | 0.16 | 12.0 (±4.3) | 0.09 |
| Sexual problems | 52.4 (±4.0) | 50.5 (±3.3) | 0.81 | 56.0 (±5.5) | 0.34 |
| Problems defecating | 14.6 (±2.7) | 13.2 (±2.2) | 0.97 | 13.4 (±2.8) | 0.21 |
| Weight loss | 37.5 (±5.9) | 27.5 (±5.7) | 0.20 | 29.3 (±6.5) | 0.67 |

$p < 0.05$; SD: standard deviation. *(3 months vs. baseline) **(6 months vs. baseline).

The observed variation in the general quality of life criteria can be considered "poor" in terms of impact (Table 6). Except for emotional well-being, which was

classified as medium, the rest of the functional and symptom scales were considered to have a small or no impact, even though a quantitative decrease in symptoms was observed in patients at the end of treatment.

**Table 6.** Analysis of the quality-of-life questionnaire (QLQ-C30) (according to the method of Cocks) at baseline and final evaluation (6 months).

| | Baseline | 6 months | Variation* | CC |
|---|---|---|---|---|
| **Overall Quality of life (QoL)** | | | | |
| QoL | 72.1 | 75.9 | 3.8 | ○ |
| **Functional scale** | | | | |
| Physical function | 75.8 | 76.7 | 0.9 | ○ |
| Daily activity | 63.3 | 69.3 | 6.0 | ▪ |
| Emotional well-being | 53.8 | 64.7 | 10.9 | ▲ |
| Cognitive function | 90.0 | 88.7 | −1.3 | ▪ |
| Social function | 82.5 | 81.3 | −1.2 | ○ |
| **Symptoms** | | | | |
| Fatigue | 35.8 | 34.2 | −1.6 | ○ |
| Nausea | 11.3 | 10.7 | −0.6 | ○ |
| Pain | 32.5 | 26.0 | −6.5 | ▪ |
| Dyspnoea | 5.0 | 1.3 | −3.7 | ○ |
| Insomnia | 35.0 | 26.7 | −8.3 | ▪ |
| Anorexia | 37.5 | 24.0 | −13.5 | ▪ |
| Constipation | 14.0 | 13.3 | −0.7 | ○ |
| Diarrhoea | 23.9 | 16.7 | −7.2 | ▪ |
| Economic impact | 20.0 | 21.3 | 1.3 | ○ |

*Variation: (6 months vs. baseline); CC: Cocks' Classification. (▪ Small, ▲ Medium, ○ No difference or trivial).

## 4. Discussion

Chemotherapy treatment for metastatic CRC has been based for more than fifty years on 5-fluorouracil (5-FU), a fluoropyrimidine analogue that acts by inhibiting thymidylate synthase. Its activity as monotherapy was limited, leading to the development of several strategies to increase its efficacy [14]. Its combination with leucovorin (LV) demonstrated a significant increase in response rates and a modest benefit in overall survival [15]. In other studies, 5-FU was replaced by its oral prodrug, capecitabine, with similar results. Until the emergence of irinotecan and oxaliplatin in various combinations with 5FU/LV, administered both as a bolus and as a continuous infusion, which showed advantages in response rates, disease-free survival, and overall survival [16].

Sophisticated molecular technologies have been developed to reveal new prog-

nostic and predictive biomarkers for CRC [17]. Molecular stratification, which underpins the current treatment algorithm for mCRC, although it does not fully capture the complexity of this disease, has been the first significant step toward a clinically informative genetic profile for implementing more effective therapeutic approaches. This has resulted in a clinically relevant increase in mCRC disease control and patient survival [18]. Current treatment options include combinations of chemotherapeutic agents with epidermal growth factor receptor (EGFR) inhibitors in RAS/BRAF wild-type patients or with antiangiogenic drugs such as bevacizumab [19].

Furthermore, the introduction of immune checkpoint inhibitors has revolutionized the treatment of patients with microsatellite instability CRC. The present investigation was developed shortly before the change in hospital and national diagnostic and treatment guidelines that included the addition of biologicals, so patients received oxaliplatin-based chemotherapy (other chemotherapy regimens were excluded to obtain greater homogenization in patient selection), either XELOX or FOLFOX regimens, supported by the results of the study conducted by Ducreux and collaborators [20], which demonstrated the non-inferiority of oxaliplatin plus oral capecitabine (XELOX) versus FOLFOX-6 (oxaliplatin plus LV, then intravenous bolus of 5-FU, followed by infusional 5-FU) in terms of efficacy in the first-line treatment of mCRC in France, achieving similar overall response rates, median progression-free survival (PFS), and median overall survival, as well as a similar proportion of patients discontinuing chemotherapy due to adverse events in both treatment groups. This trial demonstrated that XELOX and FOLFOX-6 were similar in terms of efficacy and safety [20].

