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Effects of Cognitive Behavioral Therapy for Depression and Anxiety, Response Rates and Adverse Events in Patients with Locoregional Advanced Nasopharyngeal Carcinoma

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Abstract

Purpose: This retrospective study investigated the effects of cognitive behavioral therapy (CBT) on depression, anxiety, response rates, and adverse events in patients with locoregional advanced nasopharyngeal carcinoma (NPC). **Methods:** A total of 269 patients with diagnosis of stage III-IVA NPC received either CBT plus chemoradiotherapy (CBT group, n = 136) or treatment as usual (TAU) plus chemoradiotherapy (TAU group, n = 133). Patients in the CBT group received a series of 6 CBT sessions for 6 weeks during concurrent chemoradiotherapy. Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) score at baseline, the completion of radiotherapy, and 6, 12, and 24 months after radiotherapy. Response rates and adverse events were also evaluated. **Results:** Patients in the CBT group showed significantly less depression and anxiety than patients in the TAU group after the completion of radiotherapy ($P < .05$). Complete response rates were 99.3% (135/136) and 92.5% (123/133) in the CBT group and TAU group with a small effect size (Phi coefficient = .171), respectively ($P = .005$). Compared with the TAU group, the CBT group showed a significantly lower incidence of acute adverse events and late toxic effects. **Conclusions:** The addition of CBT to chemoradiotherapy significantly reduced depressive and anxiety symptoms. CBT combined with chemoradiotherapy is associated with improved response rates, with reduced incidence of toxic effects in patients with locoregional advanced NPC. Based on this study, we registered a randomized controlled clinical trials to better define the role of CBT in patients with locoregional advanced NPC (Registration number: ChiCTR2000034701).

Keywords

anxiety, cognitive behavioral therapy, chemoradiotherapy, depression, nasopharyngeal carcinoma

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Background

Nasopharyngeal carcinoma (NPC) is particularly endemic in southern China, Southeastern Asia and North Africa. NPC affected an estimated 130 000 patients worldwide in 2018.[1] More than 70% of NPC patients are diagnosed at a locoregional advanced stage.[2] Radiotherapy combined with systemic chemotherapy has been considered the main regimen for locoregional advanced nasopharyngeal carcinoma (LA-NPC).[3] Previous studies have reported that treatment-related toxicity in patients with head and neck cancer, such as dry mouth, weight loss, loss of taste, and low libido, is significantly associated with the incidence of anxiety and depression.[4,5] These reactions may seriously affect the physical and mental health, treatment compliance, and quality of life (QOL) of patients, and these effects can last a long time after the cessation of treatment.[6,7] In a cross-sectional cohort study of 107 patients, McDowell et al[8] reported that depression (25%), anxiety (37%), and

fatigue (28%) were common and strongly correlated with QOL among patients with NPC treated with radiotherapy. Reducing the anxiety and depression of patients and reducing the incidence of toxic effects are urgent priorities.

Psychological interventions, especially cognitive behavioral therapy (CBT), have been proven to be effective psychotherapy options for anxiety and depression in patients with various malignant tumors, such as breast cancer, head and neck cancer.[9-12] However, the effects of CBT combined with chemoradiotherapy on LA-NPC remain unclear. Therefore, the primary aim of this study was to compare the effects of CBT with treatment as usual (TAU) on depressive and anxiety symptoms, adverse events and response rates in patients with LA-NPC.

