



Web-Based Stress Management for Newly Diagnosed Patients With Cancer (STREAM): A Randomized, Wait-List Controlled Intervention Study

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ABSTRACT

Purpose

Being diagnosed with cancer causes major psychological distress; however, a majority of patients lack psychological support during this critical period. Internet interventions help patients overcome many barriers to seeking face-to-face support and may thus close this gap. We assessed feasibility and efficacy of Web-based stress management (STREAM [Stress-Aktiv-Mindern]) for newly diagnosed patients with cancer.

Patients and Methods

In a randomized controlled trial, patients with cancer who had started first-line treatment within the previous 12 weeks were randomly assigned to a therapist-guided Web-based intervention or a wait-list (control), stratified according to distress level (≥ 5 v < 5 on scale of 0 to 10). Primary efficacy end point was quality of life after the intervention (Functional Assessment of Chronic Illness Therapy–Fatigue). Secondary end points included distress (Distress Thermometer) and anxiety or depression (Hospital Anxiety and Depression Scale). Treatment effect was assessed with analyses of covariance, adjusted for baseline distress.

Results

A total of 222 of 229 screened patients applied online for participation. Between September 2014 and November 2016, 129 newly diagnosed patients with cancer, including 92 women treated for breast cancer, were randomly assigned to the intervention ($n = 65$) or control ($n = 64$) group. Adherence was good, with 80.0% of patients using $\geq$ six of eight modules. Psychologists spent 13.3 minutes per week (interquartile range, 9.5–17.9 minutes per week) per patient for online guidance. After the intervention, quality of life was significantly higher (Functional Assessment of Chronic Illness Therapy–Fatigue: mean, 8.59 points; 95% CI, 2.45 to 14.73 points; $P = .007$) and distress significantly lower (Distress Thermometer: mean, -0.85 ; 95% CI, -1.60 to -0.10 ; $P = .03$) in the intervention group as compared with the control. Changes in anxiety or depression were not significant in the intention-to-treat population (Hospital Anxiety and Depression Scale: mean, -1.28 ; 95% CI, -3.02 to 0.45 ; $P = .15$). Quality of life increased in the control group with the delayed intervention.

Conclusion

The Web-based stress management program STREAM is feasible and effective in improving quality of life.

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ASSOCIATED CONTENT



Appendix
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Data Supplement
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INTRODUCTION

Diagnosis of cancer elicits high levels of distress in a majority of patients,¹ which is associated with decreased quality of life as well as diminished treatment tolerance^{2,3} and potentially worse disease course.^{4,5}

Psychosocial support for patients with cancer is effective in alleviating distress and improving quality of life, including fatigue, the most common complaint of patients with cancer.^{2,6} However, a majority of newly diagnosed patients with cancer lack psychosocial support because of constraints on the part of both providers and patients.^{6,7} Use of the Internet, which

has become an integral part of our lives, has the potential to change this. At least 70% of patients with cancer use the Internet as a source of information shortly after diagnosis,⁸ making it a powerful platform for reaching these patients. Recent approaches to integrating the Internet into patient care range from patient forums to information sites and even therapeutic games.^{9,10} Internet programs based on cognitive behavioral techniques with patient guidance via regular online contact with a health care professional (ie, therapist-guided programs or guided self-help) have emerged as particularly effective options. For a range of psychological disorders, including anxiety disorders and depression in those without cancer,^{11,12} therapist-guided online interventions seem similarly effective as face-to-face interventions.¹³ The success of Web-based guided self-help in psychological disorders^{9,13} coupled with the need to further improve access to psychosocial support for patients with cancer, especially outside of inner cities with large cancer centers,⁶ has boosted interest in online interventions in oncology. Numerous piloted and ongoing trials in patients with cancer seek to define suitable indications, formats, and settings.¹⁴ The few larger published randomized controlled trials¹⁵⁻¹⁷ show encouraging results, with improvement in a number of relevant psychosocial domains, including coping with cancer,¹⁵ sexual functioning,¹⁶ and distress¹⁷ in breast cancer survivors.

We designed the STREAM (Stress-Aktiv-Mindern) intervention specifically for the particularly vulnerable period immediately after first diagnosis of cancer.¹⁸ The rationale behind this early intervention was three-fold. First, distress in patients with cancer peaks shortly after diagnosis,¹⁸ irrespective of cancer type. Second, the time after diagnosis is busy with appointments for diagnostics and treatment. Therefore, the self-management of time and location allowed by Web-based interventions⁹ might be of particular value. Third, successful early psychosocial interventions have shown potential to affect disease course beyond psychosocial outcomes.¹⁹ We assessed feasibility and efficacy of our therapist-guided Web-based stress management program STREAM for newly diagnosed patients with cancer receiving first-line treatment.

PATIENTS AND METHODS

Details are provided in the Appendix (online only) and the published protocol.²⁰ We included adult patients (age ≥ 18 years) with newly

diagnosed cancer who started first-line treatment (either systemic treatment, including chemotherapy, hormonal treatment, or targeted therapy, or radiotherapy) no longer than 12 weeks before study registration. Patients were required to provide written informed consent, read and write in German, and have Internet access as well as basic computer skills. The ethics committee approved the study (EKNZ339/13). Patients were recruited online via the STREAM Web site of STREAM. We randomly assigned eligible patients at a ratio of one to one using blocked randomization with randomly selected block sizes to an intervention group or a wait-list control group (Fig 1). Patients were stratified according to baseline distress using an internationally accepted cutoff of ≥ 5 points on the 10-point visual analog scale (VAS) of the Distress Thermometer (DT).²¹

Intervention

We developed the Web-based intervention STREAM²⁰ based on established stress management intervention manuals²² that incorporate cognitive behavioral- and mindfulness-based stress reduction techniques, which we adapted to the Web context. STREAM consists of eight modules (Appendix Table A1, online only), which can be completed in 60 to 90 minutes each. Daily use of downloadable audio files with relaxation and guided-imagery exercises was encouraged. Participants were asked to complete one module per week. Our therapists provided weekly written feedback via integrated secured e-mail.

Patients in the control group underwent their cancer treatment locally as planned and were recontacted by the study team 8 weeks after random assignment (T2; Fig 1). After T2 assessments, they received access to the online program. For patients in both groups, cancer treatment was determined locally, and supportive care according to local standards may also have included face-to-face psychosocial support and psychotropic drugs.

