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Original Article

The impact of behavioral activation on depressive symptoms in colorectal cancer patients within a medical environment: the mediating role of physical activity

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Abstract: Colorectal cancer (CRC) treatment often affects patients' quality of life, leading to depressive symptoms. Behavioral activation (BA) therapy, which increases engagement by enhancing positive reinforcement and reducing avoidance, has shown potential in managing these symptoms. Physical activity (PA) is also known to alleviate depression, though its role as a mediator in BA's effectiveness remains unclear. This clinical trial was retrospectively registered in ClinicalTrials.gov on April 5, 2024 (Effects of Behavioral Activation on Negative Emotions, Cancer-related Symptoms and Clinical Indicators in Cancer Patients, NCT06348940). This study explores PA's mediating effect within BA interventions. A total of 109 CRC patients with depressive symptoms were randomly assigned to a BA group (n=52) or a Usual Care (UC) group (n=57). Assessments occurred at baseline (T0), after the fourth session (T1), and post-intervention (T2). The BA group showed significant improvement compared to the UC group. Repeated measures ANOVA confirmed BA's effectiveness in reducing depressive symptoms, improving quality of life, alleviating psychological distress, increasing activation, and raising PA levels. PA changes accounted for 36.91% of the intervention's total effect on depression reduction. BA effectively reduces depression and enhances life quality in CRC patients. Changes in PA intensity are significantly associated with depression reduction, suggesting PA's mediating role in BA's impact. Incorporating PA into BA may enhance therapeutic outcomes for CRC patients with depression.

Keywords: Behavioral activation, colorectal cancer, quality of life, depression, physical activity

Introduction

Colorectal cancer (CRC) exhibits a notably high global prevalence, ranking as the third most commonly diagnosed cancer and the second leading cause of cancer-related death worldwide [1]. In 2020, CRC's incidence rate was 10%, with a mortality rate of 9.4%. This trend is particularly marked in China, where the number of cases is projected to increase by 64%, from 560,000 to 910,000, over the next two decades [2]. For CRC patients, prolonged treatment and frequent complications significantly reduce the quality of life and heighten the risk of negative psychological outcomes, such as depression. Beyond the physical burden, patients often face substantial emotional challenges. A comprehensive, multi-level exploration of the mechanisms behind this decline in quality of life is essential for improving the psychological well-being of these individuals. Cancer patients, in general, have a higher likelihood of depression compared to the general population [3, 4]. Stomach, breast, colorectal, and other cancers are closely associated with psychological distress, such as depression and anxiety, which exacerbate adverse complications in patients with negative moods [5, 6]. Meta-analysis find-

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ings indicate that depression prevalence among CRC patients ranges from 1.6% to 57%, while anxiety prevalence ranges from 1.0% to 47.2% [7]. Notably, CRC patients face a significantly higher risk of depression compared to cancer-free individuals, with an adjusted hazard ratio of 2.65 over five years post-diagnosis [8].

Depression, a serious mental health disorder, has profound global implications, with the World Health Organization (WHO) estimating that over 120 million people worldwide are affected. It is not merely a psychological impairment but a significant health issue requiring urgent attention from public health systems and society. In China, approximately 54 million individuals suffer from depression, and an additional 41 million experience anxiety symptoms. Depression is a primary risk factor for suicide attempts, contributing to 28% of the attributable risk in affected populations. Cancer patients, however, face even greater challenges. Depression can influence the onset, progression, and treatment of cancer in multiple ways. For example, the chronic inflammatory state commonly seen in depressed individuals can impair the body's ability to detect and eliminate cancer cells. Depressed patients often show reduced natural killer (NK) cell activity and lower levels of helper T cells and cytotoxic T lymphocytes [9, 10]. Animal studies have demonstrated that chronic stress promotes tumorigenesis in mice, partly through elevated cortisol levels, which attenuate p53 function [11]. In an ovarian cancer model, chronic stress was also found to increase tissue catecholamine levels, leading to the upregulation of downstream angiogenic factors. This stimulation of angiogenesis may enhance tumor invasiveness [12]. Depression can also significantly affect treatment adherence in cancer patients. A cohort study of breast cancer patients revealed that only 51% of those with depression adhered to treatment, compared to 92% in the control group [13]. Epidemiological evidence further underscores the harmful impact of depression in cancer patients. A meta-analysis of depression and breast cancer mortality found that depression was associated with a 30% increase in the risk of all-cause mortality and a 29% increase in the risk of breast cancer-specific mortality [14]. Depressive symptoms, including sleep disturbances, dietary issues, and low activity levels, may accelerate tumor progression through mechanisms involving stress, inflammation, and immune activation [15]. While antidepressant medications can effectively alleviate depressive symptoms in cancer patients, their efficacy is limited. Furthermore, interactions between antidepressants and chemotherapy drugs may reduce treatment effectiveness or increase toxicity [16]. Pharmacological treatment remains a common approach for depression, but its efficacy in cancer patients presents unique challenges. A meta-analysis revealed that, compared to placebo, antidepressants provided very low-quality evidence for improving depressive symptoms in adults [17]. Moreover, cancer patients demonstrate low medication adherence, with approximately 21% using antidepressants. However, many discontinue within one month of prescription, and the discontinuation rate increases to 68.8% after six months [18].

Psychological interventions have been shown to be effective for cancer patients and, in some cases, may even improve survival rates [19]. As a first-line treatment for depression, cognitive behavioral therapy (CBT) is known for its efficacy, sustainability of therapeutic effects, and high adherence. However, the high costs associated with therapist training and employment, along with the complexity of the treatment, limit its widespread application. These challenges are particularly pronounced for cancer patients, highlighting the need for psychological interventions that are better suited to address depression in this population.

Behavioral activation (BA) therapy, derived from CBT, is a more structured and simplified form of psychotherapy. Its primary goal is to increase engagement in adaptive activities that typically provide pleasure or a sense of control while reducing those that may sustain or worsen depressive moods [20]. BA also addresses negative experiences resulting from insufficient rewards. During treatment, activity and mood monitoring helps set goals, develop plans to increase engagement in anti-depressive activities, and modify environmental triggers for depression through problem-solving strategies. The final stages of BA focus on consolidating gains and creating relapse prevention plans. In cases where activity impairments are present,

therapists collaborate with patients to assess the functions of their behaviors and devise solutions for future activation tasks [21]. BA has been shown to effectively alleviate depressive symptoms, demonstrating outcomes comparable to those of CBT and antidepressant medications [22].

