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Clinical and psychological moderators of the effect of Mindfulness-Based Cognitive Therapy on persistent pain in women treated for primary breast cancer – Explorative analyses from a randomized controlled trial

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ABSTRACT

Background

Mindfulness-Based Intervention has been found efficacious in reducing persistent pain in women treated for breast cancer. Little, however, is known about possible moderators of the effect. We explored clinical and psychological moderators of the effect on pain intensity previously found in a randomized controlled trial of Mindfulness-Based Cognitive Therapy (MBCT) with women treated for breast cancer with persistent pain.

Materials and Methods

A total of 129 women treated for breast cancer reporting persistent pain were randomized to MBCT or a wait-list control. The primary outcome of pain intensity (11-point Numeric Rating Scale) was measured at baseline, post-intervention, 3, and 6 months follow-up. Proposed clinical moderators included age, Axillary Lymph Node Dissection (ALND), radiotherapy, and endocrine treatment. Psychological moderators included psychological distress (the Hospital Anxiety and Depression Scale (HADS)), the adult attachment dimensions anxiety and avoidance (the Experiences in Close Relationships Short Form (the ECR-SF)), and alexithymia (the Toronto Alexithymia Scale (TAS-20)). Multi-Level Models were used to test moderation effects over time, i.e., time × group × moderator.

Results

Only attachment avoidance (p=0.03, d=0.36) emerged as a statistically significant moderator. Higher levels of attachment avoidance predicted a larger effect of MBCT in reducing pain intensity compared with lower levels attachment avoidance. None of the remaining psychological or clinical moderators reached statistical significance. However, based on the effect size, radiotherapy (d=0.49, p=0.075) was indicated as a possible clinical moderator of the effect, with radiotherapy being associated with a smaller effect of MBCT on pain intensity over time compared with no radiotherapy.

Conclusion

Attachment avoidance, and potentially radiotherapy, may be clinically relevant factors for identifying the patients who may benefit most from MBCT as a pain intervention. Due to the exploratory nature of the analyses, the results should be considered preliminary.

INTRODUCTION

Pain after breast cancer treatment is a prevalent late effect with one out of five women reporting pain 7-9 years after surgery [1]. This has stimulated research on the efficacy of psychosocial interventions in reducing pain in breast cancer patients with Mindfulness-Based Intervention (MBI) being among the interventions shown to be efficacious [2–4].

While MBIs appear to be promising pain management approaches for cancer-related pain, existing studies generally report intervention effects at the study group-level only, thereby neglecting the possible moderating effects of patient characteristics. However, a number of specific clinical and psychological characteristics could be possible candidates.

Several studies have investigated clinical risk factors for persistent pain after breast cancer surgery, providing strong evidence for younger age, Axillary Lymph Node Dissection (ALND), radiotherapy, and endocrine treatment as risk factors of persistent pain [5,6]. It is possible that these risk factors are differentially associated with various treatment responses to pain interventions as patients characterized by younger age, having undergone ALND surgery, radiotherapy, and/or endocrine treatment may experience higher levels of pain after breast cancer treatment, which may in turn predict susceptibility for change during pain interventions. Only one study has investigated radiotherapy, chemotherapy, and endocrine therapy as moderators of the effect of MBI on somatic symptoms in breast cancer patients, but found no statistically significant

interactions [7]. So far, no studies have specifically investigated possible clinical moderators of MBI on persistent pain in breast cancer patients.

There are also a number of possible psychological moderators. As mindfulness, defined as bringing attention to the experience that unfolds moment-by-moment in a non-judgmental way [8], and psychological distress have been negatively associated [9], it could be hypothesized that initial distress levels may influence the susceptibility for symptom improvement during MBI. A number of studies have investigated the possible moderating role of baseline psychological distress on the effect of MBI on various outcomes in breast cancer patients [7,10–12]. The reported results vary, with two of the studies showing that higher baseline distress predicted greater reductions in psychological symptoms [12], fear of recurrence, and fatigue [(10)]. In contrast, no statistically significant moderation effects were found for somatic symptoms [7] or general health [11]. None of the available studies had specifically included pain as their primary outcome measure.

Alexithymia, defined as deficits in the cognitive processing of emotions, could also be theoretically proposed to predict the effect of MBI on pain. As cognitive processing of emotions, e.g., identifying and describing emotions, is stimulated during MBI by fostering a more open and accepting way of relating to bodily sensations and emotional discomfort [8], patients with high levels of alexithymia could be hypothesized to experience greater treatment gains through the targeting of maladaptive pain cognitions in the intervention. Furthermore, higher levels of alexithymia have previously been

found to predict persistent pain in breast cancer patients [13], and results from a randomized controlled trial suggested that higher levels of alexithymia were associated with larger reductions in cancer-related distress in breast cancer patients [14]. However, the intervention investigated was Expressive Writing, and it remains unknown whether these results can be generalized to MBI.

