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ORIGINAL RESEARCH

Mindfulness-based stress reduction in patients with differentiated thyroid cancer receiving radioactive iodine therapy: a randomized controlled trial

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Objective: The aim of this study was to evaluate the efficacy of mindfulness-based stress reduction (MBSR) on health-related quality of life (QoL), depression, and anxiety in patients with differentiated thyroid cancer (DTC) receiving radioactive iodine therapy (RIT).

Patients and methods: A randomized controlled trial of MBSR with 120 DTC patients was performed. They were randomly assigned into the MBSR intervention group and usual care (UC) group. An 8-week MBSR program was administered to the MBSR group starting 8 weeks before RIT. Health-related QoL, depression, and anxiety were measured immediately before the start of MBSR (T1), immediately after RIT hospitalization was concluded (1 week after concluding the last MBSR session, T2), and 3 months after RIT hospitalization (T3), using the QoL Questionnaire Core 30 Items (QLQ-C30), Self-rating Depression Scale (SDS), and Self-rating Anxiety Scale (SAS).

Results: Fifty-three patients in the UC group and 49 patients in the MBSR group completed the study and were analyzed. Both the UC and MBSR groups reported low QoL and high SDS and SAS scores immediately after RIT hospitalization. Patients randomly assigned to the MBSR group showed significantly greater improvements in emotional function (P=0.012, d=–0.03 for T2 and d=1.17 for T3), fatigue (P=0.037, d=1.00 for T2 and d=–0.69 for T3), global QoL (P=0.015, d=1.61 for T2 and d=1.56 for T3), depression (P=0.027, d=–1.19 for T2 and d=–0.83 for T3), and anxiety (P=0.043, d=–1.00 for T2 and d=–0.86 for T3).

Conclusion: An 8-week MBSR program significantly improved a wide range of scales in health-related QoL and mitigated depression and anxiety among DTC patients receiving RIT.

Keywords: mindfulness-based stress reduction, differentiated thyroid cancer, radioactive iodine therapy, quality of life, anxiety, depression

Introduction

Thyroid cancer, the most frequently occurring endocrine malignancy, is becoming increasingly prevalent worldwide and accounts for more deaths than all other endocrine cancers combined.[1] In China, the incidence of thyroid cancer has increased five times during the past 10 years and is now ranking as the seventh most prevalent malignancy among all cancers.[2] Differentiated thyroid cancer (DTC), which includes papillary and follicular histologies, accounts for 70%–90% of all thyroid cancers. According to the American Thyroid Association (ATA) guidelines, standard management of DTC includes surgical removal of thyroid gland (thyroidectomy) followed by radioactive iodine therapy (RIT) and thyroid-stimulating hormone (TSH) suppression therapy.[3]

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With an estimated overall 20-year relative survival rate of 95.4%, DTC is known to have a favorable prognosis upon effective treatment.[4] However, in clinical practice, while patients were told they have the "good" cancer, this does not reflect their personal experience with this disease. For example, although RIT after thyroidectomy is associated with dramatic decreases in locoregional recurrences, distant metastasis, and disease-related mortality,[5] patients receiving high-dose radioactive iodine still experience significant depression and anxiety associated with previous surgical complications (such as neck pain, dysphonia, and hypocalcemia), hormone withdrawal (causing a state of transient hypothyroidism symptoms such as fatigue, neurological deficiencies, and depression), fear of radiation, loneliness of isolation (being housed within radiation isolation wards), and side effect of radioactive iodine (such as swelling neck, sialadenitis, gastrointestinal symptoms, appetite loss, and insomnia).[6]

In modern medicine, psychological intervention has become an essential part of patient management. Mindfulness is a state of meditation that originated from Buddhist philosophy. It can be defined as the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment.[7] Mindfulness-based stress reduction (MBSR) was introduced to psychological treatment in 1979 by Kabat-Zinn[8] to help patients cope with their stress, pain, and emotions. It is widely used in the field of clinical cancer on patients and has shown improvement in several psychosomatic problems, such as insomnia, stress, anxiety, and depression.[9–11] However, to the best of our knowledge, no previous research has investigated the effects of MBSR on patients with thyroid cancer receiving RIT.

Therefore, the aim of this study was to explore whether MBSR intervention is effective in improving health-related quality of life (QoL) and reducing depression and anxiety in DTC patients receiving RIT.

