ORIGINAL RESEARCH

Clinical Efficacy of Bevacizumab Plus XELOX Chemotherapy in Colorectal Cancer and Application Value of Mindfulness-Based Stress Reduction Intervention

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ABSTRACT

Background and Objectives • Colorectal cancer (CRC) is a malignant tumor with an extremely high incidence rate worldwide. This study explores the influence of mindfulness-based stress reduction (MBSR) in the care of patients with CRC undergoing bevacizumab (BVZ) plus XELOX chemotherapy, aiming at providing reliable reference and guidance for further improving their rehabilitation and prognosis.

Methods • Between January 2019 and March 2020, 88 patients with CRC admitted consecutively to Jiangsu Cancer Hospital in China were enrolled in the study. Of them, 42 patients receiving BVZ plus XELOX chemotherapy, conventional care and MBSR intervention were assigned to the intervention group, and the remaining 46 patients receiving XELOX chemotherapy and conventional care were included in the control group. Clinical efficacy, safety and improvement in functional status were compared. Patients' psychological state, treatment compliance and self-care ability were evaluated. Finally, prognostic quality of life (QoL) was recorded at 1-year follow-up.

Results • The overall response rate and incidence of adverse events in the intervention group were not different in the control group, but the total control rate and improvement rate in the intervention group were higher. After treatment, Sedation-Agitation Scale (SAS) and Self-Rating Depression Scale (SDS) scores in the intervention group were decreased, compliance and self-care ability were improved, all of which were better than in the control group. Prognostic follow-up showed that the QoL in the intervention group was also higher than in the control group.

Conclusions • The combined use of BVZ in XELOX-based chemotherapy can improve the clinical outcome and functional status of patients with CRC. In addition, MBSR intervention implemented during chemotherapy can effectively optimize patients' psychological state and treatment compliance, strengthen their self-care ability and improve their prognostic QoL (*Altern Ther Health Med.* 2022;28(6):65-71)

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INTRODUCTION

Colorectal cancer (CRC), which originates from the large intestine epithelium, has an extremely high incidence rate worldwide, affecting more than 1.8 million people every year, and has an ever-higher incidence year after year.[1] The prognostic mortality of advanced CRC is 60% to 80%, with approximately 900 000 patients dying from CRC on a yearly basis.[2] For early-stage tumors, radical tumor resection usually has an excellent therapeutic result.[3] However, due to the early concealment of CRC and the lack of patient medical and health knowledge, by the time most patients are diagnosed, the disease has already reached the middle and late stages. At this time, surgery alone has been unable to achieve a complete cure of the tumor, and chemotherapy is needed to kill tumor cells.[4] The XELOX regimen (oxaliplatin combined with capecitabine) is one of the most commonly used

Table 1. Baseline Patient Characteristics

Group		BMI	Gender	Family history	Intestinal inflammation	Smoking	Drinking	Type of tumor	Stage
G	Age	(kg/cm)	Male/Female	Yes/No	Yes/No	Yes/No	Yes/No	Colon/Rectal Cancer	I-II/III-IV
Intervention	58.07±5.72	22.8 ± 2.08	24/18	9/33	34/8	26/16	24/18	17/25	27/15
Control	56.89±5.79	22.60 ± 2.27	28/18	12/34	35/11	30/16	25/21	16/30	28/18
t or χ^2	0.960	0.430	0.126	0.262	0.307	0.104	0.070	0.304	0.109
P value	.340	.669	.723	.609	.580	.747	.792	.582	.741

Abbreviations: BMI, body mass index.

chemotherapy regimens with stable effects and a very good safety profile.[5] BVZ, on the other hand, is currently the first-line treatment for metastatic CRC; it can inhibit tumor vascular endothelial proliferation and angiogenesis and significantly prolong patient survival.[6] With the development of cancer treatments, change in drug resistance and other factors, the combination of BVZ and XELOX can be used in current clinical chemotherapy in CRC to further improve the killing effect in tumor cells.[7]

As we all know, chemotherapy in cancer is usually accompanied by significant toxic adverse events (such as myelosuppression, hair loss, nausea and vomiting, etc.), which predisposes patients to negative thoughts, resistance to chemotherapy and loss of confidence in treatment.[8,9] Mindfulness-based stress reduction (MBSR)—a non-drug systematic psychological intervention based on "mindfulness" created by Professor Kabat-Zinn of the University of Massachusetts Medical Center in 1979—mainly awakens inner concentration, improves self-regulation and relieves pain related to physical and mental disorders through mindfulness meditation, physical awareness, yoga and so on.[10] At present, MBSR has shown remarkable results in a number of tumor diseases that require chemotherapy,[11] but its employment in CRC has rarely been reported.