Finally, adult attachment orientation, conceptualized as the two dimensions attachment anxiety and attachment avoidance, has been argued to be relevant in a pain context [15]. The two dimensions are based on perceptions about self and others [16]. Insecure attachment is conceptualized as high attachment anxiety and/or high attachment avoidance, with attachment anxiety being characterized by negative perceptions of the self as fragile and incapable of coping with stress, and attachment avoidance being characterized by negative perceptions of others as unavailable or unreliable during distress [17]. Secure attachment is described as low levels of attachment anxiety and attachment avoidance, facilitating a sense of personal efficacy in coping with stressors [17]. A review found attachment anxiety and attachment avoidance to be associated with increased pain intensity and poorer pain coping abilities in various (non-cancer) pain populations (e.g., patients with chronic pain, migraine) [15]. Hence, adult attachment orientation could be hypothesized to moderate the effect of pain interventions as patients with high attachment anxiety and attachment avoidance may gain more from learning how to adaptively cope with pain during MBI. So far, no studies have investigated adult attachment as a possible moderator of MBI for pain.

On this background, the aim of the present study was to explore 1) clinical risk factors for persistent pain and 2) psychological factors associated with persistent pain as possible moderators of the effect of Mindfulness-Based Cognitive Therapy (MBCT) on pain intensity in women treated for breast cancer with persistent pain.

MATERIAL AND METHODS

Study design and participants

The present study utilizes data from a RCT evaluating the efficacy of Mindfulness-Based Cognitive Therapy (MBCT) on persistent pain, previously reported elsewhere [2]. In summary, 129 women treated for primary breast cancer at the Department of Oncology, Aarhus University Hospital, were recruited to participate in the study. Inclusion criteria were: a diagnosis of primary breast cancer, time since surgery $\geq$3 months, completed chemotherapy and/or radiotherapy, ability to understand Danish, and a score $\geq$3 on perceived pain intensity or pain burden on a 10-point numerical rating scale (NRS). Specifically, if the woman had a score of $\geq$3 on either one of these NRSs, she was considered eligible. These data were used for screening purposes only. Male patients and patients with metastatic breast cancer, other cancers, serious psychiatric diagnoses (e.g., psychosis), and severe medical conditions related to the musculoskeletal system (e.g., arthritis) were excluded. The study was approved by the Regional Science Ethical Committees (registration no.: 1-10-72-460-12), and pre-registered at clinicaltrials.gov (NCT01674881).

Procedures

During control visits at the Department of Oncology, oncologists asked patients about their current pain status. Women who were eligible to participate were informed orally and in writing about the study. If the patient agreed to participate, she was asked to return a signed consent form and was sent a baseline questionnaire.

The randomization was conducted by an independent researcher not otherwise involved in the recruitment procedures, using the statistical software Power And Sample Size (PASS) v.12 (NCSS, Kaysville, Utah). After having returned the completed baseline questionnaires, participants were randomly allocated to the MBCT program or a wait-list control group. No blinding of study condition was feasible due to the design of the present study (i.e., wait-list control group).

Data collection

Data were collected at four time points: prior to randomization (baseline, (T1)) post-intervention after the 8-week MBCT program (T2), and 3 months (T3) and 6 months (T4) after the intervention. The wait-list control group was not contacted during the study period except from when asked to complete questionnaires at T1, T2, T3, and T4.

MBCT

The 8-week Mindfulness-Based Cognitive Therapy (MCT) intervention generally adhered to the program outlined in the original manual and has been described in detail elsewhere [2]. No pain-specific adaptations were made in the intervention, but as the

main focus in MBI is on the participants' here-and-now experiences and as the women included in the study presented with pain, pain-related issues were predominant in the inquries and group discussions.

All treatment groups were facilitated by an experienced mindfulness instructor with training from Oxford University, receiving supervision from Centre for Mindfulness Research and Practice, Bangor University, UK, during the study.

Measures

Socio-demographic and clinical data

All patients provided socio-demographic information. Clinical data were retrieved from the Danish Breast Cancer Cooperative Group (DBCG) registry, which includes information on diagnosis and treatment of the cancer disease reported by all breast cancer-treating departments [18].

Primary outcome: Pain intensity

All included measures have been described in detail elsewhere [2]. In the present study, we included pain intensity as the primary outcome. Pain intensity was measured with an 11-point Numeric Rating Scale (NRS), which has been shown to be a sensitive and reliable pain measure in cancer patients [19].