Methods

Participants

The clinical characteristics of LA-NPC patients between January 2016 and March 2019 were reviewed retrospectively. The inclusion criteria included the following: histologic confirmation of WHO types II-III, stage III-IVA NPC (8th American Joint Committee on Cancer, AJCC); an age between 18 and 70 years; a Karnofsky performance-status score of at least 70; adequate hematologic (leukocyte count $\geq 4.0 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 109$/L, and hemoglobin ≥ 90 g/L), renal, and hepatic function; and ability to participate in CBT; The exclusion criteria were: a history of previous radiotherapy, another malignancy, pregnancy, or lactation, and severe psychological or mental disorders (such as suicidal ideation). All patients were screened from Hunan Cancer Hospital at The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University. Informed consent was obtained from all patients. This study obtained ethics approval from the Ethics Committee of Hunan Cancer Hospital. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Treatments

Chemotherapy. All patients received induction chemotherapy followed by concurrent chemotherapy. The induction chemotherapy regimens were TPF (docetaxel at 60 mg/m^2/day on day 1, cisplatin at 60 mg/m^2/day on day 1 and 5-fluorouracil at 600 mg/m^2/day on days 1-5), and TP (docetaxel at 75 mg/m^2/day on day 1, cisplatin at 75 mg/m^2/day on day 1). Concurrent chemotherapy was prescribed as 80 to 100 mg/m^2 cisplatin alone on days 1, 22, and 43 for 3 cycles concurrently with radiotherapy. All patients were scheduled to receive concurrent chemotherapy, except those who declined the treatment or presented severe adverse events.

Radiotherapy. Radical radiotherapy treatment with intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) was mandatory in this trial. Target volumes and radiotherapy doses of IMRT in the nasopharynx and nodal regions were defined according to the RTOG 0615.[13] Gross tumor volume (GTV) of the nasopharynx was irradiated at a dose of DT70.4 Gy/32 and DT72.6 Gy/33 Fx in patients with T1-2 and T3-4 disease, respectively. GTV of the lymph node (GTVnd) was irradiated at a dose of 69.96 to 72.6 Gy/32 to 33 Fx. High risk subclinical lesions were irradiated at a dose of DT60.06 to 64 Gy/32 to 33 Fx. Lower-risk subclinical disease was treated at a dose of DT52.0 to 56.0 Gy/26 to 28 Fx.

Cognitive behavioral therapy. The CBT group and the TAU group were treated in different radiotherapy departments. CBT was derived from the work of Ellis (1962) and Beck (1976), and gained status from a large body of empirical data that supported its efficacy in treating anxiety, depression and various other psychological conditions.[14] The participants in the CBT group received 6 sessions based on the manual codified by Beck et al[15] along with concurrent

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Table 1. Weekly Themes and Main Content of CBT Sessions.

Week	Weekly theme
1	Introduction and establishment of a therapeutic relationship
	Introducing the group and gaining the trust of patients
	Understanding the psychosocial background of patients (including family structure, economic status, current life background work experience, etc.)
	Understanding the possible adverse events that can occur during the treatment of NPC
	Obtaining information on anxiety and depression (including physical symptoms related to anxiety and depression, such as fatigue, insomnia, loss of appetite, etc.)
2	Understanding the relationships between thoughts, emotions(depression and anxiety), and behavior
	Introducing the CBT model
	Identifying of automatic thoughts (thought interactive questioning, imagination, case discussion, role play, etc.)
	Understanding the automatic thoughts and emotional and behavioral reflection associated with NPC
3-5	Cognitive restructuring
	Changing unreasonable cognition through authenticity test, thought-records and generating alternative thoughts, etc.
	Strengthening positive cognitive style through role play and self-direction
	Teaching relaxation skills, including mindfulness meditation, abdominal breathing, progressive muscle relaxation training, and imagery relaxation
6	Consolidating the experiences of dealing with emotional problems
	Sharing attitudes and experiences related to depression and anxiety before and after the group
	Sharing experiences of applying cognitive-restructuring skills
	Establishing the long-term personal goals and ending the treatment relationship

chemoradiotherapy, and the treatments were specifically designed according to the previous studies[10,16,17] and the psychological characteristics of NPC patients. The intervention combined behavioral, cognitive, and educational strategies. In the first few sessions participants were taught basic cognitive skills, including how to identify automatic thoughts and restructure cognition, and provided examples of their thought process. The participants were invited to share personal experiences of negative emotions caused by NPC. They were also taught behavioral strategies and some psychological techniques to cope with depression and anxiety, such as deep-relaxation and meditation. Moreover, they were guided to review the process of emotional changes and related physical symptoms during concurrent chemoradiotherapy, which helped them identify the connection between psychological and physical symptoms. In the final session, the therapist would encourage all the participants to provide a review and summary of what they had learned in the intervention and to share a maintenance plan. The main themes and content are summarized in Table 1.