Moreover, BA offers several advantages that may be particularly beneficial for cancer patients: its structure is simple, and the therapeutic components are less complex than those of CBT, making it more accessible for patients [23]. BA is also easier to implement, requiring fewer qualifications for therapists. Individuals without a background in psychology can competently deliver BA after appropriate training [24]. The treatment settings are flexible, allowing interventions to be administered through the Internet or by telephone with comparable results. Additionally, BA is more cost-effective, reducing financial costs by 21% compared to traditional CBT [25]. Cancer patients, who frequently visit healthcare facilities for treatment or check-ups, often face a higher frequency of hospital visits due to tumor progression and treatment side effects [26]. Consequently, they have more contact with healthcare systems than the general population and a greater need for psychological care [27]. Given these factors, BA, as a simple and effective psychological intervention, is particularly well-suited for cancer patients. CRC patients, in particular, may benefit from BA's behavioral guidance and planning due to the lower survival rates associated with their condition, significant treatment side effects, and common care issues such as stoma bags. Furthermore, the low demands placed on therapists by BA allow clinical staff, such as nurses or attending physicians with available time, to implement the approach effectively. Overall, BA is a highly appropriate psychological intervention for cancer patients within medical settings, with substantial potential for broader application.

Behavioral activation (BA) is recognized as an evidence-based treatment for depression, yet it presents several challenges. A key limitation lies in its narrow focus on cognitive processes. While BA alleviates depressive symptoms, it does not directly address the negative cognitive patterns that are typical in depressed individuals. As a result, its effectiveness may be restricted, and its long-term sustainability compromised, particularly for patients who are heavily influenced by cognitive distortions and rumination [28]. Furthermore, while BA is lauded for its simplicity and flexibility, variability in its implementation and the diverse designs of its courses may result in a lack of standardized practices [29]. For therapists, despite the availability of various supportive methods, aiding patients with severe depression in breaking the cycle and engaging in activities remains a significant challenge [30].

Therefore, investigating the underlying mechanisms of BA could enhance treatment outcomes, address individual differences, and provide a foundation for future research. One promising mechanism to explore is the role of physical activity (PA). Research by Misiąg et al. demonstrated that higher levels of PA can reduce the side effects of cancer treatment, alleviate fatigue, improve quality of life, and positively impact mental health in cancer patients [31]. Meta-analyses have also shown that moderate aerobic interventions significantly alleviate depressive symptoms in breast cancer patients undergoing chemotherapy [32]. The relationship between PA levels, depression, and quality of life extends throughout the diagnostic and treatment process for cancer. Cancer patients with higher PA levels tend to report better psychological well-being [33]. Depressed individuals typically exhibit substantial changes in PA, with reduced activity not only serving as a symptom of depression but potentially exacerbating depressive symptoms [34]. However, the pathway through which PA mediates the effects of BA on depressive symptoms remains unclear. If PA indeed serves as a mediating factor, enhancing therapist guidance to promote PA-related activities during BA could improve therapeutic outcomes. To date, no research has specifically examined the effects of BA on CRC patients. This study, therefore, aims to explore: (1) the effects of BA intervention on depressive and anxiety symptoms, as well as quality of life, in CRC patients, and (2) whether PA levels change during the intervention and if PA mediates the effects of BA.

Materials and methods

Study design

This clinical trial was retrospectively registered in ClinicalTrials.gov on April 5, 2024. Eligible

CRC patients were screened using the HADS-D scale. After obtaining informed consent following comprehensive communication with the patients, a general survey and scale assessments were conducted. Between March 2024 and July 2024, 109 eligible patients participated in the study. Patients were randomly assigned to either the BA group or the UC group. Professional assessors, blinded to the group assignments, conducted measurements of quality of life, psychological distress, activation-avoidance states, and PA levels at baseline (T0), after four intervention sessions (T1), and at the completion of the intervention (T2). Baseline data were collected prior to enrollment.

Participants

Inclusion criteria: Participants must be adults aged 18 years or older, with no upper age limit; Have the ability to comprehend instructions and read study materials, or the capacity to receive assistance if needed; Have a Karnofsky Performance Status (KPS) score of ≥80, indicating sufficient physical ability to participate in the intervention; Have a HADS-D score of ≥8, indicating the presence of depressive symptoms; Have a confirmed diagnosis of colorectal cancer with an expected survival of no less than six months, regardless of disease stage; Be able to understand the study's purpose and procedures, and voluntarily sign the informed consent form; Not have any uncontrolled severe underlying diseases, such as severe cardiovascular disease, end-stage kidney disease, or severe pulmonary disease; Have sufficient cognitive ability to engage in the behavioral activation intervention and comprehend its steps and goals.

Exclusion criteria: Participants were excluded if they had severe neurological diseases, such as post-stroke conditions, severe traumatic brain injury, epilepsy, Alzheimer's disease, or other neurological disorders that affect cognitive function; Had any condition that affects cognitive abilities, including psychiatric disorders such as schizophrenia; Were using antidepressants, antipsychotics, cognitive-enhancing drugs, or had a history of long-term use of such medications; Had uncontrolled psychiatric disorders, such as bipolar disorder, severe depression, or schizophrenia, at the time of enrollment; Were unable to understand or comply with the behavioral activation intervention due to physical, cognitive, or emotional impairments; Were pregnant or lactating due to the potential effects the intervention may pose to pregnancy or breastfeeding; Had participated in other psychological treatments, such as CBT or psychodynamic therapy, within the past three months, as these interventions may interfere with the current study; Had severe chronic physical illnesses, such as heart failure, end-stage renal disease, or late-stage liver disease, that affect their ability to complete the intervention; Were currently using or planning to use antidepressants, antipsychotics, anxiolytics, or other medications that may impact the treatment outcomes; Had a history of suicidal ideation, self-harm behaviors, or severe emotional instability that has not been adequately addressed; Cannot understand the language of the intervention or face significant cultural barriers that prevent effective participation in the behavioral activation therapy.