Clinical moderators

Data on possible clinical moderators were retrieved from the DBCG registry [18] and included age, ALND, radiotherapy, and endocrine treatment.

Psychological moderators

Possible psychological moderators included psychological distress, adult attachment orientation, and alexithymia.

Psychological distress was assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) [20]. The HADS total score, which has shown good psychometric properties, was used as an overall measure of psychological distress [21].

Adult attachment was measured with the short-form 12-item version of the Experiences in Close Relationships (ECR-S) [22]. The ECR-S consists of the two continuous dimensions anxiety and avoidance and has previously shown good psychometric properties [22].

Alexithymia was measured with the 20-item Toronto Alexithymia Scale (TAS-20) [23]. The TAS-20 yields a total score and scores on three subscales (difficulties describing feelings, difficulties identifying feeling, and externally-oriented thinking). In the present study, alexithymia was investigated as an overall personality trait [24], and only the total score was used.

Statistical analysis

IBM SPSS statistics, v.21 (IBM, Chicago, IL) was used for all analyses. The main effect of MBCT on pain has previously been established using Mixed Linear Models (MLMs). For a full description, see [2].

MLMs were chosen to test the moderation effects over time, i.e., *time* × *group* × *moderator*. The data were hierarchically arranged in two levels, where time at level 1 was nested within individuals at level 2. The best model fit was obtained with a random intercept, a diagonal covariance structure for the residuals, and a log-transformation of time. The individual proposed moderators of the effect were explored in separate models. As expected, a substantial overlap between ALND and radiotherapy (94%) and radiotherapy and ALND (65%) was observed. This overlap was accounted for by the two following analyses: as only n=4 women in the ALND group did not receive radiotherapy, these women were excluded. Thus, the first analysis included all women +/-ALND, all having received radiotherapy, thereby holding radiotherapy constant in the analysis. The moderator was thus defined as radiotherapy +/-ALND. In the second moderator analysis, all women +ALND were excluded, leaving women that had or had not received radiotherapy.

Statistically significant results were defined as $p<0.05$ with a two-tailed significance level. Effect sizes were expressed as Cohen's *d* with 0.2, 0.5, and 0.8 considered a small, medium, and large effect size, respectively [25].

RESULTS

Descriptives

Study flow is shown in Figure 1 [2]. Of the women approached, 20.4% were eligible to participate in the present study. Of the eligible women, 64% were interested in the study of which 41% were enrolled in the trial. The main reason reported by eligible women for not participating in the study was scheduling conflicts.

[Insert Figure 1 near here]

As seen in Figure 1, the dropout rates were unbalanced between study groups, with higher dropout rates in the intervention group at T2. Dropout analyses have been described in detail elsewhere. No statistically significant differences between dropouts and participants returning the questionnaires were found for any primary outcome measures [2]. In the current study, we used logistic regression to further explore whether any of the proposed moderators predicted dropout at T2. This was not the case for any of the moderators (*p*s=0.30-0.92).

Socio-demographic, clinical, and psychological baseline data are summarized in Table 1.

[Insert Table 1 near here]

Primary outcome

Main effects: Pain intensity

In summary, the main effect analyses revealed a statistically significant time × group effect for pain intensity (p=0.002, d=0.61) [2]. As we had included several pain outcomes, we corrected for multiple comparisons using the Benjamini-Hockberg procedure and performed sensitivity analyses, finding that the effect on pain intensity remained statistically significant and robust [2].

Moderators

Clinical moderators

We did not find statistically significant interactions effects for any of the proposed clinical moderators (Table 2). However, when interpreting the results in terms of effect sizes, the effect size for radiotherapy (d=0.49; p=0.075) was small to medium (Table 2). Specifically, +radiotherapy was associated with a smaller effect of MBCT on pain intensity over time compared with –radiotherapy (Figure 2).

[Insert Table 2 and Figure 2 near here]

Psychological moderators

Of the proposed psychological moderators, only attachment avoidance emerged as a statistically significant moderator, corresponding to a small to medium effect size (Table 2). As seen in Figure 3, higher levels of attachment avoidance was associated with a

larger effect of MBCT on pain intensity over time compared with lower levels of attachment avoidance.

[Insert Figure 3 near here]

DISCUSSION

The present study explored a number of possible clinical and psychological moderators of the effect found in a previously reported trial of MBCT on persistent pain. Only adult attachment orientation emerged as a statistically significant moderator of the effect with high attachment avoidance being associated with larger reductions in pain intensity following the intervention. However, when interpreting results in terms of effect sizes, radiotherapy was indicated as a possible moderator of the effect of MBCT on pain intensity. That the result did not reach statistical significance could be due to insufficient statistical power. Taken together, the results point to specific individual differences, i.e., attachment avoidance and radiotherapy, to be investigated further, which may be of clinical value when attempting to identify patients for whom MBCT may be most efficacious in reducing persistent pain.

