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The Auxiliary Effects of Low-Molecular-Weight Fucoidan in Locally Advanced Rectal Cancer Patients Receiving Neoadjuvant Concurrent Chemoradiotherapy Before Surgery: A Double-Blind, Randomized, Placebo-Controlled Study

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Abstract

Patients with cancer use low-molecular-weight fucoidan (LMF) as a supplement to therapy. However, most studies of LMF are *in vitro* or conducted using animals. Concurrent chemoradiotherapy (CCRT) is the gold standard for locally advanced rectal cancer (LARC). This study investigated the quality of life (QoL) and clinical outcomes of patients with LARC taking LMF as a supplement to neoadjuvant CCRT. This was a double-blind, randomized, placebo-controlled study. The sample comprised 87 patients, of whom 44 were included in a fucoidan group and 43 were included in a placebo group. We compared their QoL scores and clinical outcomes before treatment, and at 1 month, 2 months, and 3 months posttreatment. Pretreatment and posttreatment gut microbiota differences were also compared. Although enhanced physical well-being (PWB) at 2 months and 3 months posttreatment in the fucoidan group were observed (both $P < .0125$), the improvements of the Functional Assessment of Cancer Therapy for Patients with Colorectal Cancer (FACT-C) were nonsignificant (all $P > .0125$). Skin rash and itching and fatigue were less common in the fucoidan group (both $P < .05$). Posttreatment, the genus *Parabacteroides* was significantly more common in the gut microbiota of the fucoidan group. LMF administration improved the QoL, skin rash and itching, fatigue, and gut microbiota composition of the patients with LARC receiving CCRT.

Clinical Trial Registration: NCT04342949

Keywords

low-molecular-weight fucoidan, locally advanced rectal cancer, quality of life, disease-free survival, overall survival

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Introduction

The use of complementary and alternative medicine (CAM) by patients with cancer has steadily increased.[1] The most common forms of CAM used by patients with cancer involve vitamins and minerals, diet therapy, massage therapy, and herbal supplements. Fucoidan is a popular natural dietary supplement for cancer therapy. In Taiwan, the use of fucoidan as a supplemental intervention by patients with

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cancer and patients with chronic disease has increased over the last decade, and the annual production value of fucoidan-related products was reported to be more than US$100 million.[2] Fucoidan is the general term for a class of sulfated and fucosylated polysaccharides found in brown seaweed. Fucoidan was first described by Dr. Kylin in 1913 after his investigation of the low incidence of cancer in Okinawa, Japan.[3] Subsequently, more than 1400 studies on its biological activities have been conducted. The reported biological activities of fucoidan are diverse and include antitumor activity, immunomodulation, anticoagulation, enzyme inhibition, blocking of lymphocyte adhesion and invasion, anti-inflammation, and enhancement of the efficacy of chemotherapy.[4-10] Therefore, fucoidan has become a widely used food supplement in the Asia–Pacific region, particularly in Japan, China, Taiwan, and Australia.

Numerous extraction methods are used to produce fucoidan products. Depending on the extraction method used, the molecular weight of fucoidan products can range from 20 000 to 200 000 Da or from 400 to 5000 Da; fucoidan in the lower molecular weight range is known as low-molecular-weight fucoidan (LMF).[11] The backbone of fucoidan consists of α-1,3-linked or α-1,4-linked repeated L-fucose and sulfate units and small quantities of D-galactose, D-xylose, D-mannose, and uronic acid.[12] The biological activities of fucoidan are reported to be associated with its structure and molecular weight.[13,14] LMF reportedly exhibits greater biological activity than does high-molecular-weight fucoidan (HMF).[13,14] Mabate et al investigated the impact of fucoidan on glucose metabolism, and concluded that fucoidan is a relevant, potentially dual therapeutic agent against diabetes and cancer.[15] Hyperglycemia was reported to be associated with the risk and prognosis of colorectal cancer (CRC).[16] The anticancer activities of fucoidan have been demonstrated in various types of cancers, including hepatocellular carcinoma, lung cancer, breast cancer, CRC, pancreatic cancer, prostate cancer, and melanoma.[7,8,13,17-20]

Previously, 3 clinical trials were conducted to evaluate the efficacy of fucoidan in patients with cancer. These 3 clinical studies were reported by Ikeguchi et al[21] Tocaciu et al[22] and Tsai et al respectively.[2] Ikeguchi reported that a randomized trial was performed on 20 patients with advanced or recurrent CRC to be scheduled to receive FOLFOX6 or FOLFIRI chemotherapy, and HMF derived from *Cladosiphon okamuranus* was administered to the fucoidan group. In Ikeguchi et al 's study, each patient received 150 mL/day of liquid that contained 4.05 g fucoidan for 6 months from the initial day of chemotherapy. Their results demonstrated that fucoidan could reduce the frequency of fatigue in patients with unresectable advanced or recurrent CRC during chemotherapy.[21] An open label non-crossover clinical trial, reported by Tocaciu et al, investigated the effects of oral fucoidan (derived from *Undaria pinnatifida*) over a 3-week period (500 mg capsule twice daily) in patients with breast cancer being treated with letrozole or tamoxifen. The results revealed that fucoidan of the studied form and dosage could be taken concomitantly with letrozole and tamoxifen without the risk of clinically significant interactions.[22] Finally, we also conducted a prospective, double-blind, randomized clinical trial including 54 patients with CRC who were divided into 2 groups. The study group (28 patients) who orally received 4 g of LMF twice daily and the control group (26 patients), who orally received 4 g of cellulose powders twice daily at least 3 months, demonstrated the benefits of LMF in improving the disease control rates (DCRs) of patients with CRC.[2]