Furthermore, patients who, in their natural history, would have required an ostomy were intentionally excluded, as there is evidence of the psychological impact of intestinal ostomy on patients. This can generate negative feelings such as sadness, fear, and anxiety, in addition to affecting quality of life and social integration, thus significantly biasing patient autonomy in decision-making regarding their healthcare [21].

All included patients had at least one metastatic site, and three-quarters of these had only one involved site. Typically, 25% of patients present with stage IV CRC (synchronous metastases), and approximately 50% of all patients develop liver metastases [22]. Eighty-five percent of patients with stage IV CRC present with liver disease considered unresectable at the time of diagnosis, with the liver being the most common metastatic site due to the abundant portal venous supply from the intestine to the liver, its immune tolerance, or the expression of chemokines in CRC cells that are responsible for liver-specific metastases [23]. The lungs are the second most common site of CRC metastasis after the liver, primarily at the expense of patients with rectal cancer, who are more prone to pulmonary metastases [24]. In the present series, less than 20% had their primary tumour in the rectum, hence the low representation of pulmonary metastases.

Advanced-stage colorectal cancer (CRC) is associated with significant morbid-

ity, which, combined with the adverse effects of cancer treatment, can further impair a patient's quality of life [25]. Chronic inflammation, malnutrition, and complications that occur in patients with CRC are due to long-term tumour consumption, inadequate nutritional intake, as well as responses to stress and metabolic disturbances caused by cancer treatments [26]. Inflammation is a determining factor contributing to cancer progression, invasion, and metastasis, and adverse clinical features such as malnutrition and weight loss can significantly affect the prognosis of these patients [27]. The prevalence of malnutrition in patients with CRC ranges from 20% to 37%, which can decrease and negatively impact patient prognosis and long-term quality of life [28].

The combination of chemotherapy and nutritional supplements has emerged as a new therapeutic approach, targeting not only the tumour but also potentially improving the immune system's response and reducing treatment-related side effects [29]. In this sense, OOS meets all the requirements that supplements with natural ingredients must meet for safe use in cancer: antiproliferative, antioxidant, and anti-inflammatory activity, lack of added toxicity, selective tumour cytotoxicity, and a synergistic effect with conventional OOS treatments [30] [31].

A study conducted at the Department of Cell Biology at the University of the Basque Country demonstrated that in an experimental model of colorectal cancer liver metastasis in Balb/c mice, OOS was able to slow the metastatic progression of CRC to the liver, inhibiting the proliferative and migratory potential of tumour cells and increasing sensitivity to apoptotic signals. Furthermore, OOS limits tumour infiltration by cancer-associated fibroblasts (CAFs) and inhibits the production of inflammatory and angiogenic factors in the tumour microenvironment, creating an unfavourable and non-permissive microenvironment for tumour growth [32]. In another preclinical study conducted by this same working group, OOS® was combined with irinotecan. Although no synergistic effect of the complementary therapy on metastatic progression in vivo was observed, there was a greater reduction in tumour cell proliferation and macrophage infiltration than with OOS® or irinotecan alone. However, it was observed that the combined therapy improved the animal's general condition, and it was concluded that the underlying mechanism could be mediated in part by the reversal, induced by the combined therapy, of the negative regulation exerted by the action of irinotecan on the expression of genes with catalytic and binding activity [33].

In the patient population studied, the mean BMI at the start of treatment was 24.4 kg/m$^2$, and 70% of patients were within the normal range. It is noteworthy that, at both three and six months, there was an increase in BMI, which does not correspond to the weight loss trend typically observed in these patients during the first months of receiving this type of chemotherapy.

In a pooled analysis of 21,149 patients from first-line mCRC trials, BMI was a prognostic factor for both OS and PFS, with a low BMI associated with a higher risk of progression and death among patients enrolled in mCRC trials, while elevated BMI was not associated with an increased risk, unlike with adjuvant therapy.

These authors propose that possible explanations include adverse effects related to oncologic cachexia in patients with low BMI, increased drug administration or selection bias in patients with high BMI, and a potential interaction between BMI and molecular signalling pathways [34]. A decreased BMI predicts a poor prognosis for patients with advanced CRC, and when this chemotherapy-induced weight loss occurs very early, it is an independent predictor of time to progression and overall survival [35] [36]. Prejac *et al.* show that body weight stabilization is an important and independent predictor of longer progression-free survival in first-line treatment of patients with mCRC, where a significantly higher number of patients with stable body weight were also eligible for second- and third-line treatments [37].