Patients and methods

Patient inclusion

Patients were recruited from the Department of Nuclear Medicine in China-Japan Union Hospital, Changchun, China, from September 2015 to June 2016. Inclusion criteria were as follows: 1) planning for RIT with a definitive total thyroidectomy record and pathological report; 2) patients from 18 years to 70 years; 3) normal electrocardiography (ECG) and blood pressure. Exclusion criteria included the following: 1) a history of RIT; 2) having metastasis to other organs; 3) having other types of cancer, cardiovascular diseases, endocrine diseases, or mental disorder; 4) declining to participate in this study. This study was approved by the local independent ethics committees and the institutional review boards of China-Japan Union Hospital, Changchun, China, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all included patients.

Design and random assignment

This study was a two-arm randomized controlled trial. The sample size was estimated by G*Power version 3.1 program with a power (1–β) of 80% and a significance level of 5%. Using an effect size of 0.59 which was reported by related studies, we established that a minimum sample size of 94 patients was required. Allowing for 20% loss to follow-up of sample, 120 patients were randomized 1:1 into the MBSR intervention group or the usual care (UC) group. The allocation sequence was generated by random permuted block randomization (with a block size of 4) conducted using a computer-based system and concealed in sequentially numbered envelopes. Patients were blinded to study hypotheses and had no knowledge of the content of the group to which they were not assigned. The research staff were not blinded to the randomization or patient outcome. The UC group underwent admission education, medication guidance, isolation protection education, and discharge guidance, as they were conventionally performed for these patients. As for the MBSR group, we designed a timetable starting 8 weeks before RIT hospitalization (Figure 1), after which they would become a radioactive source. For these patients, in addition to routine guidance, a brief overview of the MBSR program, emphasizing the 8-week session schedule, was given 8 weeks before RIT hospitalization. All sessions were based on the original 8-week MBSR program that was developed by Kabat-Zinn[12] and were adjusted according to the corresponding conditions (Table 1). Each session also included group discussions and individual reports to create an interactive learning environment. The MBSR program was provided by a psychologist who was qualified in delivering mindfulness skills. Prior to the study, we also performed an 8-week pilot feasibility MBSR program with eight patients. The pilot study was designed to help provide the psychologist practice in running the program under clinical supervision and to resolve any potential practical problems.

Data collection

The assessments were conducted at three time points, which were the initial baseline that was immediately before the

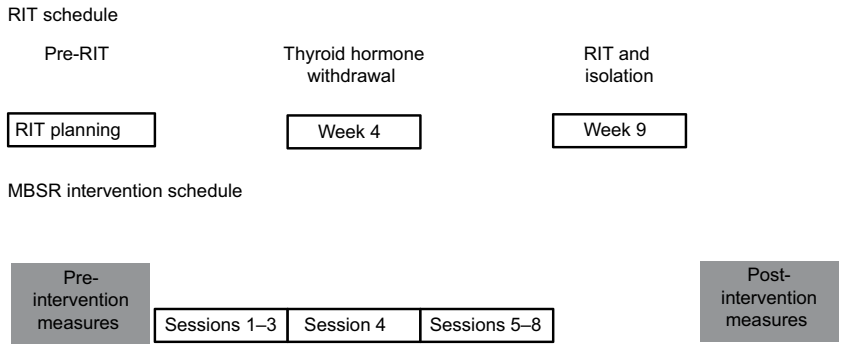

Figure 1 The relationship of time schedule between RIT procedure and MBSR intervention.
Abbreviations: MBSR, mindfulness-based stress reduction; RIT, radioactive iodine therapy.

Table 1 Concise content of the 8-week MBSR program

Week 1
Content summary: MBSR theory, intervention process, and corresponding requirements were introduced to the patients in an easy-to-understand manner. Mindful breathing training was explained and patients encouraged to practice it.
Week 2
Content summary: The meaning of sitting meditation, which emphasized breathing as a primary object of attention, was explained, and patients were guided to enter into and practice sitting meditation and nonjudgmental awareness of things with music being played at the same time.
Week 3
Content summary: Walking meditation and its key points were introduced to explore the relationship between motion and emotion. Patients were encouraged to expand their mindfulness practice to walking.
Week 4
Content summary: The meaning and requirements of body scan, which allows the body to experience the self-motion perception feedback of every part of the body, were explained, and patients were encouraged to practice it.
Week 5
Content summary: Yoga-based stretches, which included lying and standing postures, were taught. Given that some patients' upper limb movement might be compromised due to surgical brachial plexus damage, gentle and appropriate stretches were encouraged to suit their capability.
Week 6
Content summary: Mindfulness listening, thinking, and emotions were introduced, and patients were guided and encouraged to practice it.
Week 7
Content summary: Nonjudgmental awareness was explained, and patients were encouraged to practice it with music played at the same time without being interrupted by the surrounding environment.
Week 8
Content summary: Patients were encouraged to internalize the practice sessions and develop a pattern suiting their personal situations. It was empathized that meditation was a useful method to maintain individual well-being and week 8 was the first week of being on their own to develop a lifetime program of MBSR.