Assessments

Assessments were conducted electronically directly within the Web-based program via the open source application LimeSurvey at baseline (T1) and after the intervention or waiting period (control group), respectively (T2). In addition, 2-month follow-up (T3) was performed in both groups.

Efficacy End Points

Primary end point was quality of life at T2, assessed using the validated German version of the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire.²³ Minimal clinically meaningful differences are not well defined but have previously been set between 7 and 9 points, both as intraindividual changes and differences in groups.^{19,24}

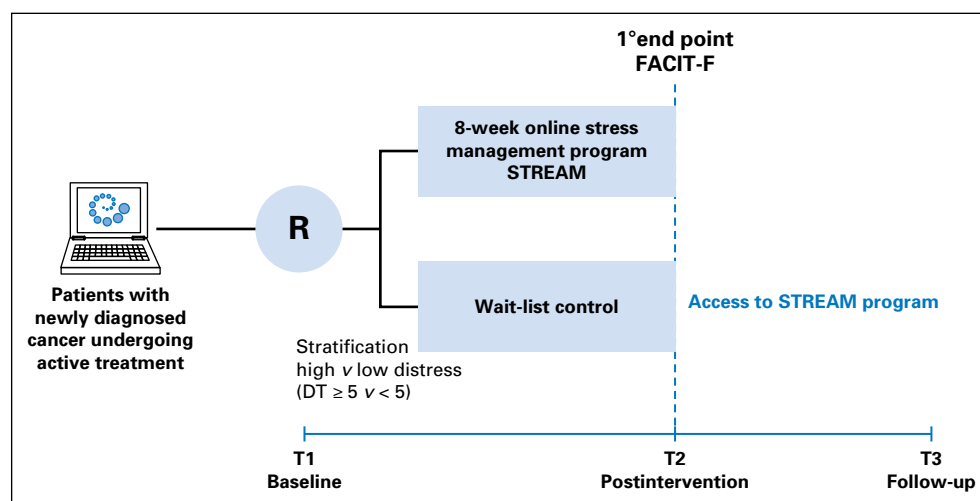


Fig 1. Trial design. DT, Distress Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; STREAM, Stress-Aktiv-Mindern.

Secondary efficacy end points were assessed at the same points in time and evaluated psychological distress and anxiety or depression using the validated German versions of the National Comprehensive Cancer Network DT²¹ and the Hospital Anxiety and Depression Scale (HADS),²⁵ respectively. Effect sizes are expressed as partial eta squared (η^2_p),²⁶ with the following cutoffs to categorize effect sizes into small (0.01), medium (0.06), and large (0.14), as suggested by Cohen.²⁷

Assessments During Intervention

Usability was evaluated after the first and last module with the System Usability Scale; scores > 70 represent good usability.²⁸ Therapeutic alliance between patients and the online therapist was assessed using the Working Alliance Inventory in its short form (12 items)²⁹ after each module. Total score ranges from 0 to 5, and scores > 3.5 have been rated as good working alliances.³⁰

Statistical Analyses and Sample Size Calculation

All analyses were performed in the intention-to-treat (ITT) population defined as all patients who were randomly assigned. The per-protocol (PP) population included all patients who underwent the program in the intended timeframe (ie, the time between random assignment and T2 assessments did not exceed 16 weeks, which is twice the minimal duration of the program). To demonstrate a 9-point difference³¹ in FACIT-F total score between baseline and T2 (after 8 weeks) in the intervention group with a statistical power of 0.80 at a significance level of .05 (two sided), 60 participants were needed in each of the two conditions.

Efficacy Analyses

Efficacy outcomes were modeled with analysis of covariance (ANCOVA), using postscore (T2) as the dependent variable, prescore (T1) as the covariate, and group allocation (intervention v control) as the independent variable. ANCOVAs were further adjusted for the stratification factor distress ($DT \geq 5$ v < 5). For the follow-up period, score changes from T2 to T3 were analyzed with paired *t* tests, separately for each group (no between-group comparisons). Multiple imputations ($n = 99$) by chained equations³² using predictive mean matching³³ incorporating all variables of the linear models underlying ANCOVA were used to impute missing outcome values.³⁴ To assess the robustness of the results, sensitivity analyses were conducted for all outcomes in the PP population. In addition, sensitivity analyses were carried out using other methods for handling missing data; more specifically, complete-case analyses and last observation carried forward analyses, as specified in the protocol,²⁰ were computed for all outcomes in both the ITT and PP populations.

RESULTS

We screened 229 patients, of whom 129 were randomly assigned between September 11, 2014, and November 24, 2016 (Fig 2). All patients received first-line cancer treatment, which they started a median of 17 days (interquartile range [IQR], 6-22 days) and 14 days (IQR, 7-20 days) after signing informed consent in the intervention and control groups, respectively. Patients were residents of Switzerland ($n = 64$), Germany ($n = 59$), Austria ($n = 5$), and the United Kingdom ($n = 1$). Medical, psychological, and socioeconomic baseline characteristics are listed in Table 1 and were balanced between the groups. All 21 patients (control group, $n = 10$; intervention group, $n = 11$) who scored 1 point in the Beck Depression Inventory suicide item at baseline were immediately contacted by telephone, but they clearly distanced themselves from acute suicidal intent.

The intervention was designed to be feasible within 8 weeks. However, median duration of the online intervention (between

first login to module one and postintervention assessment at T2) was 11.7 weeks (IQR, 9.1-18.6 weeks). In the intervention group, 52 patients (80.0%) used at least six modules, and 49 (75.4%) worked with all eight modules. Our psychologists spent a median time of 165 minutes (IQR, 127-210 minutes) for administering the online intervention (ie, 13.3 minutes [IQR, 9.5-17.9 minutes] per patient each week). Usability of the program was rated high, with a mean System Usability Scale score of 87.5 (IQR, 81.2-95.0) after module one and of 90.0 (IQR, 82.5-95.0) after module eight. As a measure of the therapeutic relationship between patient and online therapist, patients reported a mean score in the Working Alliance Inventory questionnaire of 3.77 (IQR, 3.38-4.14), similar to that of previously reported online working alliances.³⁰

Primary and secondary efficacy outcomes are listed in Table 2 and illustrated in Figures 3 and 4. Quality of life (FACIT-F) after the intervention (T2; the primary end point) was significantly higher in the intervention group as compared with the control group (ANCOVA $P = .007$; Table 2). With a mean increase in total FACIT-F score of 8.59 (95% CI, 2.45 to 14.73; $P = .007$) in the ITT population and of 10.71 (95% CI, 4.49 to 16.94; $P = .001$) in the PP population, changes were clinically meaningful.^{19,24} Effect sizes were medium²⁷ ($\eta^2_p = 0.063$ and 0.114 in the ITT and PP populations, respectively; Table 2). Increased scores within the fatigue (4.51; 95% CI, 1.81 to 7.22; $P = .002$), physical well-being (2.01; 95% CI, 0.43 to 3.59; $P = .01$), and functional well-being subscales (1.53; 95% CI, 0.11 to 2.95; $P = .04$) were major contributors to the increase in total FACIT-F score, whereas social well-being and emotional well-being scores were not (Table 2.).