Accordingly, our study investigated the influence of MBSR intervention during BVZ plus XELOX-based chemotherapy in patients with CRC in order to provide reliable reference and guidance for improving patients' rehabilitation and prognosis in the future.

MATERIALS AND METHODS

Patient Information

A total of 88 patients with CRC admitted consecutively to Jiangsu Cancer Hospital in Nanjing, China from January 2019 to March 2020 were enrolled in the study. Of these, 42 patients (27 with colon cancer and 15 with rectal cancer) receiving BVZ plus XELOX-based chemotherapy were assigned to the intervention group, and the remaining 46 patients (28 with colon cancer and 18 with rectal cancer) receiving XELOX chemotherapy were assigned to the control group. Cinical baseline data were comparable in both groups ($P > .05$; see Table 1).

Inclusion criteria. All enrolled patients were diagnosed with CRC via biopsy in our pathology department, and met the indications of the XELOX protocol; age range was 18 to 70 years. All patients signed an informed consent form.

Exclusion criteria. Patients were excluded from the study if they had: multiple tumors, other cardio-cerebrovascular diseases, mental diseases, autoimmune defects, liver or kidney dysfunction, drug allergies or were pregnant or lactating.

METHODS

XELOX Chemotherapy

Oxaliplatin (Zhejiang Hisun Pharmaceutical Co., Ltd., SFDA Approval No. H20093487), 50 mg/s, 130 mg/m2, was given intravenously (IV) on day 1 of each cycle, as well as oral capecitabine (Shanghai Roche Pharmaceutical Ltd., SFDA Approval No. H20073024), 1000 mg/m2 twice a day for 14 days. BVZ (Roche Pharma [Switzerland] Ltd., Registered Number of Approval: S20120069) was given IV at a dose of 7.5 mg/kg after oxaliplatin administration. Each chemotherapy cycle lasted 3 weeks and both groups were treated for 6 cycles.

Conventional Nursing

Measures mainly included strengthening nutrition, ensuring sleep, proper exercise, health education, information concerning CRC prognosis, the role of chemotherapy and precautions, as well as psychological counseling as necessary.

MBSR Intervention

During the first week of chemotherapy, MBSR concepts, principles, procedures and precautions were introduced to the patients. Meanwhile, the ward was kept quiet, and soothing, relaxing music was played to assist patients in the practice of mindfulness breathing 15 to 20 minutes/day: patients were instructed to relax their entire bodies, take deep breaths, and focus on emotional changes and thoughts while slowly exhaling and inhaling.

At the second week, mindfulness meditation training was started. Patients were asked to imagine themselves in a safe, warm environment and recall what they yearn for or good memories while feeling their own emotional and physical changes, without subjective evaluation or criticism of any feelings.

At the 3rd week, mindfulness diet training was conducted. After a diet suitable for patient rehabilitation was developed, patients could first choose familiar or favorite foods, and then gradually transition to unfamiliar and

disliked foods. At the same time, patients were instructed to eat slowly and feel the changes in smell, taste and the chewing sensation while eating.

In the 4th week, a whole body scan was performed. In the state of mindfulness meditation, patients were asked to feel changes in sensation of various body parts and organs while maintaining a state of non-judgement and non-criticism.

In the 5th week, patients were trained in mindfulness yoga, during which they needed to feel their inner and physical movements. When discomfort or pain was experienced during the training, patients were instructed not to worry, be agitated or resist the pain, but to relax their bodies and try to gradually accept the feeling.

At weeks 6 to 7, patients were instructed to summarize the skills and experience of mindfulness and encouraged to implement mindfulness into their lives, so they could start mindfulness self-training (mindfulness walking, mindfulness reading, etc.).

At week 8, patients were instructed to review MBSR and reinforce their impression of the concept of mindfulness. At the same time, they were encouraged to share the changes and effects of the concept with other patients and their families, and integrate that concept into their lives.

