Original Article

Impact of oral nutritional supplements on chemotherapy tolerance and overall survival in postoperative colorectal cancer patients undergoing chemotherapy

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Background and Objectives: The primary objective of this study was to evaluate the efficacy of oral nutritional supplements (ONS) on chemotherapy tolerance and long-term survival outcomes in postoperative colorectal cancer patients undergoing chemotherapy. **Methods and Study Design:** This study was a secondary analysis based on a randomized controlled trial, and patients undergoing chemotherapy after hospital discharge were included. Patients in the ONS group received dietary advice as well as ONS for three months, while the control group received only dietary advice. Clinical characteristics and nutritional indicators were collected at baseline and three months after hospital discharge to assess nutritional status. These included body weight, body mass index, skeletal muscle index, serum albumin, and hemoglobin levels. Chemotherapy modifications including dose reduction, delay, and discontinuation were recorded to represent chemotherapy tolerance. The survival information within 5 years was collected and analysed. **Results:** There were 157 patients included in this study, with 80 patients in the ONS group and 77 in the control group. At three months after hospital discharge, nutrition-related parameters showed no significant differences between the two groups. However, the ONS group demonstrated a significant improvement in chemotherapy tolerance comparing to the control group (17.5% vs. 35.1%, $p = 0.01$). Additionally, the ONS group exhibited a lower 5-year all-cause mortality rate and significantly improved survival outcomes compared to the control group (hazard ratio 0.58, 95%CI: 0.34-0.98, $p = 0.04$). **Conclusions:** The administration of ONS after hospital discharge can improve chemotherapy tolerance and long-term survival rates in colorectal cancer patients undergoing chemotherapy, highlighting the importance of nutritional support during postoperative chemotherapy. Further studies are warranted to validate the underlying mechanisms and other long-term effects.

Key Words: oral nutrition supplements, nutritional support, malnutrition, colorectal cancer, chemotherapy

INTRODUCTION

With the rapid growth of the prevalence of colorectal cancer (CRC) around the world,[1] the advantage of comprehensive anti-cancer treatment, which includes surgical resection, chemotherapy and other treatments, has gradually been recognized and become a part of standardized therapy for CRC.[2,3] While surgical resection still remains the primary curative approach, a growing number of patients with advanced CRC require chemotherapy after surgery to achieve better survival rates.[4] However, a large number of patients with weight loss and muscle wasting had reduced dosage or even discontinued chemotherapy due to intolerance.[5] This is closely related to malnutrition, which is a state of metabolic imbalance caused by multiple factors, including malignancy and systemic inflammation. The typical manifestations of malnutrition include involuntary weight loss, low body mass index (BMI) and muscle loss.[6,7] Meanwhile, a significant proportion of cancer patients simultaneously suffer from sarcopenia, a progressive skeletal muscle disorder characterized by the decline in muscle strength, muscle quantity/quality, and physical performance,[8] concurrently posing a great threat to cancer patients.

The prevalence of malnutrition and sarcopenia is notably high in patients with advanced cancer, where the overall prevalence reaches nearly 50%, leading to poor

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prognosis.[9,10] Muscle mass depletion occupies a crucial position in the diagnosis of both malnutrition and sarcopenia.[6,8] To assess skeletal muscle quantity, skeletal muscle index (SMI), often measured via computed tomography (CT), is widely utilized in current research and clinical practice.[11,12] Current studies have revealed that low SMI in cancer patients is correlated with poor overall survival.[13,14] Therefore, early nutritional risk screening and timely intervention are critical for cancer patients to achieve better clinical outcomes.