Termination criteria: Participants were removed from the study if they experienced severe adverse reactions, such as allergic reactions or significant medication side effects, that necessitate discontinuation of the intervention; There was a substantial deterioration in depressive symptoms or other mental health conditions that interfere with the continuation of the intervention; There was a deterioration in the patient's physical health, such as rapid cancer progression or severe physical weakness, that prevents participation in the intervention; New, severe symptoms emerged that impede their ability to undergo the intervention or significantly affect their quality of life; Missed more than the maximum allowed number of sessions, such as more than three weeks of absence, as defined by the study protocol; The attending physician recommended initiating or modifying the treatment plan to include psychotropic medications, rendering the patient unsuitable for behavioral activation therapy; The attending physician recommended discontinuing the intervention due to health risks. Additionally, participants were allowed to withdraw voluntarily from the study or intervention for any reason, such as privacy concerns or life changes.

Sample size calculation

In the sample size calculation, based on meta-analysis results regarding the impact of BA on

depressive symptoms [35], Hedges' g=0.83 was converted into an effect size suitable for a repeated measures design. Hedges' g, typically used for independent samples, was adjusted to Cohen's d for compatibility with repeated measures designs. Following empirical guidelines, the effect size for repeated measures is generally about 0.7 times that of independent samples, resulting in an estimated Cohen's d of 0.581. This value was then converted into Cohen's f to facilitate its use in the ANOVA model, yielding a Cohen's f of approximately 0.411, signifying a substantial effect size for BA's impact on depressive symptoms. Using G*Power 3.1.9 software, a repeated measures ANOVA (interaction effect) model was selected, with statistical power (1-β) set to 0.95 to ensure robust detection and a significance level (α) of 0.05 to control for Type I error. Based on an effect size of Cohen's f=0.411, the minimum required sample size to detect a significant interaction effect was determined to be 18 participants. With a total of 109 participants enrolled, this study exceeds the calculated minimum sample size, ensuring sufficient statistical power and enhancing the robustness and reliability of the findings.

Sample recruitment

Patient recruitment occurred between March and July 2024 at the Department of Oncology, Second Affiliated Hospital of Anhui Medical University. Eligible patients were screened using the HADS scale, after which baseline data were collected, and key study information was provided. Patients were then asked to provide informed consent. Upon consent, participants were informed of the need to attend the fourth and eighth sessions at the hospital after the treatment began. To enhance patient adherence, the intervention schedule was aligned with their treatment cycles, and in-person interventions and data collection were coordinated with their attending physicians.

Randomization

A statistician used a computer-generated randomization table to assign participants to either the BA or UC group at a 1:1 ratio. BA therapy was delivered one-on-one in the Oncology Department conference room at the Second Affiliated Hospital of Anhui Medical University. Evaluations of quality of life, depression, anxiety, PA, and psychological distress were performed by assessors 30 minutes after each offline session. Throughout the study, the statistician notified therapists of group assignments, while evaluators assessed patients' psychological and life conditions. Statisticians were not involved in the practical aspects of the experiment, and both assessors and data analysts were blinded to group assignments during the trial.

Intervention

The BA intervention followed the revised Brief Behavioral Activation Treatment for Depression (BTAD-R) manual, comprising five specific sessions and three follow-up sessions, each lasting between 30 minutes and an hour, with 5-10 minutes of homework assignments. Upon completion of the intervention, patients were capable of independently undertaking the follow-up sessions, with the total intervention period spanning two months. The course content, designed and reviewed by certified counselors, ensured both practical relevance and scientific rigor. Assessments of quality of life, psychological distress, and PA levels were conducted before the intervention, after four sessions, and at the conclusion of the intervention.

The BA intervention was delivered in the Oncology Department conference room at the Second Affiliated Hospital of Anhui Medical University. The research team included three graduate students, an oncologist, and a psychologist, all specializing in psycho-oncology. The intervention was implemented by a qualified counselor from the team. Weekly group meetings were held to supervise the therapists and address any challenges, ensuring consistency and standardization of treatment. Interview notes and session documentation were maintained in written form within the patients' records to ensure thorough documentation throughout the intervention process.

Scales

Hospital anxiety and depression scale (HADS): The HADS comprises two subscales: Depression (HADS-D) and Anxiety (HADS-A), each with seven items, scored from 0 to 21. Higher scores indicate more severe symptoms. In this study, the HADS-D subscale was utilized for participant screening, with a cutoff score of 8 [36].

European organisation for research and treatment of cancer quality of life questionnaire (CORE-30) (EORTC QLQ-C30): The EORTC QLQ-C30 is a quality-of-life tool designed for cancer patients, assessing symptom, functional, and overall health domains. This scale has been widely validated and used in clinical research [37]. The total score is derived from the mean of 13 items (excluding global health and financial status), expressed as a percentage, with higher scores reflecting a better quality of life. The total score is only calculated when all 13 items are completed [38, 39].

Distress thermometer (DT): The DT is a self-assessment tool measuring psychological distress experienced over the past week, encompassing social, physical, emotional, and spiritual aspects. Scores range from 0 to 10, with higher scores indicating greater distress and psychological discomfort [40].

Behavioral activation for depression scale - short form (BADS-SF): The BADS-SF consists of nine items assessing behavioral activation levels, commonly used to monitor changes during BA therapy. It includes two subscales: Activation and Avoidance, both with established validity [41].

International physical activity questionnaire - short form (IPAQ-SF): The IPAQ-SF assesses physical activity over the past seven days or a typical week, through four general items reflecting various levels of physical activity. Scores are categorized into low, moderate, or high PA levels. The IPAQ-SF has demonstrated good test-retest reliability across different countries, with a Spearman correlation coefficient of approximately 0.8, meeting standards for self-report questionnaires [42].