The intervention was led by an oncology doctor, and there were 3-day training sessions for the multidisciplinary team that included 1 psychotherapist, 2 oncology experts, and 2 nurses. In a group of 6 participants, CBT was once a week in 45 minutes sessions for 6 weeks during concurrent chemoradiotherapy. Before the study, all the assessors and therapists had received rigorous unified training and complied with the standard operation procedure (SOP) to ensure the quality of this research. To ensure protocol adherence, we recorded sessions and scripts, and we randomly chose and assessed the fidelity of the recordings and provided feedback to the psychotherapist.

Treatment as usual. All patients received TAU according to the standards of the radiotherapy department from oncology teams. TAU consisted of education given at irregular intervals that included information about health, nutrition, and psychology, and the provision of explanations addressing the patients or families' questions.

Patient Assessment and Follow-up

Tumor responses were assessed after 2 cycles of induction chemotherapy and 3 months after radiotherapy completion. Response was classified into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to the WHO response criteria. The Common Terminology Criteria for Adverse Events (version 4.0) scale was used to assess chemotherapy-related toxic effects. We graded radiotherapy-related toxic effects in accordance with both the Acute and the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG). The primary endpoints were anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS). Secondary endpoints included initial response rates after induction chemotherapy and radiotherapy, and toxic effects.

Both groups were evaluated for anxiety and depression measured by a trained psychotherapist using the Hospital Anxiety and Depression Scale (HADS) at baseline (T1), the