Systemic inflammation and immune dysfunction have been shown to be significantly associated with cancer progression and metastasis in many cancer types, including colorectal cancer, where inflammation plays a pivotal role in tumour initiation, progression, and prognosis [38]. There is growing evidence that peripheral blood parameters serve as surrogate markers reflecting inflammatory and nutritional status in cancer patients. The mechanism underlying the potential prognostic value of NLR lies primarily in the importance of neutrophilic and lymphocytic infiltrates in tumour tissue [39]. The systemic inflammatory response promoted by tumour cells triggers neutrophil infiltration, which promotes progression through the production of proinflammatory substances such as interleukin-2 (IL-2), interleukin-6 (IL-6), tumour necrosis factor (TNF), and vascular endothelial growth factor [40].

In the present investigation, a reduction in the absolute neutrophil count was observed, as well as a decrease in the NLR, which was most significant at three months. In animal models of colorectal cancer liver metastasis, OOS reduced the gene expression of the inflammatory molecules IFN$\gamma$, TNF$\alpha$, COX-2, IL6, and IL1$\beta$ in liver tissue, quantified by qPCR [32]. Similar results have been reported with the use of OOS in animal models of pancreatic cancer, with a reduction of these proinflammatory cytokines and an increase in anti-inflammatory cytokines such as interleukin 10 (IL-10) [41].

In the patient population studied, a decrease in absolute platelet count was observed at both three and six months. Similar results were obtained in a clinical study combining Ocoxin with chemoimmunotherapy in patients with advanced pancreatic cancer [42]. Platelets have been widely recognized as a component of the tumour microenvironment; their activation can release various factors that regulate this microenvironment, such as vascular endothelial growth factor (VEGF), TGF$\beta$1, fibroblast growth factor (FGF), and proinflammatory cytokines [43]. Platelets interact with fibroblasts to modulate the tumour microenvironment, which can promote cancer growth and progression by activating cancer-associated fibroblasts (CAF) and enhancing tumour stroma formation [44].

Presumably, we think that there is a synergistic action of OOS with the chemotherapy used in this type of patient, where oxaliplatin could stimulate immuno-

logical effects in response to damage-associated molecular patterns (DAMPs) that interact with the immune system and induce immunogenicity, triggering immunogenic cell death [45]. On the other hand, OOS decreases the expression of the genes that encode these molecules and the polarization of macrophages towards a proinflammatory M2 phenotype by reducing the production of free radicals [46]. This alters the recruitment of stromal cells that generate a proinflammatory and proangiogenic microenvironment, thus increasing the sensitivity of tumour cells to chemotherapy [41].

The assessment of quality of life in cancer patients has gained significant importance, constituting one of the predictors of survival in patients with CRC, not only in clinical trials but also in the real world, where it predicts overall survival independently of routine social and clinical assessments [47]. Typically, in patients with mCRC undergoing chemotherapy, a general deterioration in quality of life is observed during induction treatment, followed by significant recovery in the maintenance phase. Specifically, this trend is evident in global quality of life, the five functional scales, and some individual symptoms (fatigue, nausea/vomiting, loss of appetite, diarrhoea) on the QLQ-C30, as well as in several symptoms or items related to social functioning (body image, dry mouth, hair loss, taste, faecal incontinence, skin irritation) on the QLQ-CR29 [48].

The data presented here differ from this behaviour, in which there is an early benefit in the global quality of life score, even greater at three months than at six months, but always higher than the initial value. A similar behaviour occurs at the level of the functional scales (physical functioning, autonomy, and emotional well-being), while the remaining two (cognitive and social function) remain stable. In other clinical studies where OOS has been used in combination with chemotherapy, optimal results have been obtained in terms of global and specific quality of life: an increase in the score in ovarian cancer in neoadjuvant intent, during chemotherapy treatment [49], as well as in hormone-refractory metastatic prostate cancer [50], while in advanced pancreatic cancer [42], and in gynaecological cancer treated with chemotherapy and radiotherapy, the score stabilized at the baseline value at the end of the evaluation [51]. In the QLQ-CR29 questionnaire, there was no deterioration in the final score with respect to the baseline in any of the symptoms (although not statistically significant), but the perception of the future (in the functional scale) that increases is striking, which differs from that reported by other authors [48]. The perception of weight loss decreases over time and closely correlates with the increase in reported BMI.