Statistical analysis

Data analysis was performed using IBM SPSS Statistics 23.0. Categorical data were analyzed with the chi-square test, and group equivalency between the BA and UC groups was assessed using independent samples t-tests. Repeated-measures analysis of covariance (RM-ANCOVA) was used to examine changes from baseline (T0) to the fourth session (T1) and post-intervention (T2), with the goal of identifying between-group differences and evaluating the effect of time on measurements. All *p*-values were calculated using two-tailed tests, with a significance level set at 0.05. The Greenhouse-Geisser method was employed to adjust degrees of freedom in RM-ANCOVA results. Effect size was estimated using partial ηp^2. Additionally, Spearman rank correlation was utilized to explore the relationship between changes in PA and depressive symptoms. The mediation effect of PA on the relationship between BA therapy and depressive symptoms was analyzed using Model 4 of the PROCESS v4.0 plugin developed by Hayes [43], with a 95% confidence interval generated through 5,000 bootstrap samples.

Results

Baseline demographic and clinical data

As shown in **Table 1** and **Figure 1**, a total of 200 patients completed the HADS, of whom 23 were excluded due to HADS-D scores below 8, leaving 177 eligible patients. Among these, 44 declined participations for various reasons, resulting in 133 patients who were randomly assigned to the BA group (n=68) and UC group (n=65). In the BA group, 16 participants did not complete the BA intervention, and in the UC group, 8 participants did not complete the final evaluation, leaving 52 participants in the BA group and 57 in the UC group for final analysis. No significant differences were observed between the BA and UC groups in baseline demographic and clinical characteristics, including age (t=-0.515, P=0.608), BMI (t=0.075, P=0.94), gender distribution (χ^2=0.701, P=0.402), education level (χ^2=1.241, P=0.538), primary caregiver (χ^2=2.047, P=0.563), KPS score (t=-0.726, P=0.469), tumor location (χ^2=4.244, P=0.121), histological type (χ^2=5.059, P=0.08), tumor stage (χ^2=5.299, P=0.151), and treatment modality (χ^2=3.236, P=0.664).

Primary outcome: changes in depression during treatment in the BA and UC groups and comparative analysis

As shown in Table S1 and **Figure 2**, participants in the BA group exhibited significant improvements in depression scores during the treatment, with a marked reduction in the HADS-D scores (F=25.447, P<0.001). In contrast, the UC group did not show any significant changes in depression scores (F=0.881, P=0.42). As shown in **Table 2**, a comparative analysis using repeated measures ANOVA revealed significant

Table 1. Demographics and characteristics of study participants

Characteristics	BA (n=52)	UC (n=57)	t/χ^2	P
Age, years, mean ± SD	62.50±12.29	61.33±11.39	-0.515	0.608
KPS, mean ± SD	89.42±6.39	88.60±5.49	-0.726	0.469
BMI, kg/m^2, mean ± SD	22.90±3.31	22.95±2.85	0.075	0.94
Gender, n (%)			0.701	0.402
Female	18(32.7%)	23 (40.4%)		
Male	37(67.3%)	34 (59.6%)		
Education, n (%)			1.241	0.538
Some college or higher	6 (11.5%)	7 (12.3%)		
High school graduate	43 (82.7%)	49 (86%)		
Less than high school	6 (11.5%)	1 (1.8%)		
Primary caregivers, n (%)			2.047	0.563
Children	23 (41.8%)	28 (49.1%)		
Spouse	23 (41.8%)	17 (29.8%)		
Nobody	4 (7.3%)	4 (7%)		
Other	5 (9.1%)	8 (14%)		
Cancer type, n (%)			4.224	0.121
Rectum	35 (63.6%)	28 (49.1%)		
Colon	16 (29.1%)	27 (47.4%)		
Other	4 (7.3%)	2 (3.5%)		
Pathological classification			5.059	0.08
Adenocarcinoma	42 (80.8%)	54 (94.7%)		
Mucinous adenocarcinoma	7 (13.5%)	2 (3.5%)		
Other	3 (5.8%)	1 (1.8%)		
Cancer stage, n (%)			5.299	0.151
Stage I	0 (0%)	1 (1.8%)		
Stage II	12 (21.8%)	6 (10.5%)		
Stage III	7 (12.7%)	14 (24.6%)		
Stage IV	36 (65.5%)	36 (63.2%)		
Previous treatment, n (%)			3.236	0.664
CT	25 (48.1%)	19 (33.3%)		
TT	9 (17.3%)	12 (21.1%)		
CT+TT	8 (15.4%)	11 (19.3%)		
CT+IT	4 (7.7%)	2 (3.5%)		
RT	3 (5.8%)	2 (3.5%)		
Other	6 (11.5)	11 (19.3)		

Abbreviations: BA, behavioral activation; UC, usual care KPS, Karnofsky Performance Status; SD, standard deviation; P, level of significance; CT, Chemotherapy; TT, Targeted Therapy; RT, Radiotherapy; CT+TT, Chemotherapy + Targeted Therapy; CT+IT, Chemotherapy + Immunotherapy.

session effects on depression (F=11.428, P< 0.001). Significant between-group differences were observed for depression (F=5.793, P= 0.018), indicating that the BA group experienced more significant reductions in depression scores compared to the UC group. Furthermore, significant interaction effects between session and group were observed for depression (F=11.168, P<0.001), highlighting that the BA group showed a more substantial decrease in depression over time.

Secondary outcomes: changes in other indicators during treatment in the BA and UC groups and comparative analysis

As shown in Table S1 and **Figure 2**, regarding secondary outcomes, participants in the BA