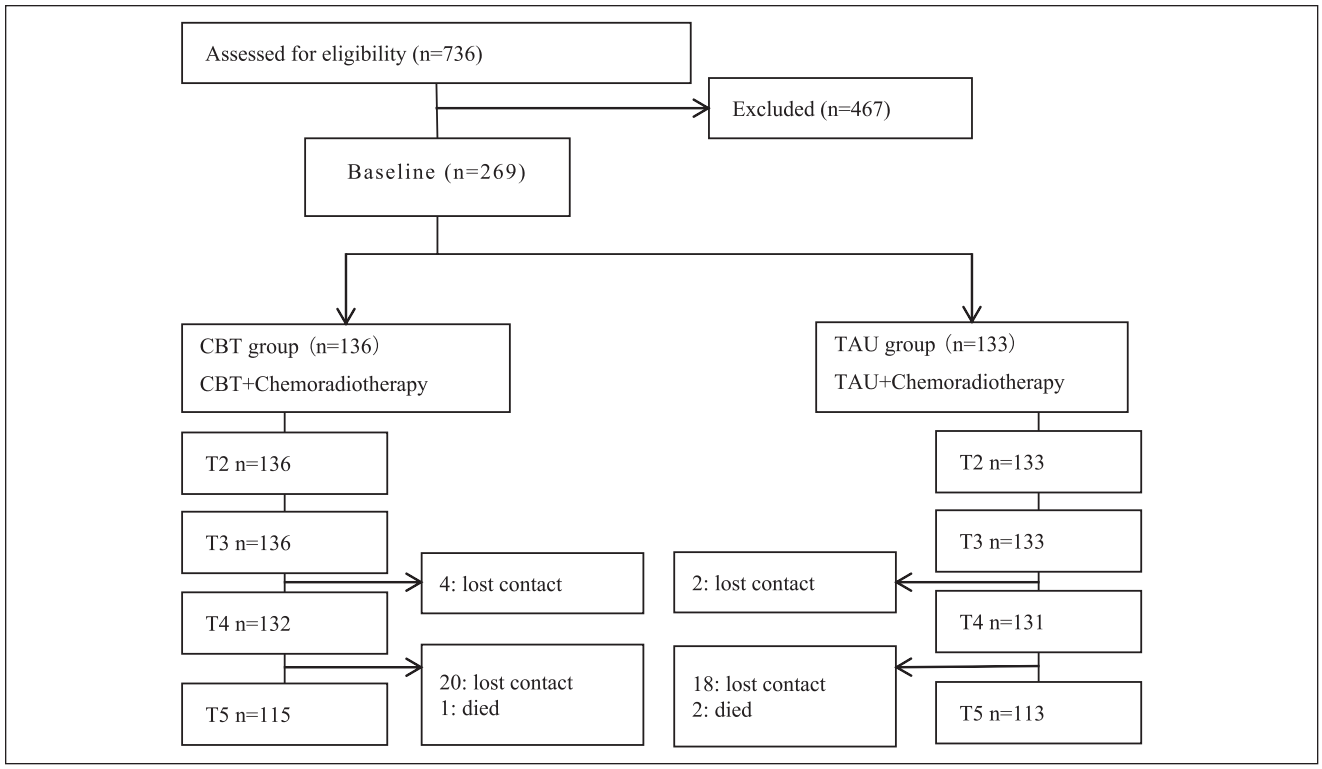

Figure 1. Flow chart of the participants.
Abbreviations: CBT, cognitive behavioral therapy; TAU, treatment as usual.

completion of radiotherapy (T2), and 6 (T3), 12 (T4), and 24 (T5) months after radiotherapy. The HADS is a 14-item self-administered questionnaire that measures symptoms of anxiety (subscale HADS-A) and depression (subscale HADS-D) in patients with a somatic illness. Each item was answered by the patient on a 4 point (0-3) scale, so the possible scores ranged from 0 to 21 for anxiety and 0 to 21 for depression. The scale has been most widely used in cancer research.[18] A higher score indicates a more severe level of anxiety and/or depression.

Statistical Analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 22 (SPSS, Chicago, IL). For HADS scores, the total scores and subscale scores of each measure at the 5 time points (T1, T2, T3, T4, and T5) were analyzed using repeated measures ANOVA. The initial response rates, toxic effects, and other categorical variables were compared by the χ^2 test. All statistical tests were 2-sided, with $P < .05$ considered statistically significant. For 2-category parameters the effect sizes were determined based on the Phi coefficient, where .01, .3, and .5 represented small, medium, and large effect sizes, respectively. Missing data were dealt by the last-observation-carried-forward (LOCF) approach. To assess the impact of missing data, we performed a sensitivity analysis. We created 5 imputation sets by multiple imputation. Missing values were imputed separately for each study group. We then using repeated measures ANOVA on the 5 sets and combined the estimates.

Results

Patient Characteristics

From January 2016 to March 2019, 269 patients with LA-NPC were included in this study (Figure 1). The CBT group comprised 136 patients, and the TAU group comprised 133 patients. At the last follow-up on November 1, 2020, the median follow-up time for all patients was 35 months (range, 19.5-57 months).The characteristics of the patients at baseline were well balanced between the 2 groups (Table 2).

Anxiety and Depression

As shown in Table 3, there were no significant differences in mean HADS scores between the CBT group (mean, 16.60; SD, 2.645) and the TAU group (mean, 16.30; SD, 2.412) at the baseline assessment ($P = .329$). The HADS scores decreased in both groups after radiotherapy. Significant improvement in the CBT group was observed in

Table 2. Baseline Characteristics.