Attachment avoidance emerged as the only statistically significant moderator of the effect of MBCT on pain intensity. Specifically, women with higher levels of attachment avoidance experienced larger reductions in pain intensity following MBCT when compared with women with lower levels of attachment avoidance. In a previous study

based on a (non-cancer) convenience sample and with stress as the primary outcome, the same pattern was observed, with higher levels of insecure attachment predicting greater stress reduction compared with secure attachment [26]. However, in this study, attachment anxiety and attachment avoidance were collapsed into insecure attachment [26] and thus, the possible differential roles of the two dimensions were not explored [15].

We did not find statistically significant interaction effects for the remaining proposed psychological moderators, namely baseline psychological distress and alexithymia, suggesting that initial psychological distress levels and alexithymia do not influence the effect of MBCT on pain intensity. With respect to baseline psychological distress, the existing studies report mixed results [7,10–12], with the comparison of study results being further complicated by the different (non-pain) outcomes used in the available studies, as the moderating role of psychological distress may vary across outcomes. Regarding alexithymia, ours is the first study to explore alexithymia as a possible moderator of MBI and the results should therefore be considered preliminary. In future studies, the conceptualization of alexithymia should be addressed, as the concept of 'secondary alexithymia', defined as a state-reaction to medical illness [27], may challenge the conceptualization of alexithymia as a trait-related moderator construct, suggesting that alexithymia could also be considered a possible outcome of treatment.

None of the proposed clinical moderators reached statistical significance. Clinically, this could be interpreted as suggesting that women treated for breast cancer with persistent

pain may benefit equally from MBCT across age groups, with or without having undergone radiotherapy, with or without the combination of ALND and radiotherapy, and with or without endocrine treatment. However, due to the considerable overlap between ALND and radiotherapy, we conducted moderation analyses with selected subgroups. As this may compromise statistical power, the results were interpreted in terms of their effect sizes, with the moderating effect of radiotherapy corresponding to a small to moderate size effect. Women who had received radiotherapy showed a trend towards smaller effects of MBCT on pain intensity compared with women who had not received radiotherapy. One tentative interpretation of this result could be that pain attributed to tissue- and nerve damages potentially caused by radiotherapy may be less susceptible to change following a psychological intervention such as MBCT.

Strengths of the present study include a randomized controlled, longitudinal design, inclusion of patients based on their initial pain levels, and inclusion of one primary outcome with a clinically relevant and statistically robust effect [2]. Some limitations should also be noted. First, as we did not include an active control group, it cannot be inferred from the results that the reduction in pain intensity was attributable to the proposed MBCT-specific change mechanisms (e.g., mindfulness, self-compassion). As a consequence, the moderators found in this study may also not be MBCT-specific. Second, due to the characteristics of the present sample, the independent moderator effect of ALND could not be addressed. However, as the large overlap between radiotherapy and ALND is representative of the patients treated at oncology departments (cf. the DBCG treatment protocols [18]), exploring the moderator effect of ALND in

combination with radiotherapy arguably has higher external validity compared to exploring the moderator effect of ALND independently. Third, there was a relatively large, unbalanced dropout at T2. We therefore previously tested whether dropout was related to the primary outcome and found no suggestions that this was the case, as pain intensity did not predict dropout at T2 (OR: 0.96, p=0.69). For the women whose reasons for dropout were available to us, the most common reason to dropout was scheduling conflict. Fourth, while we proposed several clinical and psychological moderators of the effect of MBCT on pain intensity, we did not adjust for multiple comparisons, as this could increase the risk of type-2 error, and recommend that the results are interpreted in terms of their effect sizes. Finally, as ours is the first study to investigate the possible moderating role of the proposed clinical and psychological moderators in the present context of MBI for persistent pain in women treated for breast cancer, the analyses are explorative, and should therefore be considered preliminary.

CONCLUSION

Taken together, our results showed that the effect of MBCT on pain intensity was moderated by attachment avoidance, with women with higher levels of attachment avoidance showing greater treatment gains following the intervention compared with women with lower levels of attachment avoidance. Although only statistically near-significant, we also found a trend indicating that women who had not received radiotherapy experienced larger reductions in pain intensity following the intervention

compared with women who had received radiotherapy. The present study may have clinically valuable implications in terms of identifying patients who may benefit most from MBCT as a pain intervention.