CRC has become the most common malignancy in Taiwan.[23] CRC is also a major contributor to cancer-associated morbidity.[24] Rectal cancers account for over one-third of CRC cases and are frequently diagnosed as locally advanced rectal cancer (LARC).[25,26] Neoadjuvant concurrent chemoradiotherapy (CCRT) followed by surgical resection is a standard treatment for LARC located in the middle or lower rectum.[26] Neoadjuvant CCRT might increase the risk of adverse events (AEs), which may lead patients to be less willing to undergo preoperative treatment. Based on the advantages of LMF in improving the disease control rates in mCRC[2] and greater potency in its bioactivities than HMF *in vitro* and *in vivo*,[27] we conducted the first prospective, randomized, double-blind, placebo-controlled trial to investigate the effects on quality of life (QoL) and clinical efficacy of LMF as a supplemental therapy in patients with LARC receiving neoadjuvant CCRT.

Materials and Methods

Study Design

The present study had a prospective, randomized, double-blind, placebo-controlled design. We enrolled 110 eligible patients with LARC and randomly assigned them to either a fucoidan or a placebo group. All enrolled patients received neoadjuvant CCRT. In the fucoidan group, each patient orally received 4 g fucoidan BID. In the placebo group, each patient orally received 4 g cellulose powder BID. The intervention period was 3 months. The primary endpoint was QoL, and the secondary endpoints were disease-free survival rates (DFS), overall survival rates (OS), AEs, and gut microbiota changes. All clinical data were collected after informed consent was obtained from the patients, and the study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital [Identification code: KMUHIRB-F(I)−20180113, approval date: November 9, 2018]. The study was registered at ClinicalTrials.gov (NCT04342949).

Materials

The LMF powders were derived from *Sargassum hemiphyllum* and prepared by Hi-Q Marine Biotech International (Taipei, Taiwan), which has a good manufacturing practice certification. Hi-Q Marine Biotech International's LMF powder has been awarded the "symbol of national quality" certification in Taiwan. LMF was obtained through enzyme hydrolysis of the original fucoidan. The characteristics of the LMF were an average molecular weight of 0.8 KDa (92.1%), fucose content of 210.9 ± 3.3 mmol/g, and sulfate content of 38.9% ± 0.4% (w/w).[28] The extraction method was conducted following previously reported protocols with technological modification.[29] The LMF and cellulose powders were packaged in aluminum foil bags with the same appearances and weights. Each package contained 4 g powder.

Participant Selection

The included participants in this study (1) were aged between 20 and 80 years, (2) had LARC confirmed through a pathology or radiology report, (3) had an Eastern Cooperative Oncology Group (ECOG) score between 0 and 2, (4) had a life expectancy of at least 4 months, (5) were prepared to not breastfeed, (5) had no major underlying diseases (e.g., cardiovascular disease, cerebrovascular disease, malignant hypertension, inadequate hematological function, kidney disease, or liver disease) or other malignancies, (6) and were willing to provide informed consent. Patients who did not meet the inclusion criteria or were unwilling to participate were excluded. In addition, patients who could not tolerate regular chemoradiotherapy or were lost to follow-up within the therapeutic period or over 1 year were excluded. The demographic and clinical characteristics of the patients were recorded.

Randomization and Blinding

Patients were randomly assigned at a 1:1 ratio to the fucoidan and placebo groups. A randomization table was created using Microsoft Excel (Microsoft, Redmond, WA, USA). After enrollment, each patient was assigned a project number representing a specific treatment plan. The randomization list was only available to the sample manufacturer and was unblinded after the completion of the research.

Neoadjuvant CCRT

Chemotherapy regimen. Patients underwent a modified FOLFOX6 (mFOLFOX6) regimen, which entailed a schedule of mFOLFOX6 once every 2 weeks. Each cycle of chemotherapy involved an oxaliplatin (85 mg/m^2) and folinic acid (400 mg/m^2) infusion on day 1 followed by a 46-hour infusion of 5-fluorouracil (2800 mg/m^2), repeated every 2 weeks. The patients received one or 2 cycles of induction mFOLFOX6 before CCRT followed by 2 cycles of mFOLFOX6 concomitantly administered during radiotherapy (RT) and an additional 2 to 3 cycles of consolidation mFOLFOX6 after CCRT. During the irradiation period, the dose of oxaliplatin was reduced to 65 mg/m^2 to prevent severe diarrhea. After irradiation completion, all patients continued mFOLFOX6 once every 2 weeks until 2 or 3 weeks before surgery.