Characteristics	CBT group (N = 136)	TAU group (N = 133)	*P*-value
Median age (range), years	47 (18-70)	47 (18-70)	.634
Sex, no. (%)			.674
Male	95 (69.9%)	96 (72.2%)	
Female	41 (30.1%)	37 (27.8%)	
Karnofsky scale, no. (%)			.174
90-100	119 (87.5%)	123 (92.5%)	
70-80	17 (12.5%)	10 (7.5%)	
Marital status, no. (%)			.793
Married	107 (78.7%)	109 (82.0%)	
Single	10 (7.4%)	8 (6.0%)	
Widowed or divorced	19 (14.0%)	16 (12.0%)	
Employment status, no. (%)			.440
Stable career	47 (34.6%)	52 (39.1%)	
Unemployed	89 (65.4%)	81 (60.9%)	
Monthly family income, no. (%), yuan			.708
≤1000	27 (19.9%)	29 (21.8%)	
1001-3000	61 (44.9%)	53 (39.8%)	
>3000	48 (35.3%)	51 (38.3%)	
Education, no. (%)			.587
Junior school and below	72 (52.9%)	74 (55.6%)	
High school	44 (32.4%)	45 (33.8%)	
College and above	20 (14.7%)	14 (10.5%)	
Medical insurance, no. (%)			.611
Own expense	7 (5.1%)	8 (6.0%)	
Urban basic medical insurance	56 (41.2%)	47 (35.3%)	
Rural cooperative medical insurance	73 (53.7%)	78 (58.6%)	
Pathology, no. (%)			.35
WHO type 2	31 (22.8%)	24 (18.2%)	
WHO type 3	105 (77.2%)	108 (81.8%)	
T category, no. (%)			.685
T1	20 (14.7%)	17 (12.8%)	
T2	32 (23.5%)	36 (27.1%)	
T3	43 (31.6%)	47 (35.3%)	
T4	41 (30.1%)	33 (24.8%)	
N category, no. (%)			.656
N0	0 (0.0%)	1 (0.8%)	
N1	17 (12.5%)	14 (10.5%)	
N2	80 (58.8%)	75 (56.4%)	
N3	39 (28.7%)	43 (32.3%)	
Disease stage, no. (%)			.429
III	64 (47.1%)	69 (51.9%)	
IVA	72 (52.9%)	64 (48.1%)	
Anemia, no. (%)			.680
Yes	11 (8.1%)	9 (6.8%)	
No	125 (91.9%)	124 (93.2%)	

Continuous variables are indicated as mean (SD) or median (IQr). Categorical values are expressed as proportions (%). The *P*-values reflect comparisons among CBT and TAU groups.

regard to depressive and anxiety symptom measures after completion of radiotherapy (T2). Patients in the CBT group showed significantly lower mean total HADS scores than patients in the TAU group from the completion of radiotherapy (T2) to 24 months after radiotherapy completion (T5) (all $P < .05$). According to the RM-ANOVA results, the HADS score of 2 groups showed a downward trend over time, but the reduction in the CBT group was much greater than that in the TAU group (Figure 2). The mean total HADS score in the CBT group was significantly lower over time than that in the TAU group ($F = 48.569$ $P < .001$). Moreover, the results showed that the mean HADS score

Table 3. RM-ANOVA for Scores of HADS among 2 Groups.

	CBT group	TAU group	
Time	Mean (SD)	Mean (SD)	*P*-value
Baseline (T1)			
Total	16.60 (2.645)	16.30 (2.412)	.329
Anxiety	8.40 (1.379)	8.20 (1.278)	.232
Depression	8.21 (1.441)	8.10 (1.260)	.513
Completion of radiotherapy (T2)			
Total	13.29 (2.482)	14.18 (2.433)	$P=.003$
Anxiety	6.77 (1.294)	7.28 (1.263)	$P=.001$
Depression	6.51 (1.311)	6.90 (1.348)	$P=.017$
6 mo after radiotherapy (T3)			
Total	11.10 (2.069)	12.43 (2.314)	$P<.001$
Anxiety	5.40 (1.064)	6.14 (1.219)	$P<.001$
Depression	5.69 (1.183)	6.29 (1.234)	$P<.001$
12 mo after radiotherapy (T4)			
Total	8.08 (2.271)	11.26 (2.679)	$P<.001$
Anxiety	3.98 (1.158)	5.50 (1.271)	$P<.001$
Depression	4.10 (1.219)	5.75 (1.515)	$P<.001$
24 mo after radiotherapy (T5)			
Total	7.61 (2.395)	10.86 (3.151)	$P<.001$
Anxiety	3.80 (1.218)	5.34 (1.532)	$P<.001$
Depression	3.74 (1.302)	5.58 (1.737)	$P<.001$