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FIGURE LEGENDS

Figure 1

CONSORT study flow diagram

Figure 2

Interaction effects of radiotherapy on pain intensity (11-point Numeric Rating Scale, (NRS))

Figure 3

Interaction effects of attachment avoidance on pain intensity (11-point Numeric Rating Scale, (NRS))

Table 1

Socio-demographic and clinical characteristics of study sample at baseline[a]

	MBCT group (n=67)	**Control group (n=62)**	***p*[c]**
DEMOGRAPHICS[b]			
Age (years), Mean (SD) [N]	56.8 (9.99)	56.7 (8.10)	0.96
Marital status, N (%)			0.50
Married/cohabiting	47 (70.1)	40 (64.5)	
Not cohabiting/single	20 (29.9)	22 (35.5)	
Educational level, N (%)[c]			0.18
Lower (<2 years of further education)	21 (31.3)	28 (45.2)	
Medium (2-4 years of further education)	36 (53.7)	29 (46.8)	
Long (≥5 years of further education)	9 (13.4)	4 (6.5)	
Missing	1 (1.5)	1 (1.6)	
Occupational status, N (%)			0.53
Full- or part-time employed	29 (43.3)	22 (35.5)	
Unemployed or on sickness benefit	10 (14.9)	8 (12.9)	
Retired	24 (35.8)	28 (45.2)	
Missing	4 (6.0)	4 (6.5)	

CLINICAL CHARACTERISTICS			
Time since surgery (months),	40.0 (24.56) [66]	43.2 (34.82) [62]	0.54
Mean (SD) [N]			
Tumor size, N (%)			0.42
≤ 20 mm	36 (53.7)	30 (48.4)	
> 20 mm ≤ 50 mm	27 (40.3)	31 (50.0)	
> 50 mm	1 (1.5)	0 (0.0)	
Not reported	3 (4.5)	1 (1.6)	
Type of surgery, N (%)			0.26
Mastectomy	27 (40.3)	32 (51.6)	
Lumpectomy	38 (56.7)	30 (48.4)	
Not reported	2 (3.0)	-	
Axillary Lymph Node Dissection (ALND), N (%)			0.32
Yes	39 (58.2)	32 (51.6)	
No	26 (38.8)	28 (45.2)	
Not reported	2 (3.0)	2 (3.2)	
ER status, N (%)[e]			0.29
Positive (≥1%)	55 (82.1)	55 (88.7)	
Negative (<1%)	12 (17.9)	7 (11.3)	
HER2 status, N (%)			0.48
Positive	6 (9.0)	8 (12.9)	
Negative	54 (9.0)	46 (74.2)	

Not reported	8 (11.9)	6 (9.7)	
Chemotherapy, N (%)			0.47
Yes	38 (56.7)	39 (62.9)	
No	29 (43.3)	23 (37.1)	
Radiotherapy, N (%)			0.20
Yes	54 (80.6)	48 (77.4)	
No	7 (10.4)	12 (19.4)	
Not reported	6 (9.0)	2 (3.2)	
Endocrine treatment, N (%)			0.26
Yes	46 (68.7)	48 (77.4)	
No	21 (31.3)	14 (22.6)	
Active endocrine treatment during study period, N (%)			0.42
Yes	41 (61.2)	40 (64.5)	
No	5 (7.5)	8 (12.9)	
PRIMARY OUTCOME MEASURE			
Pain intensity (11-point NRS), Mean (SD) [N]	5.5 (2.09) [60]	5.3 (2.56) [56]	0.57
PSYCHOLOGICAL MEASURES			
HADS total score[f], Mean (SD) [N]	16.5 (6.66) [67]	18.1 (7.47) [61]	0.22
ECR-SF[g], Mean (SD) [N]			
Anxiety	22.2 (6.87) [67]	23.8 (7.53) [61]	0.21

Avoidance	17.9 (7.67) [66]	19.0 (8.16) [61]	0.41
TAS-20[h], Mean (SD) [N]	44.8 (12.2) [67]	46.6 (11.6) [61]	0.39

[a]The total sample consists of 129 women

[b]When reporting categorical variables, number of patients and percent are shown. When reporting continuous variables, Mean (M), Standard Deviation (SD), and number of patients [N] are shown

[c]Statistically significant group differences ($p<0.05$) are shown in boldface

[d] "Further education" refers to years of education further than high school

[e]The number of women with ER-positive tumors and the number of women receiving endocrine treatment differs slightly. This can be explained by i) the indication for endocrine treatment was changed in 2010 (from $\geq$10% to $\geq$1% ER-positive tumor cells), thus women with 1-9% ER-positive tumor cells treated prior to 2010 were not offered endocrine treatment, ii) a number of patients will have declined receiving endocrine treatment or may have ended their endocrine treatment prematurely due to side effects

[f]The Hospital and Depression Scale [20]