Abbreviation: MBSR, mindfulness-based stress reduction.

start of MBSR (T1), immediately after RIT hospitalization was concluded (T2), and 3 months after RIT hospitalization (T3).

QoL questionnaire (QLQ)

QoL was assessed using the QoL Questionnaire Core 30 Items (QLQ-C30) of the European Organization for Research and Treatment of Cancer (EORTC), which is a validated, self-reported, cancer-specific measure of QoL, with high functional scores and low symptom scores representing better functioning. It has been translated and validated in 81 languages and is used in more than 3,000 studies worldwide. It consists of five functional dimensions (eg, physical, emotional, cognitive, social, and role), three symptomatic dimensions (including pain, fatigue, and nausea), and other dimensions, such as insomnia, appetite, and economic burden. The scoring has been linearly transformed to a 0–100 scale according to the EORTC scoring manual.

Self-rating Depression Scale (SDS) and Self-rating Anxiety Scale (SAS)

The level of depression and anxiety was assessed by the Zung SDS and the Zung SAS, respectively. Each scale contains 20 items based on a 0–4 scale, with a higher score indicating a higher level of anxiety or depression. The possible range of scores was 0–80 for each scale.

Statistical analyses

Statistical analysis was performed using MedCalc software (version 17.4.4; Broekstraat, Mariakerke, Belgium). Comparisons of categorical variables were performed with either chi-squared test or Fisher's exact test as appropriate. Student's *t*-test was used for normally distributed continuous variables, and the Mann–Whitney *U* test was used for non-normally distributed continuous variables. Linear mixed models were used to assess the interaction between patients' assignment (UC group vs MBSR group) and time (T1, T2, and T3) in relation to QoL, SDS, and SAS scales, testing whether the rate of scale change varied by study assignment. Linear mixed models were also used to account for baseline differences. $P<0.05$ was considered to indicate statistical significance for all analyses. Cohen's *d* was calculated for the evaluation of effect size.

Results

Patients

Figure 2 shows an overview of the number of subjects who were randomized and retained. In total, 18 patients (15%) dropped out before the end of this study, resulting in 53 patients in the UC group and 49 patients in the MBSR group for data analysis. The demographic information of the included patients is summarized in Table 2. There were no statistical differences in age, gender, marital status, residence, educational level, employment status, religion, TNM stage, and radioiodine dose between the two groups (all $P<0.05$).

Linear mixed models were used to test the efficacy of MBSR on each QoL, SDS, and SAS. Descriptive data for each outcome are summarized in Table 3.

Health-related QoL

Statistically significant QoL improvements were observed in patients in the MBSR group through the 3-month period. Patients randomly assigned to the MBSR group showed significantly greater improvements in emotional function ($P=0.012$, $d=-0.03$ for T2 and $d=1.17$ for T3), fatigue ($P=0.037$, $d=1.00$ for T2 and $d=-0.69$ for T3), and global QoL ($P=0.015$, $d=1.61$ for T2 and $d=1.56$ for T3).

SDS and SAS

Patients randomly assigned to the MBSR group demonstrated greater scale improvement in depression ($P=0.027$, $d=-1.19$ for T2 and $d=-0.83$ for T3) and anxiety ($P=0.043$, $d=-1.00$ for T2 and $d=-0.86$ for T3).

Discussion

Our study was the first to explore the effects of MBSR on DTC patients receiving RIT. Important findings from this study include statistically significant improvements in emotional function, fatigue, global QoL, depression, and anxiety scales after MBSR intervention compared with those after UC.

Usually several weeks ahead of RIT, DTC patients come to our department for RIT consultation and seek guidance