Prognosis

A 2-year follow-up survey was administered to record the overall survival of patients. Both groups received routine care, and the intervention group also received MBSR.

Outcomes Measurement

Clinical Efficacy. Clinical efficacy was divided into the following categories in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) criteria:

Complete remission (CR). After treatment, the diameter of the patient's lesion was decreased by more than 50% or completely disappeared, and tumor marker detection results were normal.

Partial remission (PR). A 30% to 50% reduction in lesion diameter.

Stable disease (SD). The lesion diameter was reduced after treatment, but did not reach the above criteria.

Progressive disease (PD). An increase in lesion diameter or the presence of new lesions.

Disease control rate (DCR). (PR+CR+SD) / total ×100%.

Overall response rate (ORR). (PR+CR)/total ×100%.

Functional status. Pre- and post-treatment functional status of patients was assessed using the Karnofsky Performance Scale (KPS). With a full score of 100, an increase of 10 points was considered improvement, a constant score or a change between 0 and 10 points was considered stable, and a decrease of >10 points was considered aggravation.

Improvement rate. (improved+stable)/total × 100%.

Psychological status. The Self-rating Depression Scale (SDS) and Self-rating Anxiety Scale (SAS) were used to evaluate patient's psychological state.

Treatment compliance. Completely refusing to accept and cooperate with nursing intervention was considered poor compliance; selective acceptance and coordination with the nursing intervention was considered moderate compliance; complete acceptance and active cooperation with the nursing intervention was considered high compliance.

Total compliance = (high + moderate)/total × 100%.

Self-care ability. Patients' self-care ability was evaluated by the Exercise of Self-care Agency Scale (ESCA) from the areas of self-care skills, self-responsibility, self-concept and health knowledge, with a possible full score of 172. The higher the score, the stronger the self-care ability.

Quality of life (QoL). The QLQ-C30 scale was used to measure 5 dimensions: role, physical, cognitive, emotional and social functioning, with a higher score indicating better QoL.

Statistical Analysis

The software used for statistical analysis was IBM® SPSS 22.0. Count data such as clinical efficacy and functional status were described as [n (%)], and chi-square test was used for comparison between the 2 groups. Self-rating depression scale (SDS) and Self-rating Anxiety Scale (SAS) scores and other measurement data were represented by ($\chi \pm s$), and intergroup comparison was made by the independent samples *t* test and paired *t* test. The difference was deemed significant at $P < .05$.

RESULTS

Comparison of Clinical Efficacy

In the intervention group, the percentage of patients with CR, PR, SD and PD was 30.95%, 45.24%, 11.90%, and 11.90%, respectively, with a DCR of 88.10% and an ORR of 76.19%. While the DCR in the control group was 80.43%. The intergroup comparison revealed no significant difference in ORR between groups ($P > .05$), while DCR in the intervention group ($P < .05$; Table 2). It indicates that BVZ+XELOX combined with MBSR intervention has no significant impact on clinical efficacy in patients with CRC.

Comparison of Adverse Events

The incidence rate of thrombocytopenia, vomiting, myelosuppression and peripheral neuropathy in the intervention group was 33.33%, 16.67%, 7.14% and 4.76%, respectively and the overall complication rate was 61.90%. The overall incidence of adverse events in the control group was 71.74%; the incidence of thrombocytopenia was the highest, reaching 33.33%. The overall incidence of adverse events in the 2 groups was insignificant ($P > .05$; Table 3),

Table 2. Clinical Efficacy in the Two Groups (n [%])

Group	CR	PR	SD	PD	DCR (%)	ORR (%)
Intervention	13 (30.95)	19 (45.24)	5 (11.90)	5 (11.90)	88.10	76.19
Control	9 (19.57)	16 (34.78)	12 (26.09)	9 (19.57)	80.43	54.35
χ^2					0.963	4.591
P value					.326	.032

Abbreviations: CR, complete remission; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable remission.