Oral Nutritional Supplements (ONS) are commercial products administered orally, which not only conform to the physiological structure of the digestive tract, but also are safe and economical.[15] Therefore, ONS are ideal postoperative nutritional products for CRC patients. Previous studies have confirmed that ONS helps improve postoperative nutritional status in patients with gastrointestinal cancer.[16-18] To investigate whether ONS benefit patients at nutritional risk following CRC surgery after discharge, we previously conducted a prospective non-blind randomized controlled trial (RCT) that enrolled 212 postoperative CRC patients with nutritional risk. Among them, 105 patients in the ONS group received ONS complemented by dietary advice for 3 months after hospital discharge. In the control group, 107 patients received only dietary advice. This study demonstrated that the administration of ONS following discharge effectively preserved skeletal muscle mass, reduced the incidence of sarcopenia, and enhanced the tolerability of chemotherapy in CRC patients. These findings highlight the significance of nutrition support for CRC patients after surgery.[19] However, since our previous study included both patients receiving chemotherapy and those who did not, whether the findings can be fully applied specifically to patients undergoing chemotherapy still requires further investigation.

Current comprehensive anti-cancer therapy researches in CRC primarily focused on the new pharmaceutical development with inadequate attention on nutrition status, overlooking the fact that patients undergoing chemotherapy are exposed to the danger of malnutrition while poor nutrition status also imposes an adverse impact on chemotherapy intolerance.[20,21] Adequate nutritional supplementation is required to help patients overcome this challenge since altered gastrointestinal structure and adverse effects of chemotherapy such as vomiting and anorexia.[22] Therefore, to evaluate the impact of ONS on chemotherapy tolerance and 5-year overall survival in postoperative CRC patients after hospital discharge, we conducted this secondary analysis based on the aforementioned RCT.[22]

METHODS

Study design and patient population

This study is a secondary analysis of a previous randomized controlled trial.[19] The research was performed in Zhongshan Hospital, Fudan University and the study protocol received approval from the Institutional Review Board. This study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki and its later amendments.

Study procedures

In the initial study, patients discharged after CRC surgery who scored ≥3 points by the tool of Nutritional Risk Screening 2002 (NRS 2002) met the inclusion criteria,[23] and exclusion criteria comprised: (i) prior receipt of other nutritional interventions; (ii) inability to consume food orally; (iii) age <18 years; and (iv) pregnancy. All subjects included were allocated to either the control group or the ONS group at random. Written informed consent was provided by each subject before discharge.

This secondary analysis included only patients who underwent chemotherapy following their enrolment in the initial study.

Intervention

Oral nutritional supplementation with Nutren® Optimum (Nestlé Health Science, Switzerland) and dietary advice was provided to the ONS group for three months after discharge. The intervention aimed to enhance nutritional and caloric intake through increased fat and protein consumption. The ONS product provided approximately 100 kcal per 100 mL, containing 11.7 g carbohydrates, 3.9 g fat, 4.1 g protein, 1.2 g fiber, and various vitamins and minerals. The standardized dietary advice was provided, with a recommended daily ONS intake of 500 mL in addition to regular meals. The timing and dosage of each administration is based on the will of patients to optimize compliance. If adverse effects (e.g. diarrhea, abdominal pain, or vomiting) occurred, ONS could be temporarily discontinued or reduced in dose. The control group received identical dietary counseling alone. Both groups received telephone follow-ups biweekly for adherence monitoring and nutritional guidance. If patients in the control group experienced weight loss ≥5% body weight during the first month, ONS supplementation would be provided.[24]

Procedure

On the day of discharge, clinical data of patients including sex, age, comorbidities, cancer site, cancer stage were collected. The nutrition related parameters including serum albumin and hemoglobin levels, body weight, BMI were also documented,[25] NRS2002 score and skeletal muscle index calculated as skeletal muscle area (SMA)/height [SMA (cm^2) / height (m^2)]. SMA was measured via CT at the level of the third lumbar vertebra (L3).[26] Additional clinical variables including tumor site and tumor stage were based on the American Joint Committee on Cancer (AJCC) 8th edition. Nutrition related parameters were reassessed at 3 months post-discharge. During the first three months after hospital discharge, all patients received telephone follow-up twice a week to achieve dietary advice. For all patients, the chemotherapy regimens and planned cycles were strictly standardized. Details of adverse effects during chemotherapy, such as hepatic and renal impairment, allergy, and myelosuppression, were systematically recorded. To ensure patient safety and treatment efficacy, decisions regarding dosage reduction, delay or cessation were strictly clinically driven. Overall chemotherapy tolerance, defined by the occurrence of any of these modifications, was evaluated as a dichotomous variable (absent or present). As a