Distress on the VAS (scored from 0 to 10) of the National Comprehensive Cancer Network DT was significantly lower at T2 in the intervention group as compared with the control (-0.85 ; 95% CI, -1.60 to -0.10 ; $P = .03$). As summarized in Table 2, anxiety and depression (HADS) after the intervention (T2) were not significantly lower in the intervention as compared with the control group ($P = .15$) in the ITT population. However, decrease in HADS score was statistically significant in the PP population (-2.09 ; 95% CI, -4.03 to -0.16 ; $P = .03$). All results were confirmed in the prespecified sensitivity analyses (Appendix Table A2). Figure 4 shows the percentage of patients who reported any changes in scores between baseline and T2 for all three assessment tools.

During the 2-month follow-up period of the intervention group (T2 to T3), quality of life (FACIT-F T2 to T3: mean, 4.69; 95% CI, -0.74 to 10.12; $P = .09$), distress (DT T2 to T3: mean, -0.29 ; 95% CI, -1.03 to 0.44; $P = .4$), and mood (HADS T2 to T3: mean, -0.82 ; 95% CI, -2.28 to 0.65; $P = .27$) did not change significantly. In the follow-up phase (ie, after T2), 51 (79.7%) of 64 patients randomly assigned to the control arm opted to start the STREAM program. For this group of patients, T2 represents the assessments immediately before and T3 the assessments immediately after the online program. In an ITT analysis ($n = 64$), quality of life increased significantly (FACIT-F T2 to T3: mean, 10.95; 95% CI, 6.18 to 15.71; $P < .001$) and distress decreased significantly (DT T2 to T3: mean, -1.25 ; 95% CI, -1.95 to -0.55 ; $P = .001$) between T2 and T3. Self-reported anxiety and depression were also lower (HADS T2 to T3: mean, -2.83 ; 95% CI, -4.29 to -1.36 ; $P < .001$). Again, results were confirmed in the prespecified sensitivity analyses (Appendix Table A3, online only).

Data for individual patients and group means are shown in Appendix Figure A1 (online only).

DISCUSSION

In this randomized controlled trial, newly diagnosed patients with cancer reported significantly better quality of life and lower distress on the DT after participating in the therapist-guided Web-based stress management program STREAM. Recruitment to the STREAM study via online channels was successful, and patients in

three countries, corresponding to a geographic area twice as large as the United Kingdom, were reached. Thus, dissemination of psychosocial interventions beyond urban centers, where face-to-face psychosocial interventions are available,³⁵ can be facilitated by a Web-based approach. The STREAM intervention was feasible in our population of patients during a period of active treatment of different types of cancer with good adherence; 80% of patients worked with at least six of the eight modules.¹⁶

Although it is indisputable that quality of life matters, it is also inherently difficult to measure.³⁶ To ensure robust and clinically relevant data, we rely on well-validated and standardized questionnaires.^{1,23,25}