Radiotherapy. Patients were simulated in a supine position with computed tomography with a customized thermoplastic immobilization device. All patients were instructed to void their bladder and then drink 300 mL of water 30 minutes before the simulation and irradiation. The total radiation dose was delivered in a range of 45 to 50.4 Gy using a daily fraction of 1.8 to 2.0 Gy. We added a 1.5- to 2 cm clinical target margin to account for the gross tumor volume. In addition to the clinical target margin, we added a planning target margin of 1 to 1.5 cm. All patients received external-beam radiotherapy with either three-dimensional conformal or intensity-modulated radiation therapy.

Estimations of QoL and Comparison of Gut Microbiota

QoL. The Functional Assessment of Cancer Therapy for Patients with Colorectal Cancer (FACT-C) was used to assess QoL.[30] The scale comprises the FACT-Generic Scale (FACT-G, 27 items) and a colorectal cancer subscale (CCS, 9 items). The FACT-G is divided into 4 domains, namely physical well-being (PWB, 7 items), social and family well-being (SWB, 7 items), emotional well-being (EWB, 6 items), and functional well-being (FWB, 7 items). Positively stated items are scored 0 to 4 points, and negatively stated items are scored on a scale ranging from 4 to 0 points. The scoring guidelines for the FACT-C were used to calculate the scores of the items, domains, and the FACT-G and FACT-C total scales.[31,32] The patient scores were validated pretreatment and at 1-month, 2-months, and 3-months post-treatment. PWB consists of the ability to perform physical activities and carry out social roles that are not hindered by physical limitations and experiences of bodily pain, and biological health indicators.

Taxon abundance. We used a Fe-Col fecal collection device (Alpha Laboratories, Eastleigh, UK) to collect stool samples and prevent contamination. Stool samples were collected from each patient before and after treatment. Metagenomics DNA extraction of the stool samples, quality control of the sequencing data, and taxonomic classification were performed in accordance with our previously reported protocol.[33] The differentially abundant microbes of the fucoidan and placebo groups were compared.

Efficacy and Safety Outcome Measures

The assessment of tumor responses was typically performed after 6 or 7 cycles of the interventional treatment. Response measurements were derived from the Response Evaluation Criteria in Solid Tumors, Version 1.1.[34] AEs were monitored and graded in each cycle in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events, Version 4.3 (http://ctep.cancer.gov/reporting/ctc.html).

Study Endpoints

The primary endpoint of QoL was determined from FACT-C scores. The secondary endpoints were DFS (defined as the time from randomization to recurrence of tumor or death), OS (defined as the time from the date of randomization until the date of death or the last date of follow-up), overall response rates (ORRs; defined as confirmed complete responses and partial responses), DCRs (defined as complete responses, partial responses, and stable disease cases), AEs, and changes in gut microbiota.

Statistical Analysis

The data of patients who completed neoadjuvant CCRT and were not lost to follow-up over 1 year were included for analysis. Continuous variables are presented as means ± standard deviations, and dichotomous variables are presented as frequencies and percentages. All statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA). The clinicopathological characteristics of the 2 groups were compared using chi-square tests and P values of $<.05$ were considered significant. The QoL scores between the 2 groups were compared using independent sample t tests and P values of $<.0125$ were considered significant due to considerations of multiple comparisons and Bonferroni correction. The DFS and OS were evaluated using the Kaplan–Meier method, and the log-rank test was used to compare time-to-event distributions.

Results

Study Population and Disposition

Between November 2018 and December 2021, 107 patients with a diagnosis of LARC were enrolled in the present study. Among these patients, 9 were excluded (4 patients were older than 80 years, 3 patients had stage IV rectal cancer after restaging, and 2 patients did not receive CCRT). Ninety-eight patients with LARC were included in this clinical trial. Although 91 completed neoadjuvant CCRT, 4 were lost to follow-up over 1 year. Finally, 87 patients with LARC were unblinded. Of these patients, 44 were included in the fucoidan group, and 43 were part of the placebo group. The CONSORT diagram is presented in Figure 1.

The demographic and clinical characteristics, including sex, age, ECOG score, ORR, DCR, relapse, and early relapse, did not differ significantly between the fucoidan and placebo groups (all $P > .05$, Table 1).

Comparison of QoL Scores

PWB consists of the ability to perform physical activities and carry out social roles that are not hindered by physical limitations and experiences of bodily pain, and biological health indicators. SWB is building and maintaining healthy relationships and having meaningful interactions with others. EWB refers to how well people are able to accept and manage their emotions and cope with challenges throughout life. FWB is defined as the ability of a person to perform the usual tasks of daily living and to carry out social roles. CCS is defined as 9 additional concerned items including stoma care for colorectal cancer patients. We compared the scores of the 8 health-related QoL (HRQoL) measures of the FACT-C between the fucoidan and placebo groups before treatment. The QoL scores of the groups were similar before treatment, with no significant differences observed (Table 2). The overall FACT-C (maximum score: 136), which is a summary measure of the PWB, SWB, EWB, FWB, and CCS domains, scores were not significantly different between the groups although the mean scores of the fucoidan group were higher than those of the placebo group at 1 month, 2 months, and 3 months posttreatment (89.98 vs 89.15, $P = .832$; 92.38 vs 88.35, $P = .335$; and 91.47 vs 86.39, $P = .226$, Table 2). The PWB (maximum score: 28) mean scores of the fucoidan group significantly differed from those of the placebo group at 2 months posttreatment (23.36 vs 21.18, $P = .007$, Table 2) and 3 months posttreatment (23.27 vs 21.12, $P = .006$, Table 2).