prospective study, all modifications of chemotherapy were recorded when happened. Patients underwent five years of follow-up, with survival data obtained through outpatient visits or telephone follow-up. The population of this secondary study is based on the initial RCT,[19] patients who did not receive chemotherapy treatment were excluded. The primary endpoint was 5-year all-cause mortality. Secondary endpoints include nutritional status and chemotherapy tolerability. Nutritional status includes body weight, weight loss, BMI, SMI, serum albumin and hemoglobin levels at 3 months after discharge, while chemotherapy tolerance was evaluated by the incidence of chemotherapy adjustments, presented as dose reduction, delay, or cessation.[27]

Statistical analysis

Continuous variables were presented as mean ± SD and the differences between each group were compared using independent samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were analyzed using χ^2 test or Fisher's exact test. p value <0.05 was considered statistically significant. The 5-year survival rate after hospital discharge was analyzed as the primary outcome using Kaplan-Meier method with corresponding survival curves. All statistical analyses were performed using SPSS software (version 23.0).

RESULTS

Patient characteristics

157 patients diagnosed with CRC from the original cohort who have received chemotherapy after hospital discharge were included in this secondary analysis. Figure 1 presents the study flow diagram. Among the 157 patients, 80 of them received ONS after discharge, while the remaining 77 patients did not receive ONS. The baseline characteristics of both groups were well-balanced between the ONS group and control group, presented in Table 1.

Effects of ONS on nutritional status in post-discharge CRC patients receiving chemotherapy

The difference in body weight, SMI and BMI between the two groups at baseline reached no statistical significance (Figure 2A, C, D). The level of serum albumin and hemoglobin also exhibited the similar results (Figure 2E, F). At 3 months post-discharge, the degree of weight loss was similar between both groups (Figure 2B). Although no statistically significant differences were found in SMI, BMI, serum albumin, and hemoglobin levels, patients in the ONS group maintained their nutritional status compared to the day of discharge (Figure 2C-F). Meanwhile, SMI exhibited a tendency toward improvement relative to the control group (Figure 2D).

Effect of ONS on chemotherapy tolerance in post-discharge CRC patients

Patients in the ONS group demonstrated a significant improvement in chemotherapy tolerance, with a lower overall chemotherapy modification rate (17.5% vs 35.1%, p = 0.01) comparing to the control group (Table 2).

Effect of ONS on 5-year survival rates in post-discharge CRC patients receiving chemotherapy

The ONS group showed lower 5-year all-cause mortality compared to the control group (71.3% vs 57.1%, hazard ratio 0.58, 95%CI: 0.34-0.98, p = 0.04), indicating a significant improvement in survival rates. The Kaplan-Meier survival curve is presented in Figure 3.

DISCUSSION

CRC is one of the most prevalent malignant tumors worldwide and is closely related to malnutrition, which contributes to reduced quality of life and poor prognosis.[28,29] Chemotherapy is a standard treatment for advanced CRC. Although extensive research exists on nutritional therapy for patients with CRC undergoing