[g]The Experiences-in-Close-Relationships-Scale Short Form [22]

[h]The 20-item Toronto Alexithymia Scale [23]

Table 2

Results from moderation analyses in mixed linear models

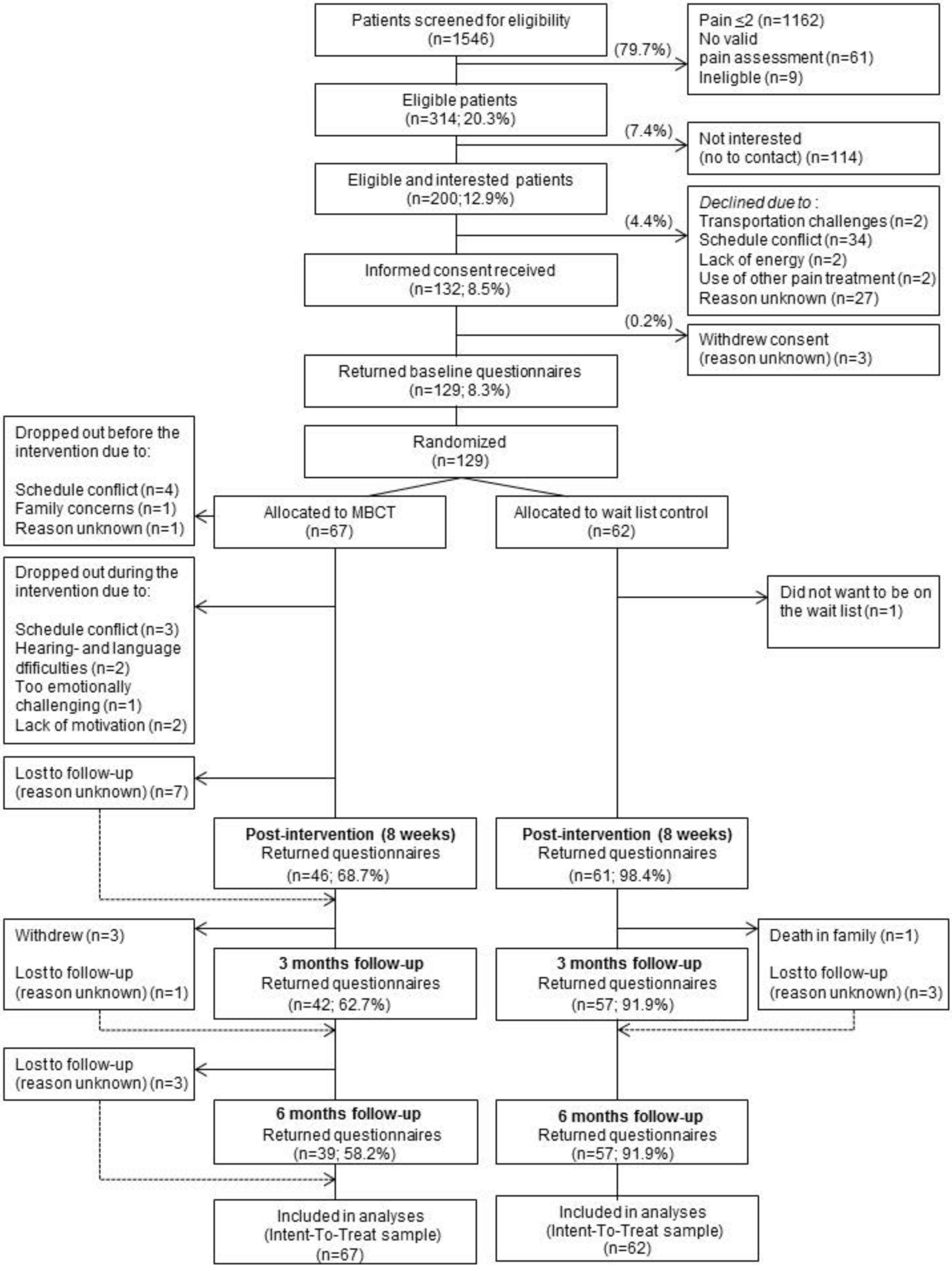
	F	*p*[a]	95% Confidence Intervals (CI)	*d*
Clinical moderators				
Age	0.3	0.582	-0.13 – 0.23	0.08
Active endocrine treatment during study period	1.1	0.300	-0.36 – 1.66	0.16
Radiotherapy	3.3	0.075	-0.56 – 11.45	0.49
Radiotherapy +/-Axillary Lymph Node Dissection	2.5	0.113	-0.72 – 6.64	0.28
Psychological moderators				
Psychological distress (HADS[b])	0.8	0.375	-0.33 – 0.12	0.14
Adult attachment: anxiety (ECR-SF[c])	1.1	0.303	-0.32 – 0.10	0.17
Adult attachment: avoidance (ECRS-SF[c])	**5.1**	**0.026**	**-0.42 - -0.03**	**0.36**
Alexithymia (TAS-20[d])	0.1	0.707	-0.16 – 0.11	0.06