Efficacy Outcomes and Safety Measures

The database used for final analysis was locked on June 30, 2022. At the cut-off time, the median time of follow-up was 25.0 months [interquartile range (IQR), 18.0-32.0 months]. The ORRs and DCRs did not differ significantly between the fucoidan and placebo groups ($P = .973$ and $P = .543$, respectively, Table 1). The median DFS were not reached and were nonsignificant in both groups (hazard ratio [HR], 0.730; 95% confidence interval [CI], 0.272-1.962, $P = .582$; Figure 2A). The 24- and 36-month DFS were higher in the fucoidan group than in the placebo group (24-month: 86% vs 76%; 36-month: 80% vs 76%, Figure 2A). The median OS were also not reached and nonsignificant in both groups (HR, 0.175; 95% CI, 0.020-1.503, $P = .071$, Figure 2B). The 24- and 36-month OS were higher in the fucoidan group

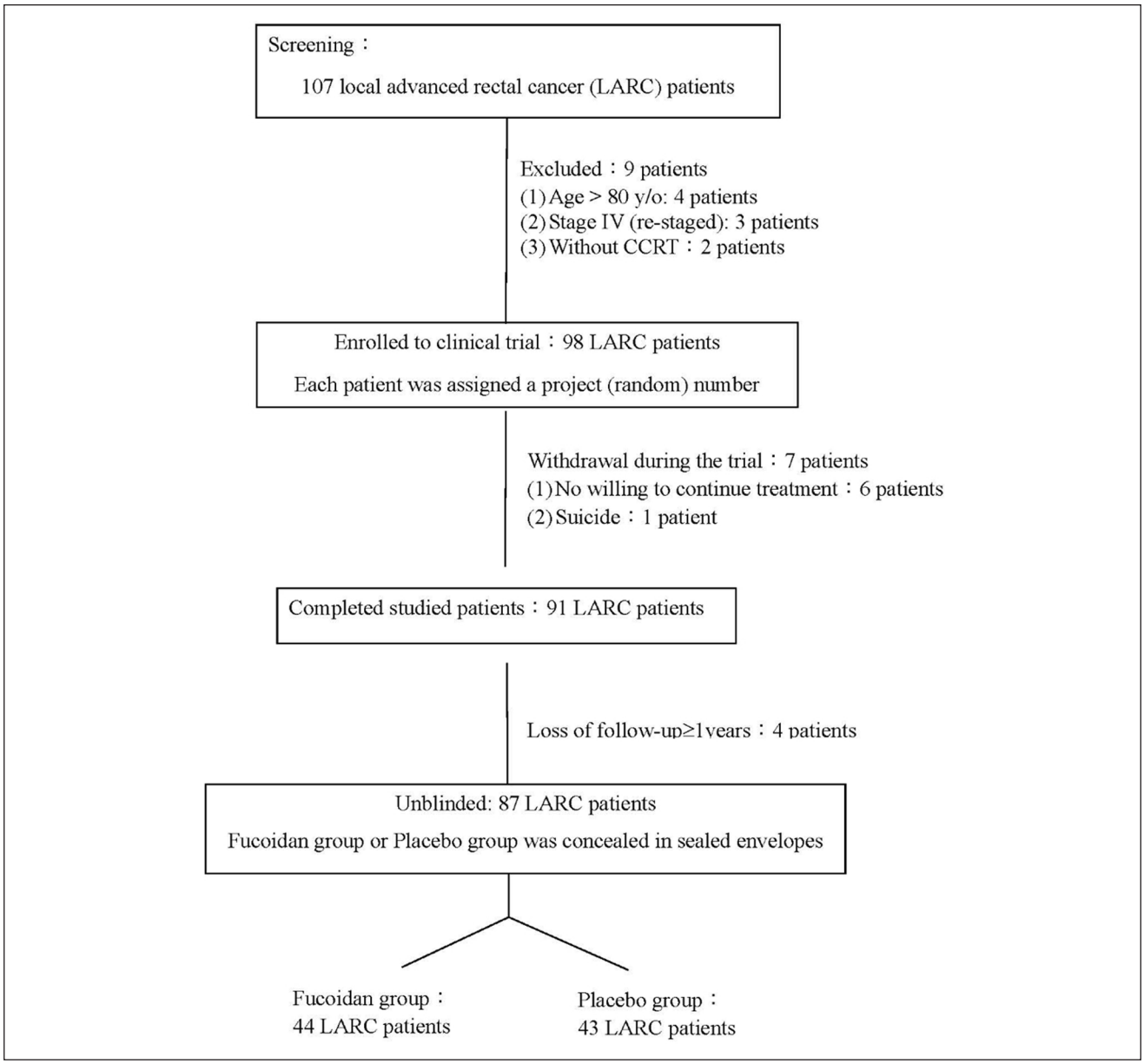

Figure 1. CONSORT diagram of this clinical trial. CCRT, concurrent chemoradiotherapy.

than in the placebo group (24-month: 100% vs 91%; 36-month: 96% vs 83%, Figure 2B).