The favourable results obtained in the study are primarily determined by the safety profile achieved. The addition of OOS to chemotherapy does not increase toxicity, even decreases its intensity, and increases patient adherence to treatment. The toxicity spectrum described corresponds to the type of chemotherapy received (FOLFOX or XELOX) [52], and was not related to the investigational product, according to the causality classification.

The highest number of adverse events was concentrated in the gastrointestinal

tract, with liver enzyme abnormalities being the most frequent, with 45 reports, although only one of these was classified as grade 2. Elevated liver enzymes and a low platelet count occurred in one patient, and immunological causes or splenic platelet sequestration were ruled out. The causes of this adverse event are primarily because all patients included in the trial had liver metastases, and another is due to the direct action of chemotherapy, primarily oxaliplatin. However, the decreased intensity of these events could be related to the effects of OOS on metastatic tumour cells in the liver, which decreases the expression of RNA levels of proinflammatory and proangiogenic factors [32]. OOS also contains agents with antioxidant and/or hepatoprotective effects (glycyrrhizin acid, ascorbic acid, and epigallocatechin), which improve oxidative stress and immunological parameters, in addition to decreasing the extent of liver fibrosis, with improvement in some histological markers of steatosis and inflammation [53] [54].

It is noteworthy that few patients reported decreased appetite, and the reported number of diarrhoea episodes was much lower than expected for these regimens, ranging from 42% to 60%, with a severity rate between 8% and 10% [15] [16] [20] [25] [52]. Similar results have been reported in clinical studies using OOS [42] [49]-[51]. Epigallocatechin [55] and glycyrrhizinic acid [56] reduce intestinal mucosal toxicity by decreasing the production of proinflammatory cytokines, modifying the intestinal microbiome, or normalizing, directly or indirectly, liver function. Nuclear factor kappa light chain-enhancer of activated B cells (NF-kB) is downregulated by glucosamine and zinc, which, in turn, reduces inflammatory mediators such as IL-1B and TNF-$\alpha$ at the intestinal mucosal level [57] [58]. Moreover, very recent research showed that OOS produces an overexpression of HMOX1, a critical mediator in ferroptosis that promotes cell death in the presence of oxidative stress and high iron concentrations inside cells. Furthermore, OOS also deregulated the expression of NQO1, a gene responsible for redox control that is also involved in ferroptosis. In fact, both HMOX1 and NQO1 are NRF2-dependent genes, which play a central role in the NRF2 pathway, which defends cells against ROS. This mechanism is closely related to metabolic processes, such as carbohydrate metabolism, lipid metabolism, and amino acid metabolism [59].

Anaemia and thrombocytopenia were the most frequently reported hematologic toxicities, and only two episodes of decreased haemoglobin were classified as grade 3. These results differ from those found in the previous study on the use of OOS in Cuban patients with advanced pancreatic cancer, where thrombocytopenia was the most frequently reported event (50.0%) [42]. However, it is important to emphasize that neither the incidence nor the severity of these cases was comparable to those reported in other clinical studies [15] [16] [20] [25] [52]. OOS can inhibit hematopoietic stem cell formation, and erythropoietin gene expression, as well as megakaryopoiesis and thrombopoiesis, through the inhibition of proinflammatory cytokines, primarily TNF-$\alpha$ and IL-1 [60] [61].

The incidence of neuropathy in the study was low (only nine episodes), and grade 3, comprised only 22.2% of these. This figure is much lower than that re-

ported in other studies [15] [16] [20] [25] [52], and even that reported by the same working group but using OOS in advanced pancreatic cancer [42]. Oxaliplatin-induced peripheral neuropathy (OIPN) is dependent on the cumulative dose and duration of treatment with this drug, as well as the combination with other drugs, and, to a lesser extent, on genetic factors [62] [63]. At the molecular level, acute neuropathy is due to dysfunction of ion channels, organic cation transport protein (OCT), and glial cells, while the main relevant mechanisms in chronic oxaliplatin-induced peripheral neuropathy (OIPN) are nuclear DNA damage, oxidative stress-induced mitochondrial damage, neuroinflammation related to glial activation, and gut microbiota-induced inflammation. The degree of acute neuropathy appears to predict the development of chronic neurotoxicity [62] [63].