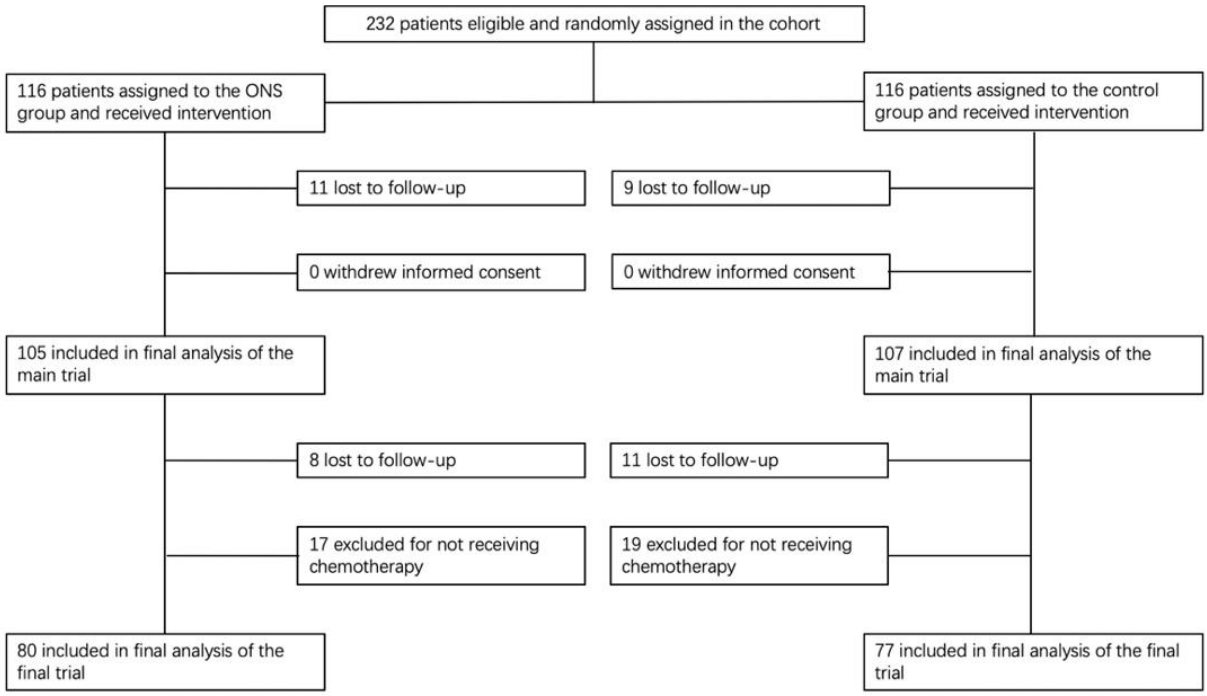

Figure 1. Patient flowchart

Table 1. Demographic and clinical characteristics at baseline in ONS and control groups

	ONS (n = 80)	Control (n = 77)	*p* value
Sex, n (%)			0.83
Men	58 (72.5)	57 (74.0)	
Women	22 (27.5)	20 (26.0)	
Age, years	60.7 ± 9.81	58.8 ± 9.16	0.20
Cardiovascular comorbidity, n (%)	16 (20.0)	16(20.8)	0.90
Respiratory comorbidity, n (%)	4 (5.0)	4 (5.2)	0.96
Diabetes, n (%)	8 (10.0)	6 (7.8)	0.63
Cancer site, n (%)			
Colon	48 (60.0)	50 (64.9)	0.52
Rectum	32 (40.0)	27 (35.1)	
AJCC stage, n (%)			
II	36 (45.0)	33 (42.9)	0.92
III	38 (47.5)	39(50.6)	
IV	6 (7.5)	5 (6.5)	

ONS: oral nutritional supplements; AJCC: American Joint Committee on Cancer.

chemotherapy, studies specifically addressing postoperative nutritional support in this demographic, particularly the impact of ONS on long-term outcomes, remain scarce. Therefore, we conducted a secondary analysis of our primary study to evaluate the influence of ONS on chemotherapy tolerance and 5-year overall survival among this specific population. Our results demonstrated that at three months post-discharge, nutrition-related parameters, including weight loss, BMI, SMI, serum albumin, and hemoglobin, showed no statistical differences between the two groups. However, chemotherapy tolerance was significantly improved in the ONS group. Additionally, the 5-year all-cause mortality rate was lower in the ONS group compared to the control group. These findings suggest that the administration of ONS improved chemotherapy tolerance and long-term survival in postoperative patients with CRC undergoing chemotherapy after discharge, highlighting the importance of nutritional support during this period.