The rates of 2 AEs occurring was significantly lower in the fucoidan group than in the placebo group (skin rash/itching: 0% vs 9.3%, $P = .038$ and fatigue: 75.0% vs 95.3%, $P = .008$, Table 3). The most common severe AEs in the fucoidan group were neutropenia (2.3%) and anemia (2.3%), and neutropenia (6.9%) was the most common severe AE (≥Grade III) in the placebo group. However, the differences in the rates of severe AEs were nonsignificant between the groups (fucoidan vs placebo group: 4.6% vs 9.3%, $P = .381$, Table 3).

Comparison of Gut Microbiota

We compared the changes in the pretreatment and posttreatment gut microbiota obtained from the stool samples of the fucoidan and placebo groups. The most significantly increased genus of microbiota in the fucoidan group compared with that in the placebo group was *Parabacteroides* ($P = .015$, Figure 3).

Discussion

CRC has been the most common cancer in Taiwan since 2006, according to data published by the Ministry of Health

Table 1. Demographic Characteristics and Posttreatment Efficacies of Fucoidan Group and Placebo Group.

	Fucoidan group (N = 44)	Placebo group (N = 43)	
Characteristic	N (%)	N (%)	*P*-value
Gender			.428
Male	25 (56.8)	28 (65.1)	
Female	19 (43.2)	15 (34.9)	
Age			.158
≧ 65 y/o	23 (52.3)	16 (37.2)	
< 65 y/o	21 (47.7)	27 (62.8)	
ECOG			NA
0	0 (0)	0 (0)	
1	44 (100)	43 (100)	
Best response			.833
pCR	19 (43.2)	16 (37.3)	
PR	21 (47.7)	23 (53.5)	
SD	3 (6.8)	2 (4.6)	
PD	1 (2.3)	2 (4.6)	
ORR			.973
pCR + PR	40 (90.9)	39 (90.7)	
SD + PD	4 (9.1)	4 (9.3)	
DCR			.543
pCR + PR + SD	43 (97.7)	41 (95.4)	
PD	1 (2.3)	2 (4.6)	
Relapse			.546
Yes	7 (15.9)	9 (20.9)	
No	37 (84.1)	34 (79.1)	
Early relapse			.438
Yes	3 (6.8)	5 (11.6)	
No	41 (93.2)	38 (88.4)	

P-value was calculated with Chi-Square test.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; pCR, pathologic complete response; PR, partial response; SD, stable disease; PD, progressivs disease; ORR, objective response; DCR, disease-control rates; Relapse, local recurrence or distant metastasis occurs during the period of follow-up; Early relapse, local recurrence or distant metastasis occurs within 12 months postoperatively.

and Welfare of Taiwan. Therefore, identifying treatment strategies for CRC has become a critical topic.[35] Neoadjuvant CCRT followed by surgical resection is a standard treatment regimen for LARC located in the middle or lower rectum.[26,36] Neoadjuvant CCRT has an effectiveness rate of approximately 40%–80%.[37,38] However, administration of CCRT induces some AEs and may decrease QoL. The results of this research indicate that LMF administration during neoadjuvant CCRT treatment may have reduced the deterioration in QoL, particularly PWB, caused by CCRT and altered the distribution of some gut microbes posttreatment.

Cancer itself induces inflammatory reactions, which cause symptoms such as pain, fever, anorexia, weight loss, fatigue, poor QoL, and cachexia in its terminal stages. These inflammatory reactions may also affect therapeutic efficacy.[39-42] In addition, chemotherapy for advanced cancer induces inflammatory reactions, which may result in many side effects and accelerate tumor growth.[43] A study reported that LMF exerts anti-inflammatory effects by inhibiting key pro-inflammatory activities in polymorphonuclear neutrophils activated by exposure to bacterial products.[44] In 2018, Takahashi et al reported that fucoidan ingestion significantly reduced the main proinflammatory factors including IL-1, IL-6, and TNF-α, but QoL scores, including fatigue, stayed almost stable without significant changes during the study period.[45] Our study demonstrated that LMF could improve PWB and significantly reduce the frequency of chemotherapy-related fatigue. In other words, LMF allows patients to maintain a healthy QoL and thus to carry out their daily activities with less fatigue or stress than the control patients.

No study has investigated the hematological effect of fucoidan administration *in vivo*. In the current study, the anemia, neutropenia, and thrombocytopenia grades were similar in the groups. Fucoidan reportedly protects against liver injury and liver fibrosis in mice.[46,47] However, the association between fucoidan administration and improvements in impaired liver function is nonsignificant. Similarly, LMF was observed to protect renal tubular cells from injury and reduce blood urea nitrogen and creatinine levels in mice.[48,49] In the present study, the rates of grade I acute renal injury in the groups were similar, and no severe renal function injury was recorded. Park et al reported that LMF could promote dermal wound healing through complex and coordinated antioxidant, anti-inflammatory, and growth factor–dependent activities.[50] In our study, increases in skin rash and itching and fatigue symptoms were significantly greater in the placebo group than in the fucoidan group.