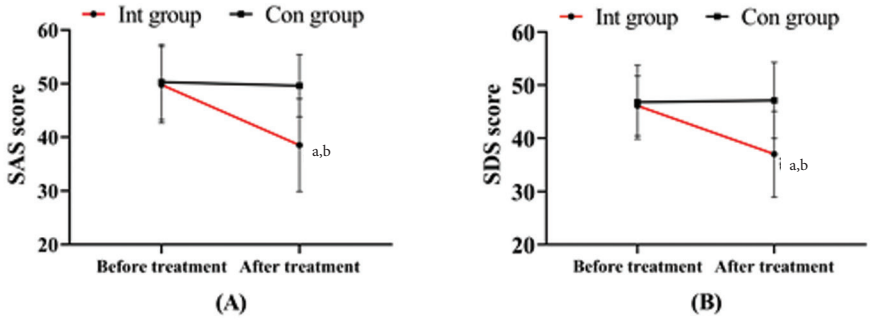
Table 3. Incidence of Adverse Events in the Two Groups (n [%)])

Group	Infection	Thrombo-cytopenia	Malignant vomiting	Myelo-suppression	Peripheral neuropathy	Overall compli-cation rate (%)
Intervention	0 (0.0)	14 (33.33)	7 (16.67)	3 (7.14)	2 (4.76)	61.90
Control	1 (2.17)	18 (39.13)	6 (13.04)	5 (10.87)	4 (8.70)	71.74
χ^2						0.961
P value						.327

Table 4. Changes in Functional Status in Patients in the Two Groups Before and After Treatment [n (%)]

Group	Improved	Stable	Progressed	Total improvement rate (%)
Intervention	18 (42.86)	19 (45.24)	5 (11.90)	88.10
Control	16 (34.78)	16 (34.78)	14 (30.43)	69.57
χ^2				4.453
P value				.035

Figure 1. Comparison of changes in psychological state between the 2 groups before and after treatment. (A) SAS scores in the 2 groups; (B) SDS scores in the 2 groups.



[a]*P* < .05 compared with the control group
[b]*P* < .05.

Abbreviations: Int, intervention; Con, control.

indicating that BVZ+XELOX combined with MBSR intervention is safe in the treatment of patients with CRC.

Comparison of Functional Status

Then, we assessed the changes in functional status in the 2 groups of patients after treatment. The results showed that the overall improvement rate in functional status in the intervention group was 88.10%, of which 42.86% were improved, 45.25% were stable and only 11.90% were aggravated. However, the total improvement rate in the control group was only 69.57%, which was significantly lower than in the intervention group ($P < .05$; Table 4). Therefore, BVZ+XELOX combined with MBSR intervention has a better effect on improving functional status in patients with CRC.