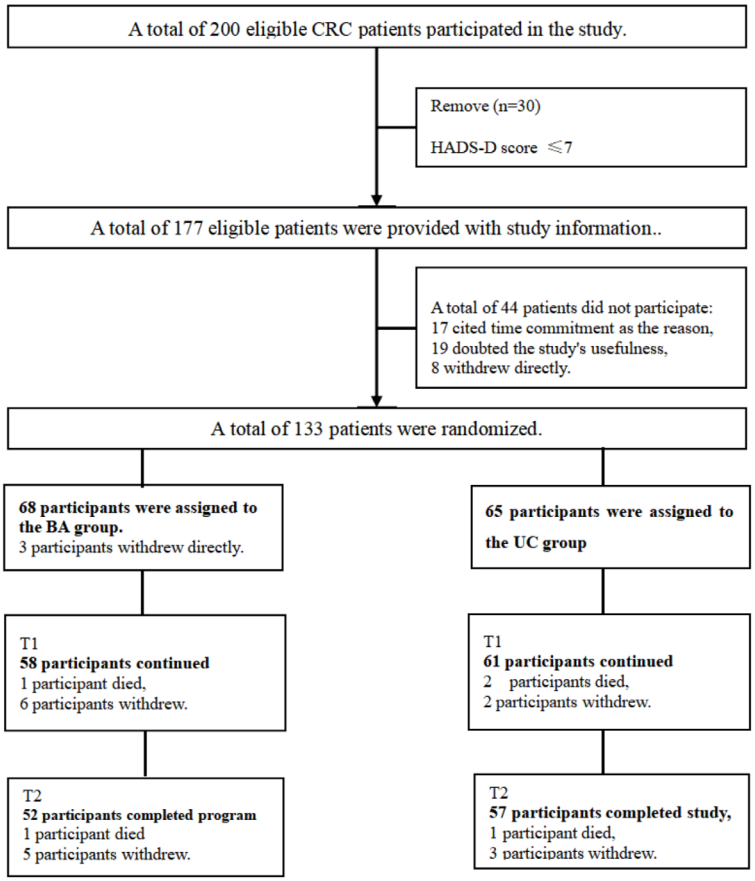

Figure 1. Study flow diagram.

group showed significant improvements in various domains during the treatment. Specifically, the BA group experienced significant improvements in quality of life (F=7.712, P< 0.001), activation (F=29.256, P<0.001), avoidance (F=7.211, P=0.002), PA levels (F=11.859, P<0.001). However, anxiety scores did not show significant changes before and after the intervention in the BA group (F=1.854, P= 0.167). In contrast, the UC group did not exhibit significant changes in any of the secondary outcomes, including anxiety (F=1.969, P=0.149), quality of life (F=1.393, P=0.253), or physical activity levels (F=0.12, P=0.877). Similarly, scores for activation (F=0.616, P=0.541) and avoidance (F=1.94, P=0.149) in the UC group did not show significant differences. However, psychological distress in the UC group significantly decreased (F=5.11, P=0.008).

As shown in **Table 2** and **Figure 2**, repeated measures ANOVA revealed significant session effects for psychological distress (F=51.529, P<0.001), quality of life (F= 5.484, P=0.005), activation (F=12.42, P<0.001), avoidance (F=7.953, P<0.001), and physical activity (F= 10.285, P<0.001). A marginal session effect was observed for anxiety (F=3.107, P= 0.049). Significant between-group main effects were found for psychological distress (F= 14.492, P=0.185) and activation (F=911.502, P=0.001). However, no significant between-group differences were found for anxiety (F=1.777, P=0.185), quality of life (F= 3.678, P=0.058), avoidance (F=0.422, P=0.517), or physical activity (F=2.304, P= 0.132). With the exception of anxiety (F=0.028, P=0.972) and avoidance (F=0.765, P= 0.46), significant interaction effects between session and group were observed for psychological distress (F=30.67, P<0.001), quality of life (F= 3.573, P=0.03), activation (F= 21.323, P<0.001), and physical activity (F=9.484, P<0.001). These findings suggest that the BA group had a more substantial improvement over time in terms of psychological distress, quality of life, activation, and physical activity levels compared to the UC group. The interaction effects indicate that the BA group's improvements were more pronounced as the sessions progressed, underscoring the efficacy of the behavioral activation intervention.

Exploratory analysis: relationship between changes in physical activity and depression in CRC patients

Spearman correlation analysis indicated a negative correlation between changes in depression and PA levels in both the BA and UC groups. In the BA group, correlations were observed for the T0-T1 period (r=-0.3244, P=0.019) and the T1-T2 period (r=-0.3101, P=0.0253). In the UC group, correlations were found for the T0-T1 period (r=-0.4885, P=0.0001) and the T1-T2