We report the long-term survival outcomes. Although the DFS and OS were not significantly different between the 2 groups in the present study, the fucoidan group seems to have a trend of better OS but not have a trend of better DFS. The 2-year DFS of the fucoidan and placebo groups were 86% and 76%, respectively. The 3-year DFS were 80% and 76%, respectively. The 2-year OS of the fucoidan and placebo groups were 100% and 91%, respectively, whereas the 3-year OS were 96% and 83%, respectively. Therefore, a longer follow-up time is required to determine if superior DFS and OS are associated with fucoidan administration. In the comparisons of the pretreatment and posttreatment gut microbiota of the 2 groups, the genus that exhibited the most significant difference was *Parabacteroides*. Ezeji et al reported that the *Parabacteroides* genus is associated with beneficial and pathogenic effects on human health.[51] To date, *Parabacteroides distasonis* has only been reported to have beneficial effects on CRC. Several researchers have reported that levels of *P. distasonis* in stool are inversely correlated with the presence of intestinal tumors.[52]

Table 2. Comparison Between The Fucoidan Group and Placebo Group by FACT-C Health-Related Quality of Life Mean Scores Before Treatment, After 1-month Treatment, After 2-month Treatment, and After 3-month Treatment.

Domains	Maximum score	Fucoidan group (N = 44) Mean (SD)	Placebo group (N = 43) Mean (SD)	*P*-value
Physical Well-Being (PWB)	28			
Before treatment		22.77 (4.23)	21.55 (3.75)	.216
After 1-mo treatment		22.70 (3.70)	21.83 (5.23)	.374
After 2-mo treatment		23.36 (3.51)	21.18 (3.80)	.007
After 3-mo treatment		23.27 (3.70)	21.12 (3.37)	.006
Social/Family Well-Being (SWB)	28			
Before treatment		19.89 (5.51)	18.50 (5.72)	.252
After 1-mo treatment		19.62 (4.73)	19.17 (6.27)	.708
After 2-mo treatment		18.77 (5.06)	19.07 (6.17)	.802
After 3-mo treatment		18.68 (5.26)	19.46 (6.31)	.529
Emotional Well-Being (EWB)	24			
Before treatment		18.29 (4.69)	17.07 (4.90)	.237
After 1-mo treatment		17.16 (4.64)	16.67 (4.59)	.626
After 2-mo treatment		16.20 (5.17)	16.04 (7.38)	.878
After 3-mo treatment		16.91 (5.66)	15.77 (3.83)	.273
Functional Well-Being (FWB)	28			
Before treatment		13.89 (6.14)	12.21 (7.55)	.259
After 1-mo treatment		14.07 (5.71)	14.09 (6.08)	.984
After 2-mo treatment		15.50 (5.22)	14.65 (7.38)	.539
After 3-mo treatment		13.89 (6.28)	13.51 (6.11)	.779
Colorectal Cancer Subscale (CCS)	28			
Before treatment		17.48 (4.52)	17.23 (5.51)	.821
After 1-mo treatment		17.05 (4.56)	17.12 (3.67)	.937
After 2-mo treatment		18.54 (5.31)	17.39 (5.39)	.319
After 3-mo treatment		18.70 (4.96)	16.53 (4.40)	.034
FACT-C Trial Outcome Index (TOI)	84			
TOI = PWB + FWB + CCS				
Before treatment		53.18 (12.75)	50.00 (16.16)	.183
After 1-mo treatment		53.66 (10.78)	53.28 (12.62)	.880
After 2-mo treatment		57.41 (11.49)	53.23 (14.30)	.137
After 3-months treatment		55.89 (13.35)	51.16 (11.70)	.083
FACT-G General scores for health-related quality of life	108			
FACT-G = PWB + SWB + EWB + FWB				
Before treatment		74.94 (16.65)	68.33 (19.70)	.095
After 1-mo treatment		73.53 (12.63)	72.00 (17.81)	.646
After 2-mo treatment		73.84 (14.10)	70.96 (15.84)	.373
After 3-mo treatment		72.79 (17.05)	69.85 (17.48)	.387
FACT-C Scores for health-related quality of life colorectal	136			
FACT-C = PWB + SWB + EWB + FWB + CCS				
Before treatment		92.41 (20.00)	85.58 (24.49)	.157
After 1-mo treatment		89.98 (15.59)	89.15 (20.60)	.832
After 2-mo treatment		92.38 (18.43)	88.35 (20.29)	.335
After 3-mo treatment		91.47 (21.12)	86.39 (17.48)	.226

The statistical analysis was used by independent *t*-test. *P* value was considered to be significant ($P < .0125$) by Bonferroni correction.