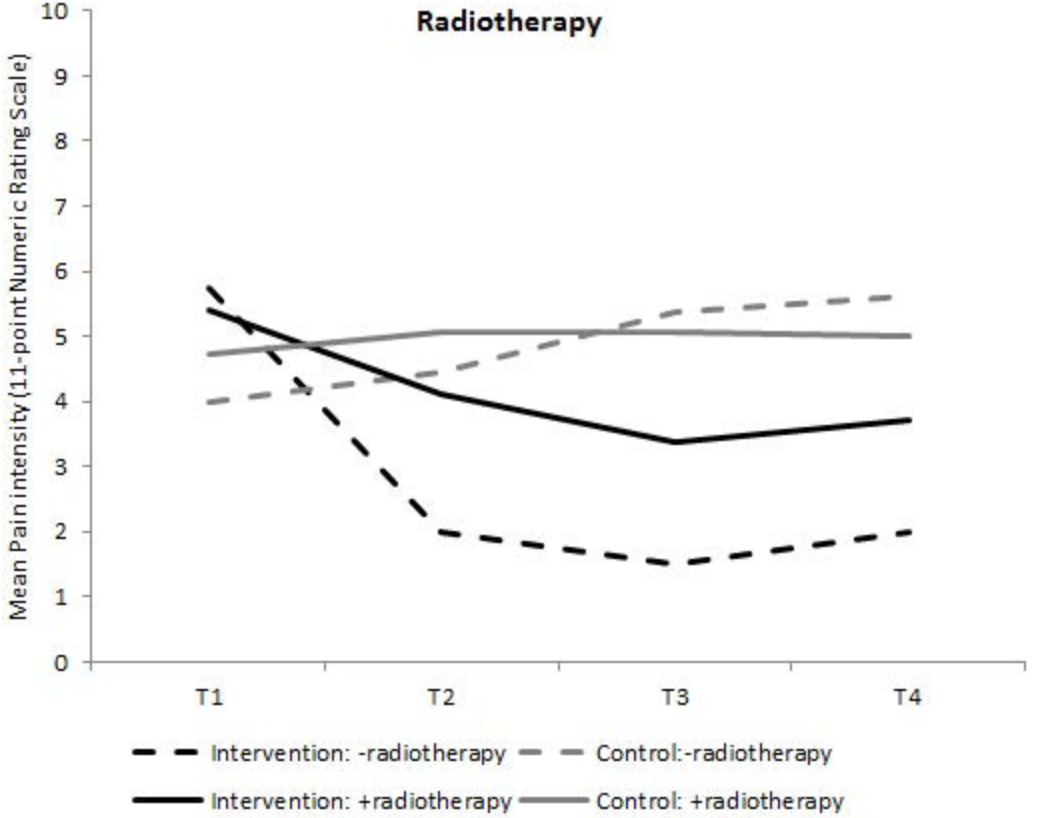
[a]Statistically significant results are shown in bold face