OOS has been shown to possess potent anti-inflammatory, antioxidant, and autophagy-, necroptosis-, and ferroptosis-regulating properties [10] [11] [59]. By inhibiting cyclooxygenase-2 (COX-2), given the regulation it performs on the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt2) metabolic pathway, it could provide neuroprotection by reducing nitrooxidative stress secondary to mitochondrial dysfunction, as well as the alteration of the levels of some neurotransmitters or the decrease of proinflammatory cytokines, which would result in a recovery of the function of $\gamma$-aminobutyric acid (GABA) [62] [63]. A very similar mechanism of action has been very recently described for the use of proton pump inhibitors in IONP [64].

Overall, and according to the method of Cocks *et al.* [13], the impact of OOS on quality of life in patients diagnosed with mCRC treated with oxaliplatin-based chemotherapy was classified as indifferent at six months of treatment. However, on the symptom scale, most variables showed a change from baseline at six months, which could be considered clinically relevant given that common and debilitating symptoms such as pain and anorexia benefit from the combination. If we performed this same analysis at just three months, the overall impact would be classified as small to medium. In the patient cohort presented here, the reduction in markers of systemic inflammation such as the neutrophil-to-lymphocyte ratio (NLR) or the stabilization of nutritional parameters such as body mass index (BMI) reflects the anti-inflammatory or metabolic effects that have been extensively studied in preclinical research, both in cell lines and in experimental animals. Although this study is exploratory and was not designed for survival analysis, a trend toward increased progression-free survival is observed. Survival studies and their analysis by prognostic factors, including genomic markers, are ongoing and will be published shortly.

However, we believe that the benefit of using OOS in this cancer location in the metastatic setting could be greater with the addition of biological therapies to chemotherapy (such as antiangiogenic agents), given that these treatments share many mechanisms of action in which OOS has been shown to have antitumor activity, and the synergy of action could prolong the benefit of tumour control and its symptoms in the patient [65]. On the other hand, colon cancer may require

a new approach to supplement dosing, requiring a higher dose and individualizing and/or personalizing it based on the risk of muscle mass loss rather than BMI, since the progressive metabolic disorders that occur during the cachexia phase following extensive weight loss may not be reversible, so a window of opportunity should be exploited in the early phase of metastatic disease when patients may still have exploitable anabolic potential [66].

## 5. Limitations

The study was conducted in a limited number of patients (n = 40) without a placebo group for comparison due to the exploratory design, which sought to determine a possible effect of OOS on this cancer site. The duration of OOS use was limited to the duration of chemotherapy treatment. It could have been much more beneficial if administered until symptomatic progression or dose-limiting toxicity, as judged by the clinical investigator.

Although it was conducted at two different institutions, the chemotherapy treatment protocols used are based on standardized clinical practice but correspond to the period prior to the incorporation of biologic agents and molecular biomarker-directed therapies in metastatic colorectal cancer. Therefore, the incorporation of these agents and the evaluation of the OOS combination would be of great interest for future clinical trial designs. Furthermore, measurements of other biochemical and inflammatory markers were not performed, nor was lean muscle mass assessed within body composition using computed tomography, bioelectrical impedance analysis (BIA), or dual-energy X-ray absorptiometry (DXA). These factors could provide further insights into the use of OOS as a nutritional supplement useful in the comprehensive treatment of patients with advanced colorectal cancer.

## 6. Conclusion

This clinical study is the first report on the use of OOS in patients with advanced colorectal cancer and demonstrates its ability to maintain and even improve some quality-of-life parameters in patients undergoing oxaliplatin-based chemotherapy, with a lower incidence and intensity of toxicity. The research team emphasizes that the use of OOS as a complement to anticancer treatments complies with the recommendations of clinical nutrition guidelines in oncology and that it can be used as an adjuvant to cancer treatments to mitigate chemotherapy-related toxicity. Future clinical trials, preferably randomized and controlled, should corroborate the mechanistic effects postulated in preclinical studies and confirm the clinical benefits reported in this study.

## Contribution of the Authors

All authors indicated with an asterisk have contributed equally to the conceptualization, methodology, administration, and funding of the project. All authors contributed to the research, writing, preparation, and drafting of the manuscript. All

authors have read and agreed to the published version of the manuscript.

## Availability of Data and Materials

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

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## Conflicts of Interest

The authors (MLP, JLSG, VFC, LEAT, DMM, VMMP, MGM, MBC, CDA, AVB, RUP, and IMH) declare that they have no conflicts of interest with respect to the publication of this article. All the authors are responsible for the content and writing of the article. The sponsors were not involved in the study design, data collection and analysis, decision to publish, or manuscript preparation.

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