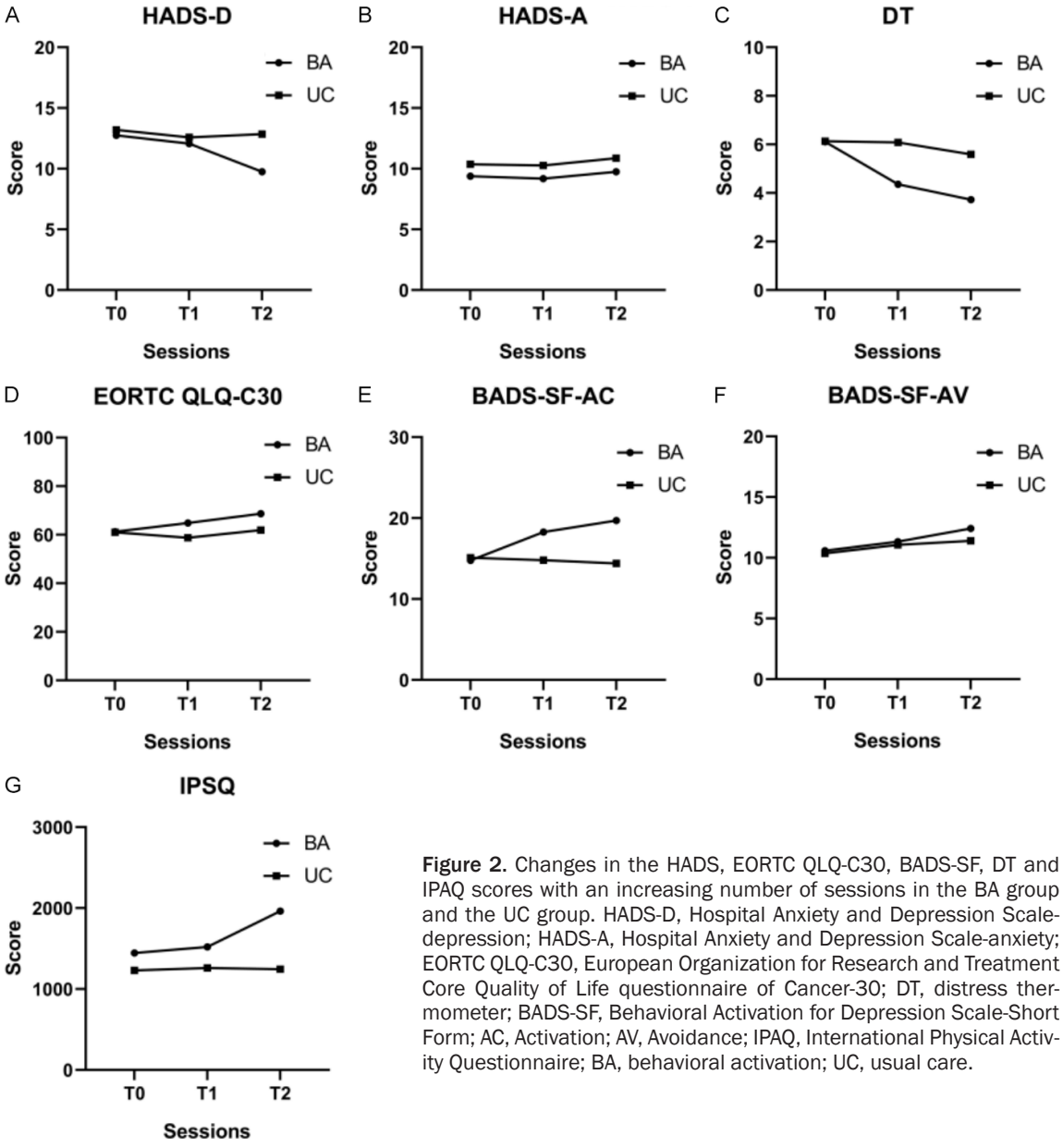

Figure 2. Changes in the HADS, EORTC QLQ-C30, BADS-SF, DT and IPAQ scores with an increasing number of sessions in the BA group and the UC group. HADS-D, Hospital Anxiety and Depression Scale-depression; HADS-A, Hospital Anxiety and Depression Scale-anxiety; EORTC QLQ-C30, European Organization for Research and Treatment Core Quality of Life questionnaire of Cancer-30; DT, distress thermometer; BADS-SF, Behavioral Activation for Depression Scale-Short Form; AC, Activation; AV, Avoidance; IPAQ, International Physical Activity Questionnaire; BA, behavioral activation; UC, usual care.

period (r=-0.4359, P=0.0001), as illustrated in **Figure 3**.

Confirmatory analysis: mediation model with PA as a mediator

We investigated whether PA mediated the relationship between BA and depressive symptoms, as shown in **Figure 4**. Changes in depression scores pre- and post-intervention were treated as the dependent variable, with BA as the independent variable and PA changes as the mediator, controlling for baseline levels. Our findings indicated that PA partially mediated the relationship between BA and depressive symptoms, accounting for 36.91% of the total effect. This suggests that enhancing PA can effectively alleviate depressive symptoms through BA interventions focused on mental health, especially for CRC patients.

Discussion

To our knowledge, this study is the first randomized controlled trial to examine the efficacy of BA in alleviating depressive symptoms among patients with CRC. Our findings highlight the significant positive effects of BA on reducing

Table 2. Comparison of HADS, EORTC QLQ-C30, BADS-SF and DT scores between the BA group and the UC group

Item	Session			Group			Group*Session		
	F	P	ηp2	F	P	ηp2	F	P	ηp2
HADS-D	11.428	<0.001	0.177	5.793	0.018	0.051	11.168	<0.001	0.174
HADS-A	3.107	0.049	0.055	1.777	0.185	0.016	0.028	0.972	0.001
DT	51.529	<0.001	0.493	14.492	<0.001	0.119	30.67	<0.001	0.367
EORCT QOL-C30	5.485	0.005	0.049	3.678	0.058	0.033	3.573	0.03	0.032
BADS-AC	12.42	<0.001	0.104	11.502	0.001	0.097	21.323	<0.001	0.166
BADS-AV	7.953	<0.001	0.069	0.422	0.517	0.004	0.765	0.46	0.007
IPAQ-SF	10.285	<0.001	0.163	2.304	0.132	0.021	10.028	<0.001	0.159

Abbreviations: P, level of significance; F, Effect size; HADS-D, Hospital Anxiety and Depression Scale-depression; HADS-A, Hospital Anxiety and Depression Scale-anxiety; EORTC QLQ-C30, European Organization for Research and Treatment Core Quality of Life questionnaire of Cancer-30; DT, distress thermometer; BADS-SF, Behavioral Activation for Depression Scale-Short Form; AC, Activation; AV, Avoidance; IPAQ, International Physical Activity Questionnaire.

negative emotions and improving the quality of life in CRC patients. Specifically, substantial improvements in depressive symptoms were observed among participants in the BA group, with secondary outcomes also showing considerable differences between the BA and usual care (UC) groups. Patients in the BA group experienced reductions in psychological distress and improvements in quality of life, whereas the UC group showed only minor reductions in psychological distress, with significant differences observed between the two groups.

Consistent with our study, a randomized controlled trial assessed the effectiveness of BA in cancer outpatients with comorbid depressive symptoms. The study found significant improvements in patients' negative emotions, quality of life, and overall treatment outcomes. These results further support the feasibility of BA as an independent approach to managing the mental health issues of cancer patients [23]. Another study focused on chemotherapy patients observed that the BA group maintained more positive daily activities, coupled with significant alleviation of depressive symptoms [44]. The core theory of BA posits that patients work with a therapist to disrupt negative behavioral cycles, improving both emotional well-being and lifestyle. A survey on BA completion rates in cancer patients found a 90% completion rate, while improvements in depressive symptoms were maintained [45]. It appears that patient activity levels are strongly associated with treatment outcomes. Ryba et al. further explored this relationship, identifying a negative correlation between beneficial activities and depressive symptoms during BA intervention. Using longitudinal data and growth curve models, they demonstrated that adherence to BA tasks had a causal relationship with reductions in depression [46]. Taken together, these findings reinforce the efficacy of BA as a psychological intervention for cancer patients, with benefits including reductions in depressive symptoms, increased daily activity, and improved quality of life.