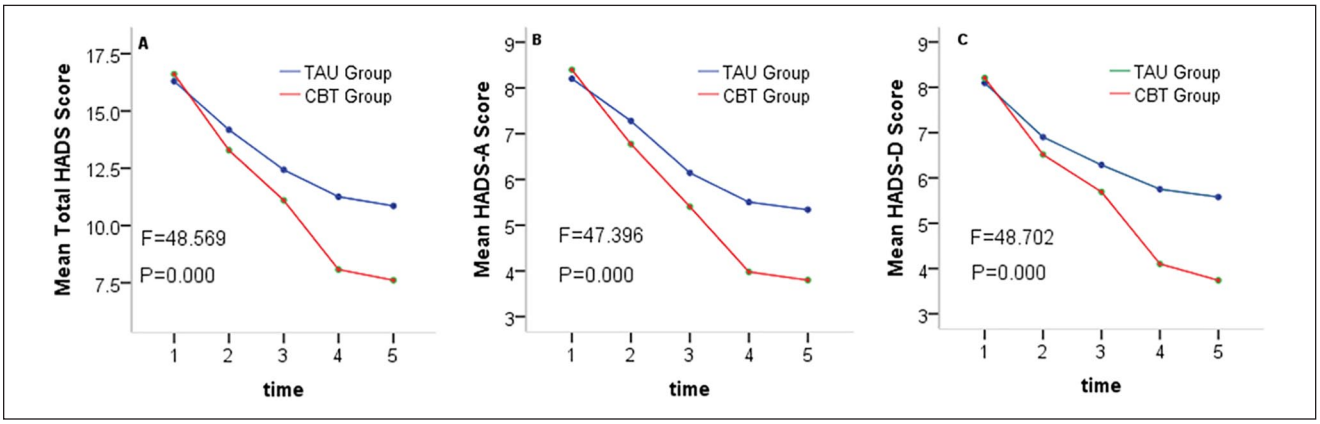

Figure 2. Mean score of HADS at baseline, completion of radiotherapy, 6, 12, and 24 months after radiotherapy. Total HADS score (A), HADS-A score (B), and HADS-D score (C).

for depression and anxiety was lower in the CBT group ($P<.001$). The sensitivity analyses accounting for missing data suggest that the results were robust.

Response Rates

There was no significant difference in the complete response (CR) rates of 2 groups (16/136 11.8% vs 17/133 12.8%, $P=.799$) after 2 cycles of induction chemotherapy. At 3 months after radiotherapy, CR rates were 99.3% (135/136) and 92.5% (123/133) in the CBT group and the TAU group with a small effect size (Phi coefficient = .171), respectively ($P=.005$). In CBT group, 1 patient had residual neck lymph nodes. Six patients in the TAU group had residual neck lymph nodes and 4 presented residual nasopharyngeal tumors.

Adverse Events

During the entire treatment course, compared to the CBT group, the TAU group had a higher incidence of grade 3 or 4 anemia (0 [(0%)] vs 6 [4.5%]), mucositis (15 [11.0%] vs

Table 4. Grade 3 to 4 Acute and Late Toxic Effects.