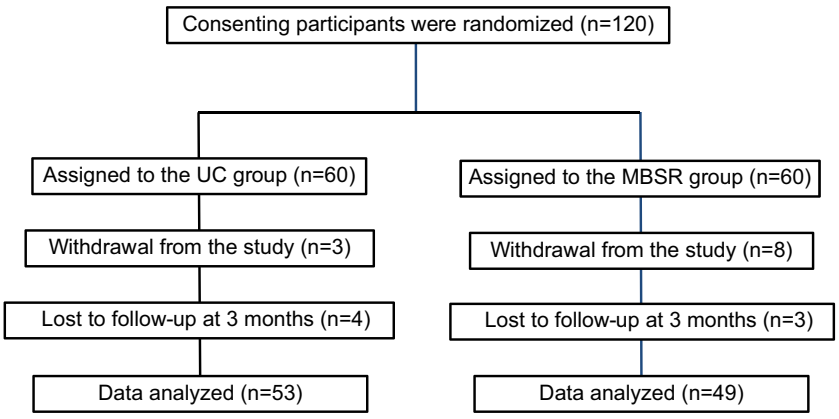

Figure 2 Flow diagram of patient randomization and retention.
Abbreviations: MBSR, mindfulness-based stress reduction; UC, usual care.

Table 2 Comparison of demographic and clinical characteristics

	MBSR intervention group (n=49)	UC group (n=53)	*P*-value
Age, mean ± SD	43.32±10.99	42.38±12.60	0.6899
Gender, n (%)			0.8307
Female	34	38	
Male	15	15	
Marital status, n (%)			0.7409
Married	35	37	
Single	4	6	
Residence, n (%)			1.0000
Urban	34	37	
Rural	15	16	
Educational level, n (%)			0.8354
Middle school or lower	16	19	
High school or higher	33	34	
Employment status, n (%)			0.6960
Employed	27	27	
Unemployed	22	26	
Religion, n (%)			0.6189
Yes	11	9	
No	38	44	
TNM stage, n (%)			0.7677
I	25	27	
II	8	7	
III	11	14	
IV	5	6	
RAI dose, mean ± SD	113.5±26.7	109.7±24.9	0.5870

Abbreviations: MBSR, mindfulness-based stress reduction; UC, usual care.

Table 3 Comparison of QoL, depression, and anxiety outcome across time points

Measurement	UC group (n=53)			MBSR intervention group (n=49)		Between-groups effect size, adjusting for baseline
	Mean	SD		Mean	SD	Cohen's *d*
Physical function						
T1 (baseline)	72.14	15.11		76.27	18.94	
T2	67.34	11.65		74.61	17.96	0.21
T3	77.09	16.10		85.72	12.30	0.31
Role function						
T1 (baseline)	74.20	12.81		71.04	21.76	
T2	58.55	11.86		68.40	12.79	1.17
T3	66.61	10.49		74.63	12.76	0.34
Emotional function						
T1 (baseline)	69.23	22.04		71.18	18.38	
T2	51.93	14.62		63.49	13.78	–0.03
T3	56.57	16.10		74.12	9.50	1.17
P*			0.012			
Cognitive function						
T1 (baseline)	71.00	19.62		73.69	16.30	
T2	61.81	19.86		69.56	13.97	0.29
T3	70.62	18.25		77.81	16.30	0.26
Social function						
T1 (baseline)	65.22	23.71		63.77	24.95	
T2	56.11	17.08		65.81	18.49	0.86
T3	62.05	14.34		74.35	17.68	0.63

(*Continued*)

Table 3 (*Continued*)

Measurement	UC group (n=53)			MBSR intervention group (n=49)		Between-groups, effect size, adjusting for baseline
	Mean	SD		Mean	SD	Cohen's *d*
Fatigue						
T1 (baseline)	18.67	12.24		20.51	11.32	
T2	55.73	24.33		37.28	14.89	1.0
T3	30.99	20.45		22.95	12.01	–0.69
P*			0.037			
Pain						
T1 (baseline)	21.67	19.15		23.10	17.08	
T2	22.64	17.52		18.79	12.18	–0.35
T3	15.78	10.38		13.84	8.67	–0.55
Nausea and vomiting						
T1 (baseline)	4.83	6.77		5.04	6.80	
T2	13.09	12.29		8.19	10.81	–0.44
T3	5.65	6.96		5.14	7.87	–0.09
Global QoL						
T1 (baseline)	69.54	15.27		66.61	10.85	
T2	49.47	10.92		62.67	10.32	1.61
T3	56.95	10.03		72.33	13.36	1.56
P*			0.015			
Dyspnea						
T1 (baseline)	16.64	16.25		15.87	13.00	
T2	8.52	8.74		7.77	9.22	0.01
T3	7.97	8.02		7.91	6.93	0.10
Sleep disturbance						
T1 (baseline)	16.59	17.63		18.84	18.89	
T2	43.55	19.60		26.34	15.91	–1.14
T3	19.28	16.40		13.30	11.76	–0.20
Appetite loss						
T1 (baseline)	11.74	15.21		10.27	13.56	
T2	18.19	15.85		18.60	15.80	0.12
T3	19.31	19.34		16.07	9.80	–0.11
Constipation						
T1 (baseline)	18.24	16.01		19.18	13.83	
T2	10.73	9.27		11.02	8.20	–0.07
T3	11.03	7.57		9.19	6.46	–0.39
Diarrhea						
T1 (baseline)	15.62	23.47		13.69	20.51	
T2	15.73	20.14		10.44	12.96	–0.18
T3	7.94	8.06		5.77	5.60	–0.03
Finance impact						
T1 (baseline)	28.32	33.78		24.29	21.24	
T2	38.26	30.75		33.23	21.64	0.03
T3	39.34	22.89		35.51	18.56	0.01
Self-rating depression						
T1 (baseline)	54.36	9.81		53.60	8.61	
T2	73.64	11.22		60.52	9.73	–1.19
T3	62.64	12.27		46.31	8.05	–0.83
P*			0.027			
Self-rating anxiety						
T1 (baseline)	58.72	8.65		59.58	9.62	
T2	77.37	14.50		65.24	11.08	–1.0
T3	60.44	10.83		48.97	9.82	–0.86
P*			0.043			