The therapeutic process of BA centers around enhancing patient engagement with positive environmental stimuli through increased behavioral activation, which in turn alleviates depressive symptoms. This process often involves an increase in PA. This study observed a marked increase in PA levels among participants in the BA group. Additionally, the mediating role of PA in the relationship between BA treatment and improvements in depressive symptoms was explored. Our findings indicate that PA significantly mediates the effect of BA on depressive symptoms, underscoring the critical role of PA in psychological interventions. This result holds particular significance for psycho-oncology, especially in managing the mental health of cancer patients. It suggests that increased PA may serve as a key mechanism through which BA alleviates depression. Therefore, BA interventions for depression may benefit from incorporating strategies that promote PA, or combining BA with interventions such as Tai Chi or yoga, which further enhance PA, thereby potentially improving therapeutic outcomes.

Our results are consistent with existing literature, which highlights the beneficial impact of PA on alleviating depressive symptoms. Numerous studies suggest that PA can reduce depression through both physiological and psy-

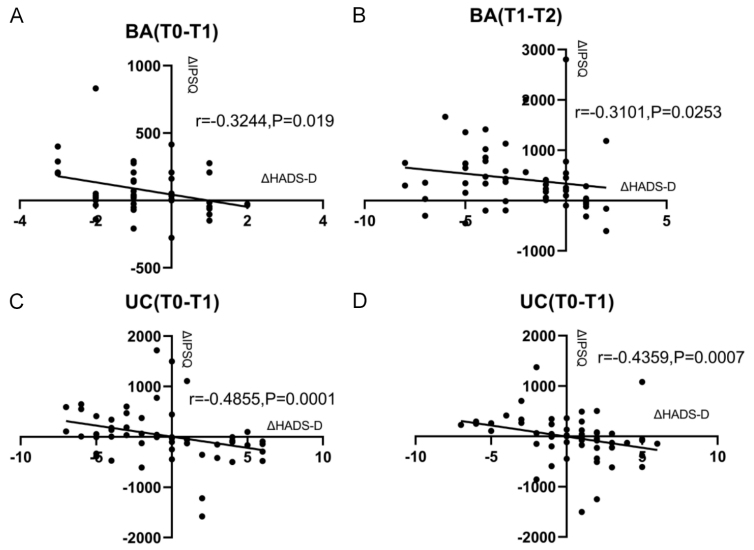

Figure 3. The relationship between changes in depression scores and changes in physical activity scores in the BA group and the UC group. ΔHADS-D: changes in depression scores; ΔIPSQ: changes in physical activity scores.

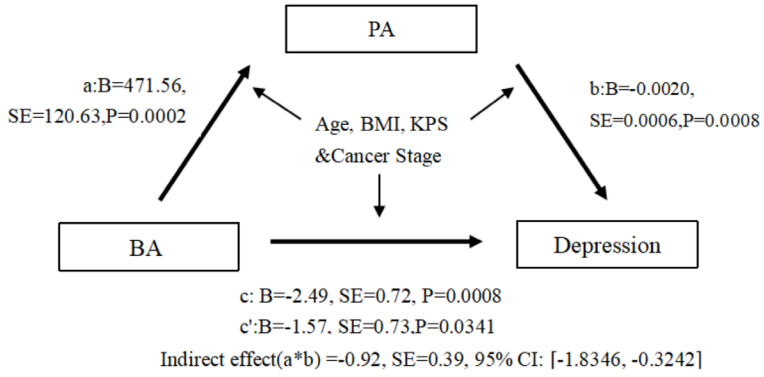

Figure 4. Mediation model of BA, PA, and depression scores. Path a represents the relationship between Behavioral Activation (BA) and Physical activity (PA). Path b represents the relationship between PA and depression scores. Path c represents the total effect of BA on depression scores. Path c' represents the direct effect of BA on depression scores when controlling PA.

chological mechanisms. Exercise promotes the release of neurochemicals such as endorphins, which enhance mood, and it also provides psychological benefits through social interaction and a sense of accomplishment [47]. As a non-pharmacological approach, PA has demonstrated considerable efficacy. Meta-analyses indicate that PA's effects on mild to moderate depression are comparable to those of antidepressant medications and psychotherapy, making it a valuable adjunct to conventional treatments for severe depression [48, 49]. In addition to alleviating depressive symptoms, exercise therapy offers significant physical health benefits, such as improving cardiovascular health and aiding in diabetes management [50].

Similar to our study, Soucy et al. compared the effects of self-help BA and PA on patients with depression and found that both interventions produced similar effects over time. They suggested that PA could be an essential component of BA and a key mechanism for the observed improvements in depression [51]. Li et al. also explored the relationship between BA and PA, using wearable devices and objective biomarkers like salivary cortisol and testosterone. Their findings suggested that, like PA, BA influences individuals' behavioral attitudes and subjective norms directly or indirectly through social cognition [52]. Our study further corroborates this connection, revealing that PA mediates the effect of BA on depressive symptoms, accounting for 36.91% of the total effect.

The mediation of PA in the effect of BA on depressive symptoms may involve several mechanisms. BA theory posits that avoidance of contingent events is a core behavior in depression, and its primary goal is to activate patients by scheduling pleasurable and rewarding activities. This approach aims to increase positive reinforcement in patients' lives while reducing avoidance behaviors, ultimately helping them re-engage in normal life activities. By emphasizing the central role of behavior in emotional regulation, BA offers a robust framework for understanding and treating depression.

Central to the theory of BA are the Behavioral Activation System (BAS) and the Behavioral Inhibition System (BIS), which play pivotal roles

in shaping emotional responses, motivation, and behavior. These systems correspond to distinct response patterns that individuals exhibit when confronted with rewards or punishments [53]. The BAS is associated with positive stimuli and the pursuit of rewards, driving individuals to seek pleasurable experiences. This system primarily operates through dopamine pathways in the brain, particularly in regions like the ventral striatum. When activated, the BAS is linked to impulsivity, social engagement, and positive emotional responses, all of which foster emotional activation, motivation, and behavioral initiative. In contrast, the BIS is activated by negative stimuli and punishment, promoting avoidance behaviors and caution. When the BIS is engaged, individuals typically experience anxiety, avoidance, and heightened sensitivity to potential negative consequences. Unlike the BAS, the activity of the BIS is associated with defensive emotional responses and negative emotions [54].