Chemotherapy is a significant risk factor for deteriorating nutritional status. Clinical practices and previous researches have demonstrated that chemotherapy induced a systemic inflammatory response, leading to enhanced catabolism.[30,31] What's worse, the side effects of chemotherapy including nausea, vomiting, as well as anorexia leads to a reduction of food intake and further exacerbate malnutrition. Consequently, patients undergo chemotherapy after hospital discharge are at high risk of malnutrition, posing a major threat to postoperative recovery as well as chemotherapy tolerance.[32,33]

ONS is non-invasive, cost-effective, and convenient. These inherent advantages make it a more acceptable and preferable form of nutritional support for patients compared to enteral or parenteral nutrition. As medical nutrition products, ONS are rich in various macronutrients and micronutrients, which are essential for maintaining basic metabolism and protein synthesis when normal diets fail to meet the need of daily energy expenditure.[34] Furthermore, certain ONS formulations are enriched with immunonutrients, such as arginine, glutamine and omega-3 fatty acids, which not only serve as a nutritional substrate, but also attenuate systemic inflammation, improve immune function, reduce postoperative infection rate and support postoperative recovery.[35,36]

Therefore, ONS effectively protect patients from skeletal muscle loss and improve nutritional status in cancer patients through providing extra energy and protein intake in addition to ordinary food intake, these advantages of ONS contribute to a better clinical outcome and were recommended by the European Society for Clinical Nutrition and Metabolism（ESPEN) guideline.[37] Previous studies have shown that ONS administration in cancer patients help reduced postoperative complications, shorten hospital stays, and improved nutrition status.[16,38] However, its impact on clinical outcomes in post-discharge chemotherapy patients remains underexplored. Our initial research demonstrated that ONS improved the nutritional status of CRC patients at three months after hospital discharge.[19] However, the earlier study population comprised both chemotherapy and non-chemotherapy patients. Thus, the objective of this study was to assess the impact of ONS on nutritional status, chemotherapy tolerability at three months after hospital discharge and long-term survival in post-operative CRC patients undergoing chemotherapy.

Nutritional status between the two groups after three-month post-discharge were analyzed. Our results indicated no statistically significant differences in terms of body weight, weight loss, BMI, serum albumin and hemoglobin levels during chemotherapy, which is consistent with the initial study findings.[19] This result might be related to the nature of surgery in CRC patients since the digestion and absorption function of the gastrointestinal tract are mainly preserved. However, unlike the initial study,[19] the ONS group showed only a trend toward improvement in SMI without reaching statistical significance. This discrepancy may be attributed to several factors, especially chemotherapy. Previous studies have demonstrated that chemotherapeutic agents, such as fluorouracil, directly induce skeletal muscle wasting and fibrosis.[39] Moreover, adverse effects of chemotherapy, including anorexia, taste issue and vomiting, induced insufficient nutritional intake and impaired absorption, further exacerbate this condition.[40-42] Since the analysis was conducted at the three-month mark, an increase in sample size and extension of