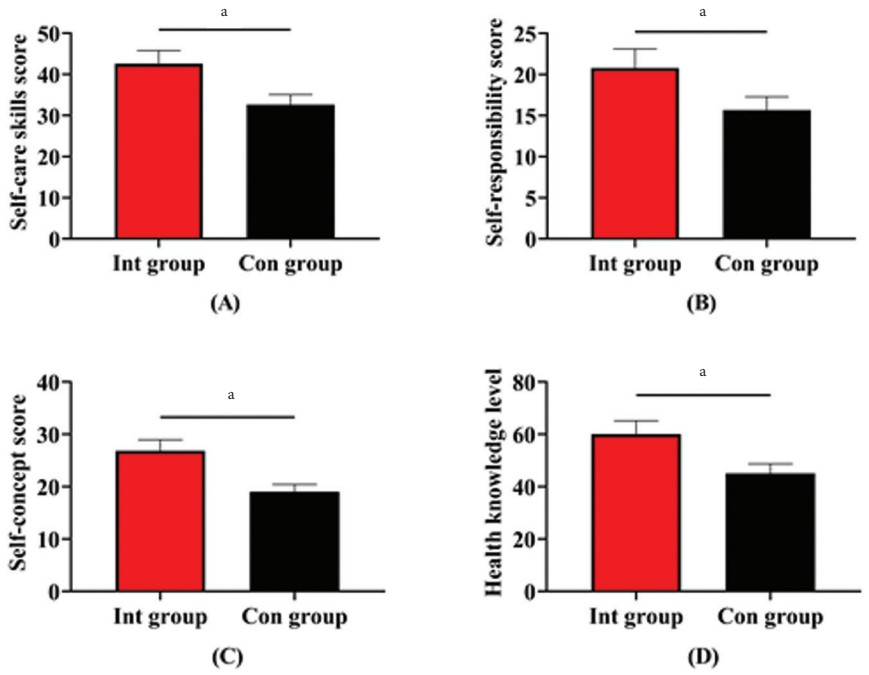
Comparison of psychological states

When assessing the psychological status of patients in the 2 groups by SAS score (Figure 1A) and SDS score (Figure 1B), we found no statistical difference in the 2 scores between the 2 groups before treatment ($P > .05$). After treatment, SAS scores in the intervention group were lower (38.52 ± 8.65) than those in the control group ($P < .05$); a lower SDS score was also found in the intervention group (37.00 ± 8.05) compared with the control group after treatment ($P < .05$). The control group showed no significant change in post-treatment SAS and SDS scores compared with pre-treatment scores ($P > .05$), but the 2 scores in the intervention group after treatment were significantly lower than before treatment ($P < .05$).

Table 5. Treatment Compliance in the Two Groups of Patients [n (%)]

Groups	High compliance	Moderate compliance	Poor compliance	Total compliance (%)
Intervention	22 (52.38)	15 (32.61)	5 (11.90)	88.10
Control group	15 (35.71)	17 (36.96)	14 (30.43)	69.57
χ^2				4.453
P value				.035

Figure 2. Comparison of ESCA scores between the 2 groups. (A) Comparison of self-care skills scores. (B) Comparison of self-responsibility scores. (C) Comparison of self-concept scores. (D) Comparison of health knowledge levels.



[a]*P* <.05.

Abbreviations: Int, intervention; Con, control

Comparison of treatment compliance

In the evaluation of patients' treatment compliance, we found that total compliance in the intervention group was 88.10%, which was higher than that in the control group (69.57%), with a significant difference between the 2 groups (*P* <.05; Table 5). In addition, 52.38% of patients in the intervention group had high treatment compliance, while most patients in the control group had moderate treatment compliance, resulting in 36.96% of all patients. It further demonstrates the excellent potential value of BVZ+XELOX combined with MBSR intervention in clinical practice.

Comparison of self-care ability

Subsequently, the self-care ability of patients was evaluated using the ESCA. It was found that the self-care skills score in the intervention group was (42.62 ± 3.17), higher than that in the control group (32.63 ± 2.44) (*P* < .05; Figure 2A). In a similar fashion, a higher self-responsibility score was seen in the intervention group compared with the control group (*P* < .05; Figure 2B). And the self-concept results showed that patients in the intervention group had higher self-care scores (*P* < .05; Figure 2C). Finally, the intervention group outperformed the control group in level of health knowledge (60.07 ± 5.09 vs. 45.11 ± 3.61, respectively) (*P* < .05; Figure 2D).

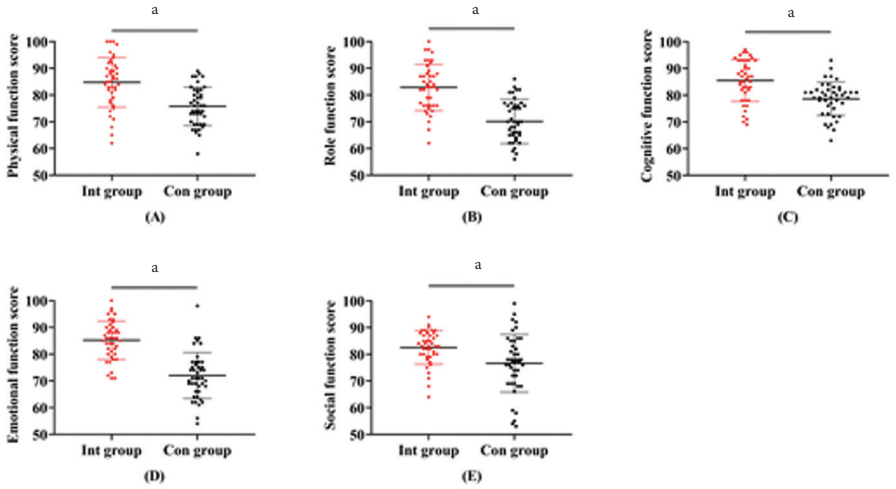
Comparison of prognoses

Of the patients, 42 in the intervention group and 43 in the control group were successfully followed up at 1 year. The QoL assessment results showed that physical function scores in the intervention group were higher (84.79 ± 9.32) than in the control group (75.77 ± 7.23) (*P* < .05; Figure 3A). In addition, there were higher role function (Figure 3B), cognitive function (Figure 3C), emotional function (Figure 3D), and social function (Figure 3E) scores in the intervention group compared with the control group (*P* < .05). These results indicated that patients in the intervention group had better prognostic QoL, suggesting that BVZ+XELOX combined with MBSR has an excellent effect on improving the prognosis of patients with CRC.