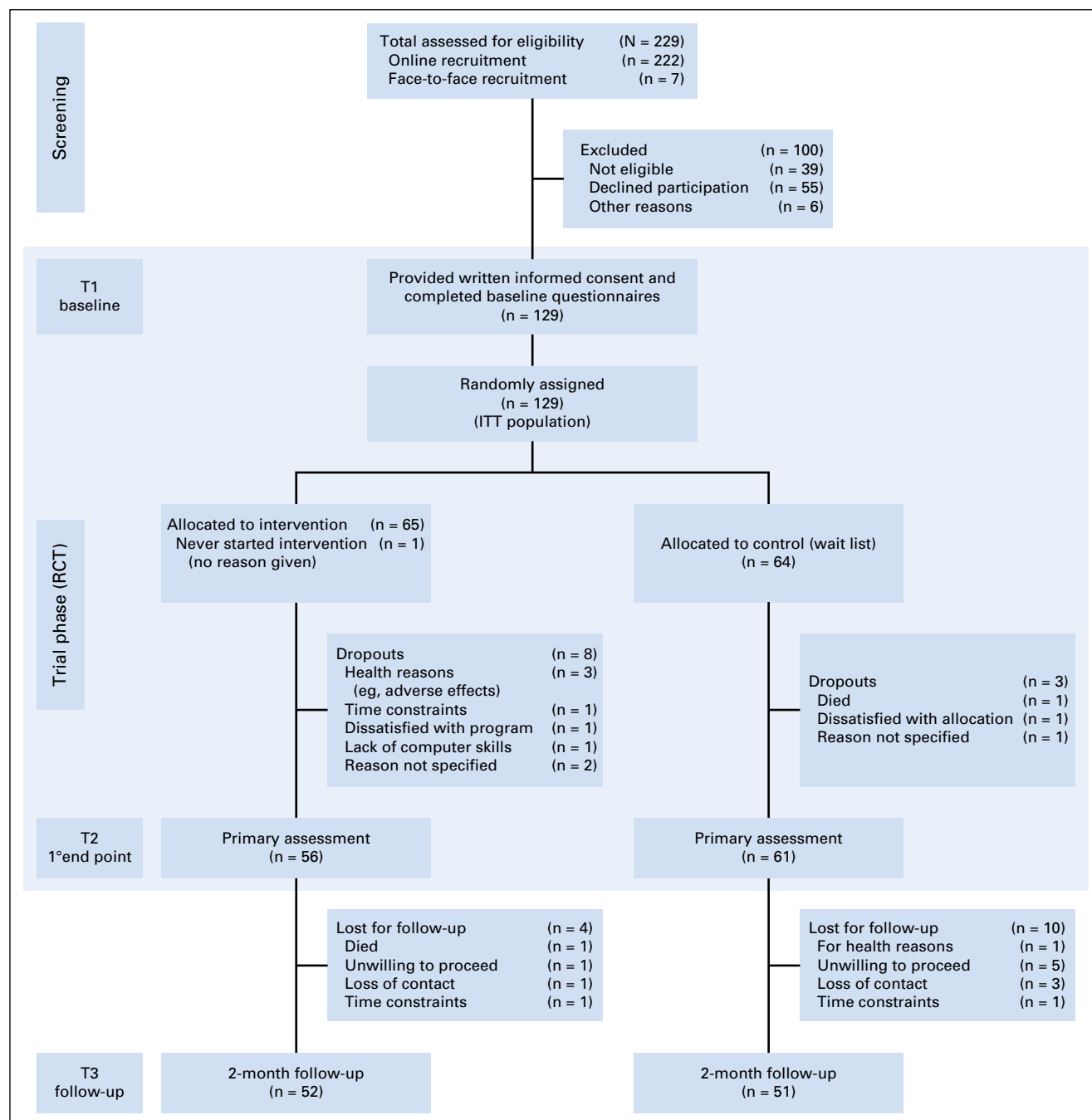


Fig 2. Patient flow (CONSORT diagram). ITT, intention to treat; RCT, randomized controlled trial.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	No. (%)		
	All Patients (N = 129)	Control Group (n = 64)	Intervention Group (n = 65)
Age, years			
Median	52	53	51
IQR	46-58	46-58	46-57
Sex			
Female	109 (84.5)	56 (87.5)	53 (81.5)
Male	20 (15.5)	8 (12.5)	12 (18.5)
Tumor origin			
Breast	92 (71.3)	47 (73.4)	45 (69.2)
Gynecologic tract	7 (5.4)	5 (7.8)	2 (3.1)
Lung	5 (3.9)	3 (4.7)	2 (3.1)
CNS/head and neck	4 (3.1)	1 (1.6)	3 (4.6)
Lymphoma	11 (8.5)	4 (6.2)	7 (10.8)
Skin/soft tissue	1 (0.8)	1 (1.6)	0 (0.0)
GI tract	7 (5.4)	2 (3.1)	5 (7.7)
Urogenital tract	2 (2.0)	1 (1.6)	1 (1.5)
Disease stage			
Localized	111 (86.0)	55 (85.9)	56 (86.2)
Metastatic	18 (14.0)	9 (14.1)	9 (13.8)
Treatment			
Radiotherapy	16 (12.4)	8 (12.5)	8 (12.3)
Chemotherapy	75 (58.1)	40 (62.5)	35 (53.8)
Hormonal therapy	32 (24.8)	14 (21.9)	18 (27.7)
Radiochemotherapy	4 (3.1)	1 (1.6)	3 (4.6)
Other	2 (1.6)	1 (1.6)	1 (1.5)
Treatment goal			
Curative	117 (90.7)	58 (90.6)	59 (90.8)
Palliative	12 (9.3)	6 (9.4)	6 (9.2)
Marital status			
Married	81 (62.8)	39 (60.9)	42 (64.4)
Married, separated	2 (1.6)	1 (1.6)	1 (1.5)
Single	26 (20.2)	12 (18.8)	14 (21.5)
Divorced	16 (12.4)	9 (14.1)	7 (10.8)
Widowed	4 (3.1)	3 (4.7)	1 (1.5)
Highest education			
Compulsory school	2 (1.6)	1 (1.6)	1 (1.5)
Apprenticeship	32 (24.8)	16 (25.0)	16 (24.6)
College	44 (34.1)	19 (29.7)	25 (38.5)
University	48 (37.2)	25 (39.1)	23 (35.4)
Other	3 (2.3)	3 (4.7)	0 (0.0)
Monthly household income, € (n = 107)			
< 1,200	2 (1.9)	0 (0.0)	2 (3.8)
1,200-2,500	7 (6.5)	6 (11.1)	1 (1.9)
2,500-4,900	35 (32.7)	18 (33.3)	17 (32.1)
4,900-8,100	36 (33.6)	18 (33.3)	18 (34.0)
8,100-12,200	19 (17.8)	9 (16.7)	10 (18.9)
> 12,200	8 (7.5)	3 (5.6)	5 (9.4)
Using complementary medicine (n = 116)			
Yes	31 (26.7)	17 (30.4)	14 (23.3)
No	51 (44.0)	23 (41.1)	28 (46.7)
I don't know	34 (29.3)	16 (28.6)	18 (30.0)
Currently seeing a therapist			
Yes	45 (34.9)	27 (42.2)	18 (27.7)
No	84 (65.1)	37 (57.8)	47 (72.3)
Currently using psychotropic drugs			
Yes	17 (13.2)	11 (17.2)	6 (9.2)
No	111 (86.0)	53 (82.8)	58 (89.2)
I don't know	1 (0.8)	0 (0)	1 (1.5)

(continued in next column)

Table 1. Baseline Demographic and Clinical Characteristics (continued)

Characteristic	No. (%)		
	All Patients (N = 129)	Control Group (n = 64)	Intervention Group (n = 65)
Baseline FACIT-F score			
Median	106.0	108.3	101.0
IQR	84.2-123.0	87.8-124.0	81.0-120.0
Baseline distress (DT)			
Low	30 (23.3)	14 (21.9)	16 (24.6)
High (score $\geq$ 5)	99 (76.7)	50 (78.1)	49 (75.4)
Baseline HADS score			
Median	12	12	13
IQR	7-17	7-16	7-18

NOTE. No significant differences ($P < .05$) between groups were identified for any category (as determined by Wilcoxon or Kruskal-Wallis test or Pearson χ^2 test).

Abbreviations: DT, Distress Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range.

There is no clear cutoff for clinically meaningful increases in overall quality of life in the FACIT-F score. However, on the basis of previous studies, changes reported in the postintervention scores of this trial were in a range that is considered highly noticeable to patients.^{19,24} Quality-of-life analyses are often complicated by a large number of missing data. In our study, the low number of missing data (90.7% of all randomly assigned patients completed the primary assessment at T2) and robustness of the sensitivity analyses (Appendix Tables A2 and A3), increase reliability of patient-reported outcomes.