Notes: *If the difference between UC group and MBSR intervention group is significant, the *P* value is provided in the middle column of the table. TI, assessment immediately before the start of MBSR; T2, assessment immediately after RIT hospitalization is concluded; T3, assessment 3 months after RIT hospitalization.
Abbreviations: MBSR, mindfulness-based stress reduction; QoL, quality of life; UC, usual care.

regarding thyroid hormone withdrawal, low iodine diet, and the time schedule. This leaves us plenty of time to communicate with them. Recognizing the inadequacy of psychological support for these patients, we begin to think over what we could do to reduce their suffering in this period.

MBSR is now regarded as a well-established adjunctive treatment to assist well-being for medical patients in the USA. Since the introduction of this psychological intervention program to China, an increasing number of studies have been conducted to test its applicability in various patient groups such as breast cancer, chronic pain, and chronic insomnia. The results have been encouraging.[13–15]

In our study, most of the improvements in QoL, depression, and anxiety can be seen immediately after RIT hospitalization was concluded, when patients were experiencing the most negative impact of 4 weeks of thyroid hormone withdrawal, RIT-associated side effects, and isolation. Previous researchers have reported such changes in other types of cancers receiving MBSR program.[9,16–19] However, we thought that the supportive interaction among the group members may also result in positive health effect. In this regard, future research might be needed to evaluate whether MBSR adds benefit over an active psychological treatment such as cognitive behavior therapy (CBT), which could provide coping skills of a different type. Nonetheless, our results indicate that an 8-week schedule ahead of RIT hospitalization is applicable and effective for patients to cope with worsened QoL, depression, and anxiety in this period.

Three months after RIT, DTC patients began to recover from the panic and fear of the disease, as well as the damage caused by necessary medical treatment. However, we still observed significant benefits in the MBSR intervention group compared to the UC group at this time point. Parameters such as emotional function, fatigue, global QoL, depression, and anxiety were significantly better in the MBSR group than the UC group. The effect of MBSR on psychological aspect is more evident in this observation time point.

Two subscales (dyspnea and diarrhea) in QLQ-C30 recovered significantly in both the UC and MBSR groups. This is due to the resumption of levothyroxine, which reverses the state of hypothyroidism and leads to less related symptoms. One subscale (appetite loss) continued to be high in the two observation time points in both the UC and MBSR groups. Appetite loss is a side effect from RIT. However, different from nausea and vomiting, which usually disappear 2 or 3 days after RIT, it lasts for a very long period of time.[20] Our results demonstrate that MBSR has no significant impact on this subscale within 3 months after RIT hospitalization.

There are some limitations to this study. First, although the study design is an RCT, this clinical trial was limited by a modest sample size. Further studies with larger study population are required to confirm our results. Second, to understand the positive effect in patients receiving MBSR, 3-month point seems to be not enough and extended follow-up is needed. Third, because the study population was from one single hospital center, the results may not applicable to the general patients due to several DTC treatment strategies. Finally, we did not evaluate whether patients continuing practicing mindfulness after 3-month time point are benefitted. Because psychological intervention can improve the adherence of traditional treatment, we anticipate that DTC patients might benefit from long-term MBSR, even in recurrence and survival. However, future studies are needed to confirm this assumption.

Conclusion

An 8-week MBSR program significantly improved a wide range of scales in health-related QoL and mitigated depression and anxiety among DTC patients receiving RIT.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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