DISCUSSION

In this study, we found no obvious difference in DCR between the groups, but a higher ORR in intervention group, which suggested that the BVZ + XELOX regimen had improved the therapeutic effect in CRC to some extent. In a similar

Figure 3. Comparison of QLQ-C30 scores between the two groups. (A) physical function score. (B) Comparison of role function score. (C) cognitive function score. (D) Comparison of emotional function score. (E) social function score.



[a]P <.05.

fashion, past evidence pointed out that the BVZ + XELOX regimen can more effectively improve treatment outcomes in patients with CRC.[14] In addition, we found no difference in the incidence of adverse reactions between the groups, which also indicated that the BVZ + XELOX regimen was safe and would not increase the adverse events. As we all know, despite the strong cell-killing effect of chemotherapy drugs, they also have certain inhibitory effects in normal cells.[15]

Therefore, leukopenia and myelosuppression, extremely common adverse events in chemotherapy, will be exacerbated with the increase of chemotherapy drugs. BVZ, as a monoclonal antibody drug, mainly acts directly on vascular growth ability, and can selectively combine with vascular endothelial growth factor to reduce vascular permeability and interstitial pressure.[16] Besides, BVZ can directly reach the interior of tumor cells to increase blood concentration and enhance the anti-tumor effect, while not reacting with normal somatic cells, so the possibility of a normal cell inhibition reaction is greatly reduced.[17]

This was also confirmed by the research results of Yokoyama, et al.[18] Subsequently, we found better improvement of functional status in the intervention group, which also indicated that improvement of treatment experience and effects resulted in obvious changes in patients' status, further validating the clinical application value of BVZ combined with XELOX. However, it may also be related to the influence of different nursing practices.

Chemotherapy is one of the necessary and effective means to treat tumors in clinic at present, and its mechanism lies in inhibiting the development of tumor lesions by killing tumor cells.[12] However, in chemotherapy, the inhibition effect may be poor or the disease may even be aggravated due to drug resistance. Moreover, the obvious toxic adverse events result in so much pain that some patients want to discontinue treatment.[13] Adopting different chemotherapy schemes and improving nursing services may be the breakthroughs that will alter this situation. Therefore, this study has important reference significance for clinical practice by exploring the impact of MBSR intervention during BVZ combined with XELOX chemotherapy in the treatment of CRC.

At present, nursing has become one of the most important links in the treatment of neoplastic diseases, and MBSR is one of the nursing modes focusing on patient psychological changes.[19] In previous studies, we have found that MBSR nursing has made remarkable achievements in the treatment of breast cancer and other diseases.[20,21] In patients with CRC, their fear of the disease and the severe blow of being diagnosed with CRC often leads to negative attitudes. In addition, due to severe adverse reactions (such as pain, hair loss, nausea and vomiting) brought by chemotherapy, patients are generally not enthusiastic about treatment and have serious negative emotions.[22] Such negative emotions not only greatly reduce patients' treatment compliance and affect their postoperative rehabilitation, but also easily affect their confidence in treatment, leading to treatment interruption in some cases.[23] The core of MBSR lies in adjusting patients' perception of adverse events, changing their attitudes and behavior, reducing psychological pressure and enhancing patients' sense of being respected, thus improving the effect of treatmentt.[24]

The results showed that the psychological state, treatment compliance and self-care ability in the intervention group were significantly improved with MBSR nursing. This confirmed the excellent effect of MBSR in chemotherapy in patients with CRC. Finally, through the prognostic follow-up, we found that QoL in the intervention group was significantly improved; this was also related to the emphasis on integrating mindfulness into the lives of patients receiving MBSR care, confirming the importance of MBSR intervention.

CONCLUSION

The combined use of BVZ and XELOX-based chemotherapy can improve clinical outcomes and functional status in patients with CRC. In addition, MBSR nursing implemented during

chemotherapy can effectively optimize patients' psychological state and treatment compliance, self-care ability, and prognostic QoL, which is worth promoting in clinics.

CONFLICT OF INTEREST

None.

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