Although the primary efficacy end point of better quality of life after the STREAM intervention was clearly met, the effect of the intervention on distress is less clear cut. The DT is an assessment tool that allows patients to summarize all subjective aspects of distress in a single number (VAS, 0 to 10). In its simplicity, the DT therefore has the advantage of covering various dimensions of distress, including physical, functional, social, socioeconomic, spiritual, and emotional distress.²¹ However, the weight that patients assign, whether consciously or not, to each dimension is not discernible from the DT score. In contrast, the HADS questionnaire covers exclusively the emotional dimension of distress, but it does so in greater depth.²⁵ Whereas self-reported distress on the DT was lower after STREAM, with a small to medium effect size²⁷ ($\eta^2_p = 0.043$ and 0.069 in the ITT and PP populations, respectively), emotional distress as assessed by HADS did not change. This leads to the hypothesis that STREAM primarily affects dimensions of distress other than anxiety or depression. Of note, in our population, HADS scores at baseline were rather low (mean, 12; IQR, 7-17), whereas baseline DT scores were high (mean, 6; IQR, 5-8). It is therefore conceivable that a potential impact of STREAM on the emotional dimension of distress (anxiety and depression) cannot be assessed conclusively in our population. A study tailored specifically toward patients with high baseline levels of anxiety or depression would be more appropriate to answer this specific question.

Although STREAM was designed for and open to all newly diagnosed patients with cancer, women with breast cancer undergoing curative treatment represented the vast majority of the study population. This leaves uncertainty regarding generalizability

Table 2. Efficacy Outcomes

Measure	ITT Population (n = 129)			PP Population* (n = 95)		
	Δ Mean [†] (95% CI)	P	ES (η^2_p) [‡]	Δ Mean [†] (95% CI)	P	ES (η^2_p) [‡]
Quality of life including fatigue (FACIT-F; 40 items; score, 0-160)	8.59§ (2.45 to 14.73)	.007	0.063	10.71 (4.49 to 16.94)	.001	0.114
Physical well-being (seven items; score, 0-28)	2.01 (0.43 to 3.59)	.01		2.64 (1.02 to 4.25)	.002	
Social well-being (seven items; score, 0-28)	0.44 (−0.95 to 1.82)	.53		0.41 (−1.13 to 1.96)	.60	
Emotional well-being (six items; score, 0-24)	0.24 (−0.77 to 1.25)	.64		0.68 (−0.38 to 1.75)	.21	
Functional well-being (seven items; score, 0-28)	1.53 (0.11 to 2.95)	.04		1.65 (0.04 to 3.26)	.05	
Fatigue score (13 items; score, 0-52)	4.52 (1.81 to 7.22)	.002		5.26 (2.37 to 8.16)	.001	
DT (score, 0-10)	−0.85 (−1.60 to −0.10)	.03	0.043	−1.11 (−1.95 to −0.26)	.01	0.069
HADS (14 items; score, 0-42)	−1.28 (−3.02 to 0.45)	.15	0.019	−2.10 (−4.03 to −0.16)	.03	0.049

NOTE. Results of analysis of covariance for postintervention scores (T2), with baseline scores (T1) as covariates, adjusted for baseline distress (stratification factor). Abbreviations: DT, Distress Thermometer; ES, effect size; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; PP, per protocol.

*PP population was defined as all patients for whom time between random assignment and T2 assessments did not exceed 16 weeks.

[†]Treatment effects estimated by analysis of covariance are reported as difference (Δ) in scores of group means for intervention v control group.

[‡]ESs are expressed as partial eta squared, with the cutoffs small (0.01), medium (0.06), and large (0.14). Multiple imputations were used to handle missing data. Results did not change significantly with other methods for handling of missing data (complete-case (CC) analysis or last observation carried forward (LOCF) analysis; Appendix Table A2, online only).

§Primary end point of the trial.

of the results, particularly toward men and toward the palliative setting. Women with breast cancer are known to have the largest social media network in the cancer community, which likely allowed for effective online recruitment. The presence of other cancer groups in the Internet community is only emerging, with platforms such as that created by the Movember Foundation for men with cancer.³⁷ Such platforms may allow for integrating more men into future studies. If targeted specifically, men with prostate cancer also seem to be reachable via the Internet, as shown by an Australian self-help online program, which integrated a patient forum called My Road Ahead.³⁸

At baseline, before random assignment, more patients in the control group reported face-to-face psychological support and use of psychotropic drugs than in the intervention group, although the number was not statistically significant. Data on the amount of time spent face to face with local psychologists during the course of the trial were not collected; hence, potential bias cannot be quantified. In contrast, attention bias toward the intervention group, possibly introduced by the time our STREAM psychologists

spent online with the patients, may have affected outcome inversely. Because we opted for a care-as-usual (ie, wait-list) rather than active control, this will need to be differentiated in future studies.

A wait-list controlled design is generally accepted to control for the effect of time on the outcome of interest. However, the duration of the wait and consequently the timing of assessments (T2) for the control group are prospectively defined and rigid, whereas the timing of assessments (T2) in the interventions group is dependent on the duration of the intervention and therefore more variable. Hence, time sensitivity is only partially accounted for. This is also true for our study, where median time between T1 and T2 was 9.4 weeks (IQR, 8.6–12.1 weeks) for the intervention group but was shorter in the control group (median, 8.7 weeks; IQR, 8.3–9.3 weeks). Dynamic wait-list controlled designs have been proposed to minimize this potential bias.³⁹

Another shortcoming of our trial is that we only show a benefit in distress and quality of life for patients early after