Adverse events	CBT group (N = 136)	TAU group (N = 133)	*P*-value
Grade 3-4 acute adverse events			
Anemia	0 (0%)	6 (4.5%)	.036
Leukopenia	11 (8.1%)	12 (9.0%)	.784
Neutropenia	31 (22.8%)	34 (25.6%)	.596
Thrombocytopenia	1 (0.7%)	3 (2.3%)	.599
Liver dysfunction	0 (0%)	0 (0%)	–
Nephrotoxicity	0 (0%)	0 (0%)	–
Nausea	0 (0%)	1 (0.8%)	.494
Vomiting	0 (0%)	2 (1.5%)	.244
Fatigue	7 (5.1%)	19 (14.3%)	.011
Dry mouth	6 (4.4%)	8 (6.0%)	.554
Mucositis	15 (11.0%)	28 (21.1%)	.025
Dermatitis	4 (2.9%)	4 (3.0%)	1.000
Dysphagia or odynophagia	4 (2.9%)	6 (4.5%)	.720
Ototoxicity	0 (0%)	1 (0.8%)	.494
Insomnia	7 (5.1%)	18 (13.5%)	.018
Weight loss	0 (0%)	6 (4.5%)	.036
Grade 3-4 late adverse events			
Skin fibrosis	0 (0%)	6 (4.5%)	.036
Dry mouth	0 (0%)	6 (4.5%)	.036
Ototoxicity	0 (0%)	0 (0%)	–
Trismus	0 (0%)	0 (0%)	–
Nasopharyngeal ulceration	0 (0%)	0 (0%)	–
Temporal-lobe necrosis	0 (0%)	0 (0%)	–

28 [21.1%]), fatigue (7 [5.1%] vs 19 [14.3%]), weight loss (0[0%] vs6 [4.5%]), and insomnia (7 [5.1%] vs18 [13.5%]). Grade 3 to 4 late adverse events included skin fibrosis and ototoxicity. The incidence of skin fibrosis and dry mouth was higher in the TAU group than in the CBT group ($P = .036$). No grade 5 toxicity (death) occurred during the treatment (Table 4).

Discussion

To the best of our knowledge, this is the first report evaluating the effects of CBT for depression and anxiety in patients with LA-NPC treated with concurrent chemoradiotherapy. We observed a significant difference in HADS scores between the 2 groups at different observation time points after radiotherapy. Furthermore, favorable improvement was maintained at 24 months after radiotherapy. The results indicate that CBT may be effective for depression and anxiety in patients with LA-NPC.

Many studies have found the high incidence of anxiety and depression in patients with head and neck cancer.[4,19] Previous studies have also offered substantial evidence for the efficacy of CBT in reducing anxiety, depressive symptoms and improving QOL for in survivors of various cancers, such as head and neck cancer, breast cancer and colorectal cancer.[10,12,20,21] Furthermore, the beneficial effects of CBT on depression appeared to be sustained.[20] However, the effect of CBT combined with chemoradiotherapy in LA-NPC remains unclear. Our results show that before the intervention, the average levels of anxiety and depression symptoms in each group approached the cutoff (a HADS score of 8), indicating clinical anxiety and depression. From the start of the study to the completion of radiotherapy, HADS scores decreased in both groups, but the magnitude of this decrease was more pronounced in the CBT group ($P < .05$). Although we found a reduction in anxiety and depression symptoms over time in the 2 groups, HADS scores in CBT group remained significantly better at each time point. The reduction associated with CBT was quicker and greater than that associated with TAU. Our results are also compatible with the study of Kangas et al[10] in which CBT and supportive counseling intervention were effective in reducing depressive and general anxiety symptoms and the improvement was maintained at the 6 and 12 month follow-ups. This outcome might be explained by the fact that the participants probably acquired CBT skills and continued practicing them after the intervention ended, which resulted in continuous improvement. Compared with TAU, CBT combined with chemoradiotherapy significantly alleviated the anxiety and depression in LA-NPC patients.