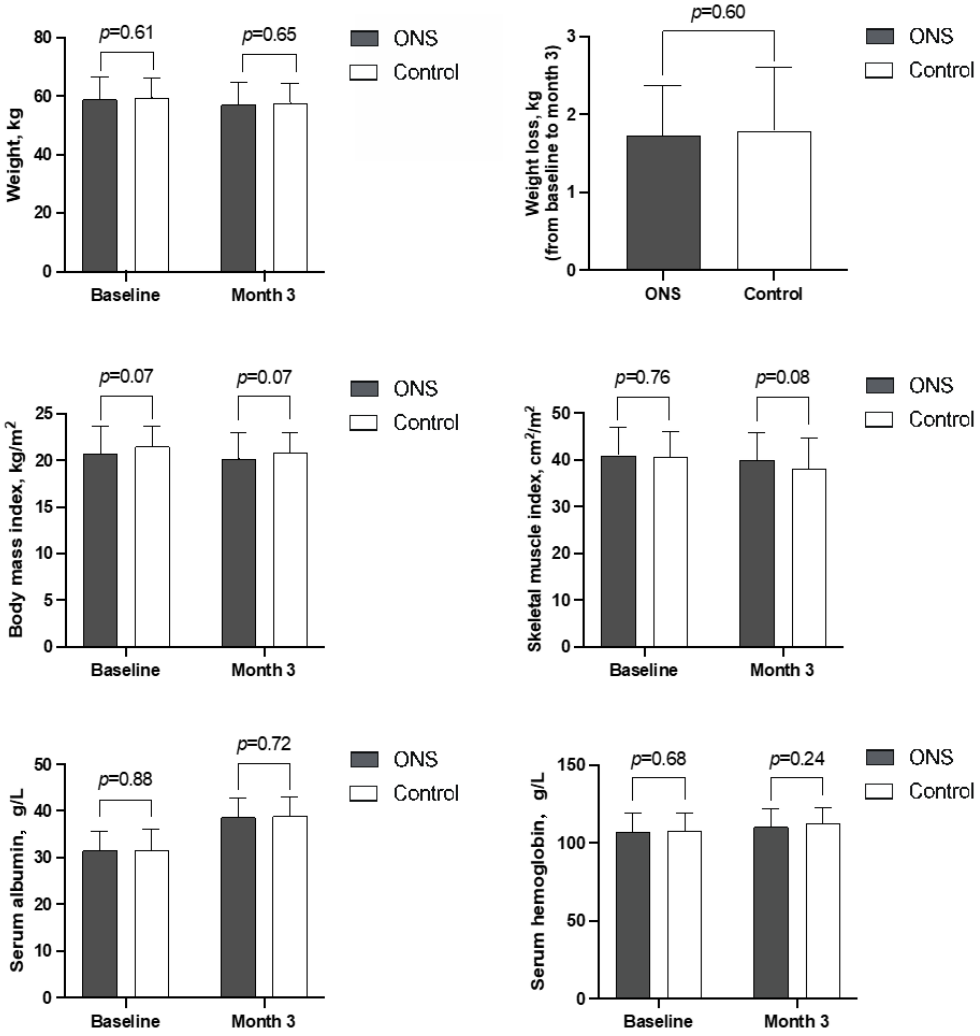

Figure 2. Nutritional outcomes in the control and ONS groups. (A) Comparison of body weight between the control and ONS groups at baseline and after 3 months. (B) Comparison of body weight loss between the control and ONS groups at 3 months after baseline. (C) Comparison of body mass index between the control and ONS groups at baseline and after 3 months. (D) Comparison of skeletal muscle index between the control and ONS groups at baseline and after 3 months. (E) Comparison of serum albumin between the control and ONS groups at baseline and after 3 months. (F) Comparison of serum hemoglobin between the control and ONS groups at baseline and after 3 months

Table 2. Effect of ONS on chemotherapy tolerance in postoperative CRC patients

	ONS (n=80)	Control (n=77)	*p* value
Chemotherapy modification, n (%)	14 (17.5)	27 (35.1)	0.01*
Delay, n (%)	6 (7.5)	12 (15.6)	
Dosage reduction, n (%)	5 (6.3)	12 (15.6)	
Cessation, n (%)	3 (3.8)	3 (3.9)	

ONS: oral nutritional supplements; CRC: colorectal cancer
*p <0.05.

nutritional support duration might yield more favorable results.