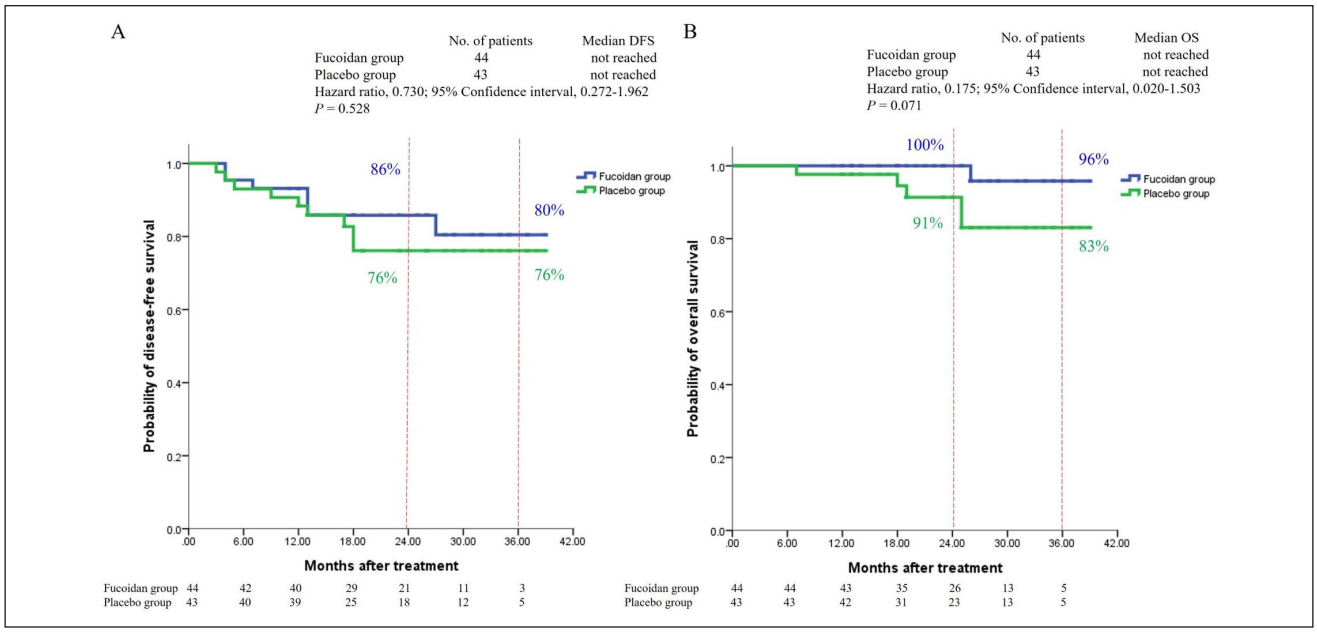

Figure 2. Cumulative disease-free survival (DFS) rates and overall survival (OS) rates of the 87 enrolled patients with locally advanced rectal cancer (LARC), obtained using the Kaplan–Meier method. Differences in DFS and OS were analyzed using the log-rank test. The results demonstrated that (A) The DFS did not significantly differ between the 2 groups ($P = .528$). The 2-year DFS of the fucoidan and placebo groups were 86% and 76%, respectively, and the 3-year DFS were 80% and 76%, respectively. (B) The OS did not significantly differ between the 2 groups ($P = .071$). The 2-year OS of the fucoidan and placebo groups were 100% and 91%, respectively, and the 3-year OS were 96% and 83%, respectively.

Table 3. Common Adverse Events and Severe Adverse Events of The Fucoidan Group and Placebo Group.

	Fucoidan group (n = 44)				Placebo group (n = 43)				
	n (%)				n (%)				
Grade	1	2	3	4	1	2	3	4	*P*-value
Hematologic AE									
Anemia	27 (61.4)	12 (27.3)	1 (2.3)	0 (0)	30 (69.8)	6 (13.9)	1 (2.6)	0 (0)	.467
Neutropenia	20 (45.5)	17 (38.6)	1 (2.3)	0 (0)	25 (58.1)	11 (25.6)	3 (6.9)	0 (0)	.357
Thrombocytopenia	19 (43.2)	1 (2.3)	0 (0)	0 (0)	24 (55.8)	1 (2.3)	0 (0)	0 (0)	.490
Non-hematologic AE									
Skin rash/itching	0 (0)	0 (0)	0 (0)	0 (0)	4 (9.3)	0 (0)	0 (0)	0 (0)	.038
Nausea	3 (6.8)	2 (4.6)	0 (0)	0 (0)	3 (6.9)	0 (0)	0 (0)	0 (0)	.368
Vomiting	14 (31.8)	0 (0)	0 (0)	0 (0)	14 (32.6)	0 (0)	0 (0)	0 (0)	.941
Diarrhea	6 (13.6)	4 (9.1)	0 (0)	0 (0)	4 (9.3)	2 (4.6)	0 (0)	0 (0)	.554
Fatigue	33 (75.0)	0 (0)	0 (0)	0 (0)	41 (95.3)	0 (0)	0 (0)	0 (0)	.008
Neuropathy	10 (22.7)	0 (0)	0 (0)	0 (0)	9 (20.9)	0 (0)	0 (0)	0 (0)	.839
Alopecia	10 (22.7)	0 (0)	–	–	15 (34.9)	0 (0)	–	–	.210
Oral mucositis	2 (4.5)	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)	0 (0)	.570
Insomnia	5 (11.4)	0 (0)	0 (0)	0 (0)	3 (6.9)	0 (0)	0 (0)	0 (0)	.479
Impaired liver function	13 (29.5)	0 (0)	0 (0)	0 (0)	21 (48.8)	0 (0)	0 (0)	0 (0)	.065
Acute renal injury	6 (13.6)	0 (0)	0 (0)	0 (0)	8 (18.6)	0 (0)	0 (0)	0 (0)	.528
Severe AEs		Grade 3&4				Grade 3&4			*P*-value[†]
		2 (4.6%)				4 (9.3%)			.381
Anemia		1				1			
Neutropenia		1				3			