Notably, the relationship between BAS and BIS with negative emotions is relatively independent. BAS is primarily associated with positive emotions and enhances sensitivity to rewards, thus triggering positive emotional experiences. Consequently, when individuals engage in physical activity, the activation of BAS typically increases their pleasure and motivation during exercise. In contrast, BIS is linked to anxiety and avoidance behaviors. When individuals perceive threats or potential negative consequences, BIS is activated, leading to the avoidance of exercise or an exaggerated response to discomfort associated with physical activity. High sensitivity to BIS is generally associated with lower levels of exercise participation, especially when negative emotions and discomfort during exercise are prominent, making the role of BIS particularly evident [55]. Physical activity significantly impacts both the BAS and BIS systems. Previous studies have shown that higher sensitivity to BAS is associated with greater participation in and enjoyment of physical activity. Individuals with high BAS sensitivity tend to respond more strongly to rewards during exercise, such as improved physical fitness and enhanced mood, which makes them more likely to continue engaging in physical activity [56]. During exercise, the activation of BAS promotes the release of dopamine, further enhancing feelings of pleasure and motivation. This creates a positive feedback loop where physical activity becomes enjoyable and reinforcing [57, 58]. In contrast, high sensitivity to BIS may lead to avoidance behaviors toward exercise. When BIS is activated, individuals may focus excessively on negative emotions such as discomfort, fatigue, or anxiety during physical activity, which in turn reduces their willingness to engage in exercise [59]. Individuals with high BIS sensitivity may experience negative emotions like anxiety and tension during exercise, making them more likely to avoid or discontinue physical activity. However, physical activity can activate BAS, helping to improve emotional regulation and self-efficacy, thus reducing the negative impact of BIS and enhancing overall mental health. Regular physical activity can alleviate anxiety, reduce avoidance behaviors, and promote healthier behaviors [54].

In summary, BAS and BIS are core psychological systems that significantly influence individual behavior and play vital roles in the Behavioral Activation process. BAS motivates individuals to pursue rewards and positive stimuli, enhancing their enjoyment and motivation for exercise. In contrast, BIS regulates negative emotions and anxiety through defensive and avoidance responses, which may suppress exercise participation. Physical activity can enhance BAS activation, improve mood, increase motivation, and reduce anxiety and avoidance behaviors induced by BIS. This, in turn, increases exercise participation and overall health. Future research could further explore how BAS and BIS are expressed in different individuals, environments, and physical activity intensities, as well as how Behavioral Activation interventions can further promote individual mental health and quality of life.

Limitations

This study has several limitations. First, the small sample size in this randomized controlled trial limits the ability to perform detailed comparisons between patients. Second, the sample was primarily drawn from a specific population, which may restrict the generalizability of the findings. Additionally, the IPAQ, as a subjective self-report questionnaire, has inherent limitations in accurately measuring physical activity, potentially introducing biases. Future research could benefit from employing objective measures, such as wearable devices, to assess

physical activity. Finally, the absence of long-term follow-up restricts the ability to evaluate the sustained effects of the intervention over time.

Conclusion

Despite these limitations, this study found that BA is an effective psychological intervention for alleviating depressive symptoms in CRC patients. The mediation analysis revealed that BA exerts its antidepressant effect by increasing physical activity levels. These findings have significant clinical implications. During the implementation of BA, particular attention should be given to the patient's physical activity levels, and patients should be encouraged to increase their daily activities. This can be achieved by offering personalized exercise plans and gradually increasing activity levels to optimize the therapeutic effects of BA. The results also provide valuable guidance for future interventions, emphasizing the critical role of physical activity in BA and suggesting new avenues for combined therapies.

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Disclosure of conflict of interest

None.

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Table S1. Changes in the HADS, EORTC QLQ-C30, BADS-SF and DT scores over the course of treatment in the BA group and UC group

Item (mean ± SD)	T0	T1	T2	F	P	ηp2
BA (n=52)						
HADS-D	12.75±2.31	12.08±2.57	9.75±3.66	25.447	<0.001**	0.504
HADS-A	9.38±3.78	9.19±3.92	9.75±5.64	1.854	0.167	0.069
DT	6.12±1.5	4.37±1.3	3.73±1.65	159.038	<0.001**	0.864
EORTC QLQ-C30	61.25±13.76	64.84±12.59	68.74±13.8	7.712	0.008	0.131
BADS-SF-AC	14.79±4.51	18.29±5.43	19.71±6.55	29.256	<0.001**	0.539
BADS-SF-AV	10.6±4.18	11.35±5.07	12.42±5.52	7.211	0.002	0.224
IPAQ-SF	1445.65±1397.09	1520.35±1475.37	1949.47±1876.80	11.859	<0.001**	0.332
UC (n=57)						
HADS-D	13.21±2.83	12.6±4.26	12.86±4.44	0.881	0.42	0.031
HADS-A	10.37±3.55	10.28±4.56	10.88±5.14	1.969	0.149	0.067
DT	6.14±1.86	6.09±2.38	5.6±2.1	5.11	0.008	0.084
EORTC QLQ-C30	61.06±11	58.83±15.9	61.92±17.72	1.393	0.253	0.024
BADS-SF-AC	15.12±4.15	14.82±4.47	14.4±5.09	0.616	0.541	0.011
BADS-SF-AV	10.37±4.11	11.07±4.16	11.4±4.56	1.94	0.149	0.033
IPAQ-SF	1230.12±1045.76	1261.02±1262.45	1245.61±1159.91	0.12	0.877	0.002

Abbreviations: BA, behavioral activation; SD, standard deviation; P, level of significance; T0, before BA treatment; T1, after4 BA sessions; T2, after 8 BA sessions; HADS-D, Hospital Anxiety and Depression Scale-depression; HADS-A, Hospital Anxiety and Depression Scale-anxiety; EORTC QLQ-C30, European Organization for Research and Treatment Core Quality of Life questionnaire of Cancer-30; DT, distress thermometer; BADS-SF, Behavioral Activation for Depression Scale-Short Form; AC, Activation; AV, Avoidance; IPAQ, International Physical Activity Questionnaire; **P<0.01.