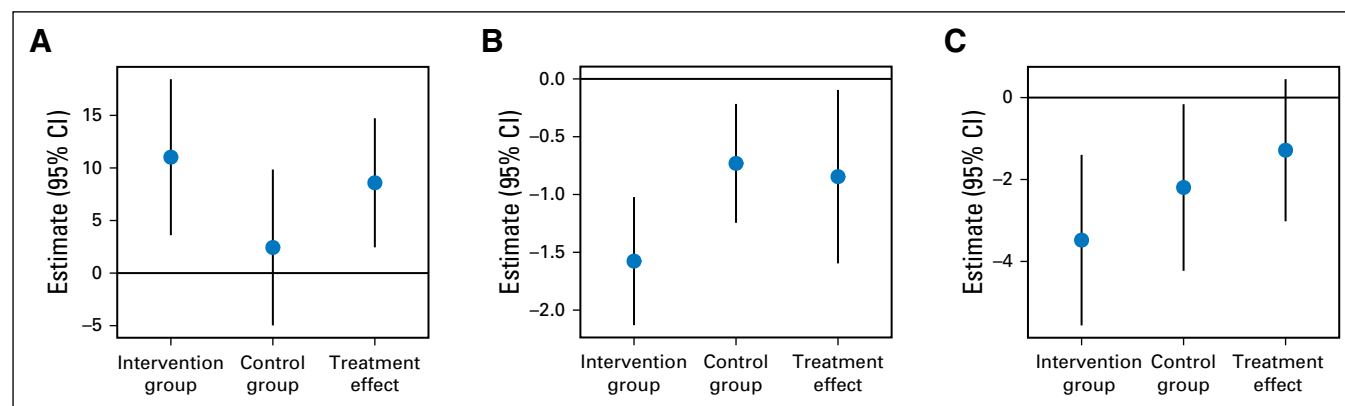


Fig 3. Treatment effects. Mean changes in scores (95% CIs) postintervention (T2) for (A) quality of life (Functional Assessment of Chronic Illness Therapy–Fatigue), (B) distress (Distress Thermometer), and (C) anxiety/depression (Hospital Anxiety and Depression Scale) for the intervention and control groups and their differences (treatment effects) based on analyses of covariance with prescores (T1) as covariates.

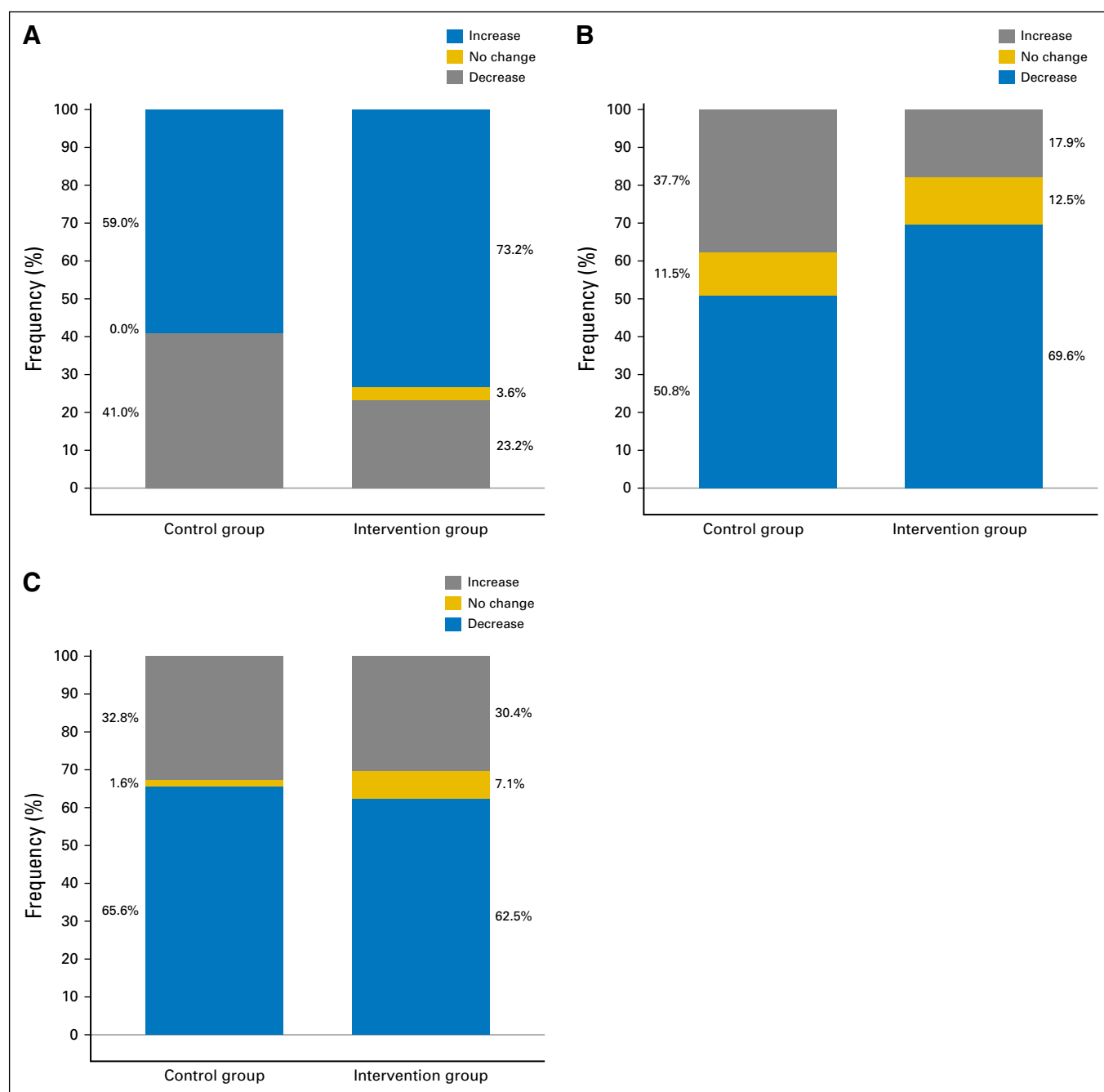


Fig 4. Percentage of patients with any increase or decrease or no change in total scores between T1 and T2 in (A) quality of life (Functional Assessment of Chronic Illness Therapy–Fatigue), (B) distress (Distress Thermometer), and (C) anxiety/depression (Hospital Anxiety and Depression Scale), where blue represents amelioration and gray deterioration within the respective assessment tool.

diagnosis, with a limited follow-up. It is conceivable, however, that such an early intervention¹⁹ may be of particular importance to prevent chronification of distress.⁴⁰ Whether lower distress and increased quality of life after STREAM translate into better treatment tolerance and favorable disease course warrants additional studies.

The unique and common feature of study participants in this trial was a recent diagnosis of cancer. In contrast, the few reported randomized controlled trials on online support for patients with cancer have mainly focused on cancer survivors (ie, interventions

later in the disease trajectory). In a randomized, wait-list controlled trial, breast cancer survivors (on average, 3 years after initial diagnosis) who participated in an online program in a similar therapist-guided format as presented here reported significantly improved sexual functioning (the primary end point of the trial) as compared with the wait-list control group.¹⁶ Breast cancer survivors were also the target population in the randomized trial for the Coping With Cancer Workbook.¹⁵ Women who participated in this Web-based self-help program reported better self-efficacy in coping with cancer. Overall quality of life was not reported. The BREATH (Breast

Cancer eHealth) intervention,¹⁷ a Web-based intervention based on cognitive behavioral techniques but without therapist guidance, led to reduced distress in breast cancer survivors; however, it was not sustained during the 10-month follow-up.