CBT is known to be effective in reducing anxiety and depression in cancer patients. However, to the best of our knowledge, no studies have explored the effect of CBT combined with radiotherapy or chemotherapy on response

rates among cancer patients. The CR rate after chemoradiotherapy for locoregional advanced NPC was between 82.8 to 98%.[22-24] In this study, CR rate was significantly higher in the CBT group than in the TAU group (99.3% vs 92.5%, $P = .005$), suggesting that the risk for local residual tumor was significantly decreased by CBT. Among the explanations of such variance could be the difference in hemoglobin (Hb) levels between the 2 groups, although this needs to be investigated further. Our study found that the TAU group had a higher incidence of anemia than the CBT group. The pretreatment and mid-treatment Hb levels have been regarded as an important determinant of outcome for NPC treated by IMRT.[25]

A meta-analysis of 8 randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors showed that CBT-I resulted in an improvement in sleep efficiency (SE), and a reduction in sleep latency and wake after sleep onset. The effects were durable up to 6 months.[26] Furthermore, Garland et al[27] reported that CBT caused significant improvement in sleep continuity in cancer survivors. Gielissen et al[28] reported the long-term effect of CBT on fatigue in 68 cancer patients. CBT, especially designed for post-cancer fatigue, is successful in reducing fatigue and functional impairment in cancer survivors. Moreover, these positive effects were maintained at about 2 years after finishing CBT. From the comparison of adverse events between the 2 groups in this study, CBT significantly reduced the occurrence of grade 3 to 4 acute adverse events (anemia, mucositis, fatigue, weight loss, insomnia) caused by radiotherapy and chemotherapy, The incidence of skin fibrosis and dry mouth also significantly improved. The results of this study show that CBT significantly reduced the occurrence of grade 3 to 4 fatigue and insomnia in patients with NPC, which is consistent with the findings of the studies by Kangas et al[10] and Gielissen et al.[28] These results validated clinical usefulness of CBT in the treatment of locoregionally advanced NPC.

Study Limitations

Our study has some potential limitations. First, CBT was conducted with patients who volunteered to participate, and they may have been more interested in self-care and more willing to follow through with action plans. Thus, there may be self-selection bias: an inherent drive and the compliance among the participants may have had an impact on the treatment response and side effects. Further randomized controlled clinical trials with a greater sample size may mitigate this limitation. Second, longer follow-up is needed to fully assess depression, anxiety, and long-term toxic effects. Finally, this study was limited by its retrospective nature and the sample size was relatively small. To investigate the usefulness and feasibility of CBT, further work, including a prospective longitudinal multicenter study, is recommended.

Clinical Implications

CBT combined with chemoradiotherapy shows preliminary efficacy for depression and/or anxiety, treatment response and adverse events in patients with LA-NPC. The study provided the theoretical foundation for the application of CBT to treat depression and anxiety in patients with LA-NPC in the clinic.

Conclusion

The addition of CBT to chemoradiotherapy significantly reduced depressive and anxiety symptoms. CBT combined with chemoradiotherapy is associated with improved response rates, with reduced incidence of toxic effects in patients with locoregional advanced NPC. Based on this study, we have registered randomized controlled clinical trials to better define the role of CBT in patients with locoregional advanced NPC (Registration number: ChiCTR2000034701) .

Authors' Contributions

Xiao-hong Liu led the design of the study, editing and submission of manuscript (Xiao-hong Liu is the corresponding authors). Fei Tong, Wang-lian Peng, Ran Zou, Min-ni Wen, Ling Jiang, Hui Yang, and Xu-fen Huang measured symptoms of anxiety and participated in cognitive behavioral therapy. Hui Wang, Ya-qian Han, Hong-zhi Ma, Qian He, Lin Liu, Yan-zhu Chen, and Ou-ying Yan participated in chemotherapy, radiotherapy and treatment as Usual. Sheng-nan Fu and Feng Liu involved in the design of the study, collection and analysis of data, and drafting of manuscript. All authors read and approved the final manuscript.

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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Availability of Data and Material

The data that support the findings of this study are available from the corresponding author up on reasonable request.

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