P-value was calculated by the Chi-Square test (2-sided).
Abbreviations: AEs, adverse events.

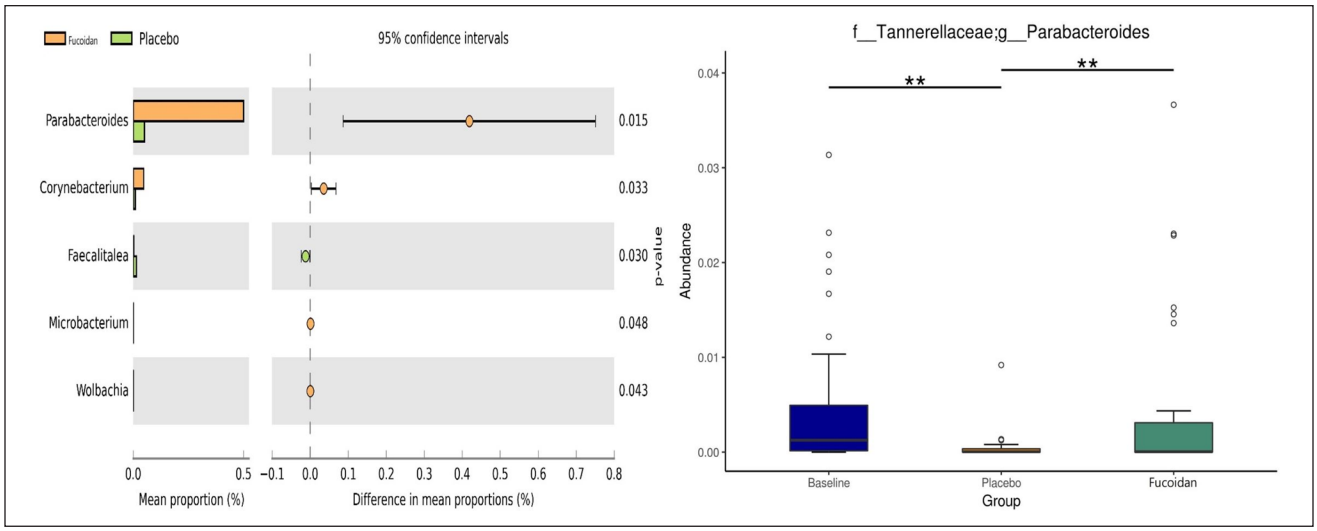

Figure 3. Comparison of the changes of the pretreatment and posttreatment gut microbiota of the 2 groups. The levels of 4 genera, particularly those of the genus *Parabacteroides* ($P = .015$), differed significantly between the fucoidan and placebo groups.

This study has some limitations. First, although this is a prospective, double-blind study, the use of a larger sample size would have enhanced the credibility of the findings. Second, some patients were excluded because of noncompletion of neoadjuvant CCRT and loss to follow-up over 1 year. Third, because of the insufficient follow-up time, an evaluation of the long-term efficacy, particularly in terms of the OS, was not possible.

Conclusions

This is the first prospective, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of LMF as a supplemental therapy in patients with LARC. Numerous studies have demonstrated the anticancer effects of LMF and reported its considerable potential for cancer treatment. Our study demonstrated the advantages of LMF for improving QoL, particularly in PWB, fatigue, and skin itching during the period of CCRT, and increasing microbial levels of the *Parabacteroides* genus. This study can inform the implementation of cancer therapies, particularly those involving the combination of chemotherapy and radiotherapy.

Animal Studies

N/A

Author Contribution

Conception and design: HLT and JYW. Development of methodology: HLT and JYW. Acquisition of data: YSY, PJC, YTC, YCC, WCS, TKC, and CWH. Analysis and interpretation of data (e.g., statistical analysis, bioinformatics, computational analysis): HLT and JYW. Writing, review, and/or revision of the manuscript: HLT and JYW. Administrative, technical, or material support: YSY, PJC, YTC, YCC, WCS, TKC, and CWH, and TCY. Study supervision: HLT and JYW. All authors contributed to the article and approved the submitted version.

Availability of Data and Materials

The data and materials analyzed in the current study are available from the corresponding author on reasonable requests.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

Approval of the research protocol by an Institutional Reviewer Board: The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital [KMUHIRB-F(I)-20180113].

Informed Consent

All informed consent was obtained from the subjects.

Registry and the Registration No. of the Study/ Trial

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