In conclusion, with digital natives approaching an age that places them at risk for developing age-associated diseases, including cancer, use of the Internet in the health care setting will likely further increase. In this randomized trial, we found that a Web-based, guided self-help intervention resulted in a clinically meaningful improvement in quality of life. Our results indicate that Web-based, guided self-help has potential to efficiently support newly diagnosed patients with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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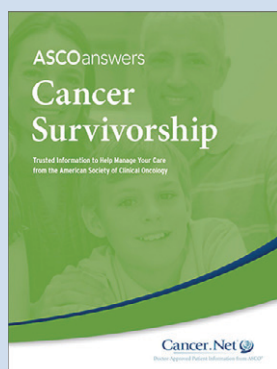
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Web-Based Stress Management for Newly Diagnosed Patients With Cancer (STREAM): A Randomized, Wait-List Controlled Intervention Study

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Appendix

Patients and Methods

Patient Eligibility Criteria and Recruitment

Rationale and design of this randomized trial have been published.²⁰ We included adult patients (age ≥ 18 years) with newly diagnosed cancer who started first-line treatment (either systemic treatment, including chemotherapy, hormonal treatment, or targeted therapy, or radiotherapy) no longer than 12 weeks before study registration. Patients were required to provide written informed consent, read and write in German, have Internet access, and have basic computer skills. To obtain informed consent, a therapist provided detailed information about the study via telephone and went point by point through the informed consent form. The informed consent form was then sent to the patient, who, if in agreement, sent the signed paper form back via post mail. The Ethics Committee of Northwestern and Central Switzerland approved the study (EKNZ 339/13). The trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02289014).

For safety reasons, patients were assessed at baseline for suicidal tendency by the suicide item of the Beck Depression Inventory (Green KL, et al: *J Clin Psychiatry* 76:1683-1686, 2015). Our online program was not designed to support suicidal patients in acute crises; therefore, patients with a score higher than 1 were contacted by telephone and referred to immediate local support.

Information on medical history was obtained from the patients during baseline assessments and confirmed by their treating physicians, who we contacted by e-mail or telephone.

Patient Recruitment

Patients were recruited via the public Web site of STREAM (Stress-Aktiv-Mindern). To foster recruitment, we linked and distributed information about the trial via the following channels: links from health-related Web sites, such as cancer leagues, cancer hospitals, and patient advocate Web sites to the public Web site of STREAM; distribution of flyers in hospitals and during cancer conferences; communication to medical lay press; and paid advertisement via Google and Facebook.

Study Design

We randomly assigned eligible patients at a ratio of one to one using blocked randomization with randomly selected block sizes to an intervention group or a wait-list control group (Fig 1). Patients were stratified according to baseline distress, using an internationally accepted cutoff of ≥ 5 points on the 10-point visual analog scale of the Distress Thermometer.²¹

Intervention

We developed the Web-based intervention STREAM²⁰ based on established stress management intervention manuals²² that incorporate cognitive behavioral- and mindfulness-based stress reduction techniques, which we adapted to the Web context. STREAM aims at improving intra- and interpersonal coping strategies, thereby reducing perceived stress, anxiety, and fatigue as well as enhancing quality of life. STREAM consists of eight modules (Appendix Table A1), which can be completed in 60 to 90 minutes each. Each module starts with a short mindfulness breathing exercise followed by text-based psychoeducation, reflection on current individual emotional status, and acquisition of coping strategies including several exercises and worksheets. Daily use of downloadable audio files with relaxation and guided-imagery exercises was encouraged. Participants were asked to complete one module per week. Access to the next module was provided after the weekly online feedback of a therapist. Patients who had to interrupt the program for medical or personal reasons were regularly contacted and offered continuation. The total duration of the program was not limited. Therapists monitored participants' progress in the program and contacted the participants via an integrated and secured e-mail system to provide feedback and structure. Patients could use the integrated e-mail system to contact their therapist whenever they felt the need to and were informed that the therapist would answer within 3 working days. Whenever patients did not log in to the program for 7 days, therapists sent an e-mail reminder.

Therapists were four female psychologists with Master's degrees in clinical psychology and clinical experience in psycho-oncology. Three of them were in postgraduate psychotherapy training programs, and one was a licensed psychotherapist (C.U.). This core team was supported by seven psychologists with Bachelor's degrees in psychology, who worked under supervision of the

licensed psychotherapist. All therapists were trained by the psychological study team leaders (A.G., C.U.) in applying the STREAM program and met for weekly discussions, with input by a medical oncologist (V.H.), to align procedures and strategies. For data protection, the program is password protected and secured by Secure Socket Layer encryption.

Control

Patients in the control group underwent their cancer treatment locally as planned and were recontacted by the study team 8 weeks after random assignment (T2; Fig 1). After T2 assessments, they received access to the online program. For patients in both groups, cancer treatment was determined locally, and supportive care, according to local standards, may also have included face-to-face psychosocial support and psychotropic drugs.

Assessments

Assessments were conducted electronically directly within the Web-based program via the open source application LimeSurvey at baseline (T1) and after the intervention or waiting period (control group), respectively (T2). In addition, 2-month follow-up (T3) was performed in both groups. Feasibility was assessed at two different levels: feasibility of online recruitment and feasibility for patients to participate in the STREAM program while undergoing first-line treatment. According to the study protocol, feasibility of online recruitment was confirmed when 120 patients (ie, the number needed to assess the primary efficacy outcome) were recruited within a 2-year period; feasibility of participation during treatment was prespecified as a descriptive end point—more specifically, the percentage of completers' in the intention-to-treat (ITT) population, where completers' were defined as patients who worked with at least six of eight modules.