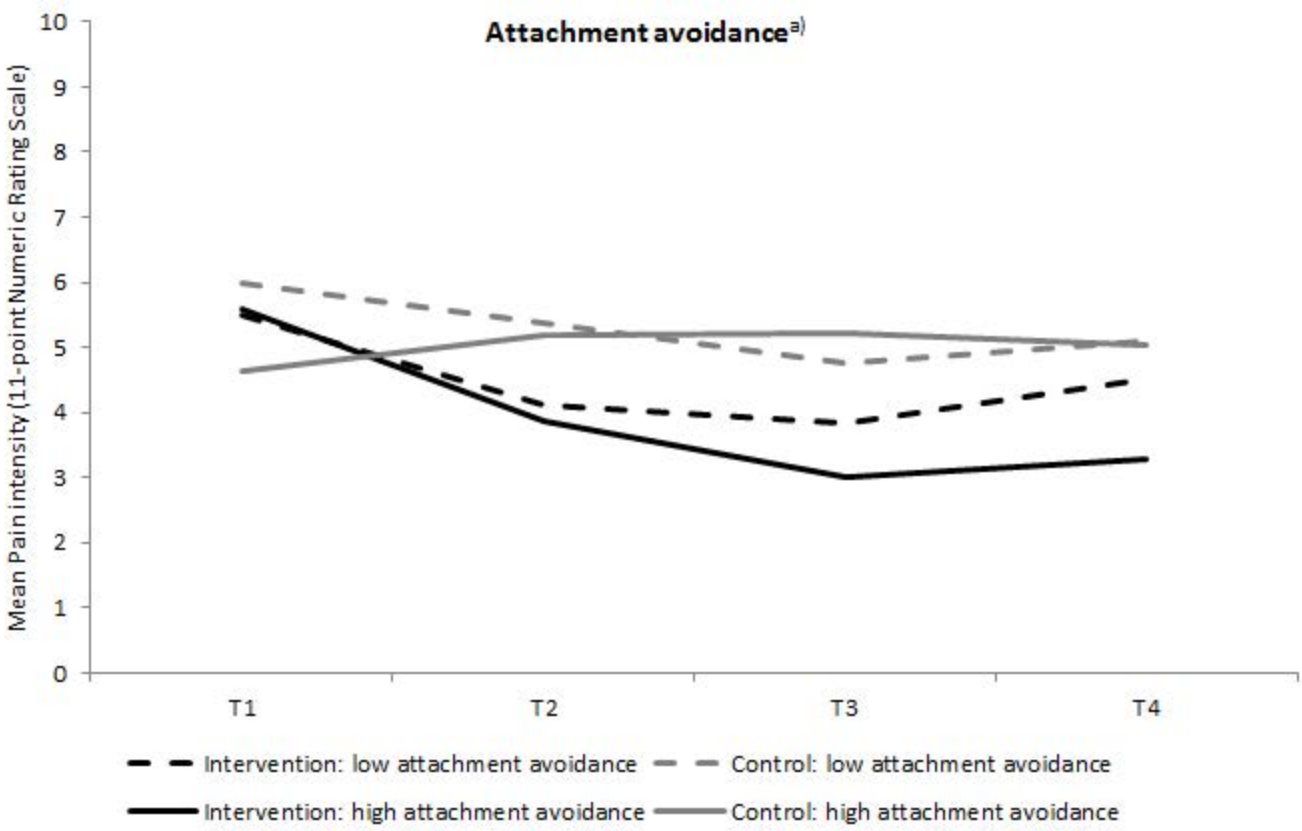
[b]The Hospital Anxiety and Depression Scale [20]

[c]The Experiences in Close Relationships Scale Short Form [22]

[d]The 20-item Toronto Alexithymia Scale [23]


Patients screened for eligibility (n=1546)
(79.7%)
Pain ≤2 (n=1162)
No valid pain assessment (n=61)
Ineligble (n=9)
Eligible patients (n=314; 20.3%)
(7.4%)
Not interested (no to contact) (n=114)
Eligible and interested patients (n=200;12.9%)
(4.4%)
Declined due to :
Transportation challenges (n=2)
Schedule conflict (n=34)
Lack of energy (n=2)
Use of other pain treatment (n=2)
Reason unknown (n=27)
Informed consent received (n=132; 8.5%)
(0.2%)
Withdrew consent (reason unknown) (n=3)
Returned baseline questionnaires (n=129; 8.3%)
Randomized (n=129)
Dropped out before the intervention due to:
Schedule conflict (n=4)
Family concerns (n=1)
Reason unknown (n=1)
Allocated to MBCT (n=67)
Allocated to wait list control (n=62)
Dropped out during the intervention due to:
Schedule conflict (n=3)
Hearing- and language dfificulties (n=2)
Too emotionally challenging (n=1)
Lack of motivation (n=2)
Did not want to be on the wait list (n=1)
Lost to follow-up (reason unknown) (n=7)
Post-intervention (8 weeks) Returned questionnaires (n=46; 68.7%)
Post-intervention (8 weeks) Returned questionnaires (n=61; 98.4%)
Withdrew (n=3)
Lost to follow-up (reason unknown) (n=1)
3 months follow-up Returned questionnaires (n=42; 62.7%)
3 months follow-up Returned questionnaires (n=57; 91.9%)
Death in family (n=1)
Lost to follow-up (reason unknown) (n=3)
Lost to follow-up (reason unknown) (n=3)
6 months follow-up Returned questionnaires (n=39; 58.2%)
6 months follow-up Returned questionnaires (n=57; 91.9%)
Included in analyses (Intent-To-Treat sample) (n=67)
Included in analyses (Intent-To-Treat sample) (n=62)


Radiotherapy
Mean Pain intensity (11-point Numeric Rating Scale)
10
9
8
7
6
5
4
3
2
1
0
T1
T2
T3
T4
Intervention: -radiotherapy
Control:-radiotherapy
Intervention: +radiotherapy
Control: +radiotherapy



[a)]Low versus high attachment avoidance were based on the median (median=18.4)