To thoroughly assess chemotherapy tolerance, we evaluated modifications in chemotherapy regimens based on three dimensions: treatment delays, dose reductions, and cessation.[43] In this study, patients in the ONS group exhibited significantly better chemotherapy tolerance compared to the control group. This aligns with existing evidence on the benefits of nutritional support in enhancing chemotherapy tolerance,[44,45] suggesting that ONS are beneficial for CRC patients undergoing postoperative chemotherapy. After five years of follow-up, we observed that the ONS group had a lower all-cause mortality than the control group. This result corroborates previous findings on the long-term prognostic benefits of nutritional support in cancer patients.[46,47] This may base on several reasons. Firstly, our results suggest that ONS helps reduce the rate of chemotherapy modifications, and standardized treatment protocols may lead to better outcomes. Secondly, postoperative nutrition support is crucial for promoting muscle synthesis, mitigating muscle wasting, and improving the patient's overall condition and quality of life.[48,49] Finally, ONS may contribute to improved immune function, thereby enhancing the capacity to resist

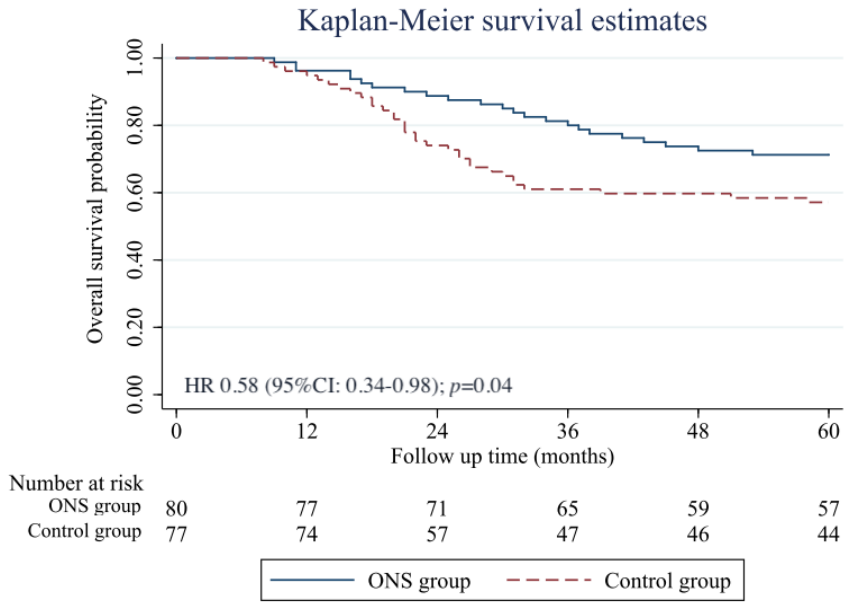

Figure 3. Kaplan-Meier survival curve of the control and ONS groups

disease and potentially improved the overall survival.[35,36] Therefore, these results highlight the potential of ONS as an accessible and cost-effective nutritional intervention, to improve the survival in advanced CRC patients requiring chemotherapy.

Our study has several limitations. Firstly, the sample size in this study was limited, because it is a secondary analysis, and the sample size was based on the initial RCT, not this study. Moreover, although the study protocol was strictly adhered to, certain biases may have existed due to the open-label design and the lack of quantitative data on nutritional intake in the initial study. These factors may explain why some outcomes did not reach statistical significance compared to the control group. Thoroughly analyzing the differences in daily average nutrient intake may uncover deeper relationships with nutritional parameters and help optimize future clinical nutritional interventions. Quantitative data on average daily consumption and patient adherence will be included in future research to better interpret the intervention effects. Additionally, nutrition-related parameters, such as weight changes and serum albumin levels, during the five-year follow-up period were in absence. Future research should involve multicenter, double-blinded prospective studies with larger sample sizes to better elucidate the impact of ONS on post-operative CRC patients undergoing chemotherapy.

Conclusion

The current findings suggest that ONS improves chemotherapy tolerance and five-year overall survival in post-operative CRC patients undergoing chemotherapy, underscoring its critical role in the antineoplastic therapy. Further research is warranted to investigate the effects of ONS on nutritional status improvement in this specific population.

DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

The authors declare that they did not use any AI or AI-assisted technologies in this study

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare that there are no conflicts of interest.

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