Efficacy End Points

Primary end point was quality of life at T2, assessed in the validated German version of the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire.²³ The first 27 items are common to all Functional Assessment of Cancer Therapy (FACT) questionnaires and cover different domains of quality of life, specifically physical well-being (seven items), social well-being (seven items), emotional well-being (six items), and functional well-being (seven items). The last 13 items focus on various aspects of fatigue, a key aspect of quality of life in patients with cancer, particularly during active treatment.⁶ FACIT-F total score ranges from 0 to 160. Higher scores represent better quality of life. Minimal clinically meaningful differences are not well defined but have previously been set between 7 and 9 points, both as intraindividual changes and differences in groups.^{19,24} For our sample size calculation, we relied on the more stringent definition of 9 points. We chose FACIT-F, rather than the distress thermometer (DT), as primary outcome because overall well-being, reflected by the multidimensional FACIT-F questionnaire, seems clinically more important than changes in a single domain.²³ Also, FACIT-F is better validated as outcome measure than DT, which often serves as screening tool.²¹

Secondary efficacy end points were assessed at the same points in time and evaluated psychological distress and anxiety and depression using the validated German versions of the National Comprehensive Cancer Network DT²¹ and the Hospital Anxiety and Depression Scale (HADS),²⁵ respectively. Effect sizes are expressed as partial eta squared (η_p^2),²⁶ with the following cutoffs to categorize effect sizes into small (0.01), medium (0.06), and large (0.14), as suggested by Cohen.²⁷ Subgroup analyses are highly explorative and, therefore, not part of this report.

Assessments During the Intervention

Usability was evaluated after the first and last module with the System Usability Scale (SUS), where scores > 70 represent good usability.²⁸ Therapeutic alliance between patients and online therapist was assessed using the Working Alliance Inventory (WAI) in its short form (12 items),²⁹ adapted with 2 additional items specific to the online context after each module. Total score ranges from 0 to 5, and scores > 3.5 have been rated as good working alliances.³⁰

Statistical Analyses and Sample Size Calculation

R version 3.4.0 software (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. All analyses were performed in the ITT population defined as all patients who were randomly assigned. The per-protocol (PP) population included all patients who completed the program in the intended timeframe (ie, the time between random assignment and T2 assessments did not exceed 16 weeks, which is twice the minimal duration of the program).

To demonstrate a 9-point difference³¹ in FACIT-F total score between baseline and T2 (after 8 weeks) in the intervention group with a statistical power of 0.80 at a significance level of .05 (two sided), 60 participants were needed in each of the two conditions. We assumed normally distributed data in both groups with a standard deviation of ± 18 (Pandey M, et al: *World J Surg Oncol* 3:63,

2005). Data preparation of all continuous dependent variables included tests for normality, homogeneity of variances, and examination of outliers.

Efficacy Analyses

Efficacy outcomes (primary end point of FACIT-F; secondary end points of DT and HADS) were modeled with analysis of covariance (ANCOVA), using the postscore (T2) as dependent variable, the prescore (T1) as covariate, and group allocation (intervention *v* control) as independent variable. ANCOVAs were further adjusted for the stratification factor distress ($DT \geq 5$ *v* < 5). Multiple imputations ($n = 99$) by chained equations³² using predictive mean matching³³ incorporating all variables of the linear models underlying ANCOVA were used to impute missing outcome values.³⁴ To assess the robustness of the results, sensitivity analyses were conducted for all outcomes in the perprotocol population. In addition, sensitivity analyses were carried out using other methods for handling missing data; more specifically, CC analyses and LOCF analyses, as specified in the protocol,²⁰ were computed for all outcomes on both the ITT and PP populations.

2-Month Follow-Up Analyses

For the follow-up period, score changes from T2 to T3 were analyzed with paired *t* tests separately for each group (no between-group comparisons). Again, multiple imputations were used for missing data. Sensitivity analyses were conducted using CC and LOCF analyses in the ITT and PP populations.

Role of Funding Bodies

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Table A1. Content of Web-Based Stress Management Program STREAM

Module	Psychoeducation	Reflection on Status	Strategies and Exercises
Introduction: What is stress?	Nature of stress in general and specifically in relation to cancer	My individual stressors	Diary,* body scan†
Bodily stress reduction	Bodily sensations during stress and adverse effects of anticancer treatment, focus on fatigue	My individual bodily stress reactions	Stress protocol*
Cognitive stress reduction	Thoughts and their interaction with emotions and bodily sensations	My negative thought patterns	Progressive muscle relaxation†
Emotional stress reduction	Feelings and cancer-related emotions such as anxiety and worries	My feelings and worries	Walk on the beach,† relaxation protocol,* negative thought cycle,† relationship of body position and thoughts,* thinking styles and reflection*
Mindfulness and acceptance of thoughts and emotions	Meaning and implementation of mindfulness and acceptance in daily life (as opposed to active strategies learned in modules one to four)	My definition and experiences with acceptance	Thoughts on clouds,† mountain meditation,† emotional emergency kitt†
Activation of resources: quality of life and pleasure	Introduction of models for balance between burden and resources	My individual resources	Acceptance story*†
Activation of resources: social network and communication skills	Social network and the role of a supportive environment	My individual social network and current needs	Body scan*†
Summary	Overview and documentation of the last 7 weeks	My experiences with the program	Integration of mindfulness,* winter walk,† spring awakening,† health cycle,* planning activities,* week planner,* friendly feelings toward our own body,† enjoyment training,* communication skills,* walk on the beach,† winter walk,† spring awakening,† four seasons†

Abbreviation: STREAM, Stress-Aktiv-Mindern.

*Instructions and worksheets.

†Audio file: story, relaxation, or guided imaginary exercise.

Table A2. Sensitivity Analyses for Efficacy Outcomes

Measure	Mean (95% CI) <i>P</i>					
	ITT/MI	ITT/CC	ITT/LOCF	PP/MI	PP/CC	PP/LOCF
FACIT-F (dependent variable: T2)						
FACIT-F (T1)	0.61 (0.47 to 0.74) <i>P</i> < .001	0.61 (0.48 to 0.74) <i>P</i> < .001	0.67 (0.54 to 0.79) <i>P</i> < .001	0.66 (0.52 to 0.79) <i>P</i> < .001	0.66 (0.52 to 0.79) <i>P</i> < .001	0.66 (0.52 to 0.79) <i>P</i> < .001
DT (T1) ≥ 5: true – false	2.50 (–5.27 to 10.27) <i>P</i> = .53	2.21 (–5.62 to 10.04) <i>P</i> = .58	3.07 (–4.27 to 10.40) <i>P</i> = .41	4.15 (–3.56 to 11.86) <i>P</i> = .29	4.15 (–3.56 to 11.86) <i>P</i> = .29	4.15 (–3.56 to 11.86) <i>P</i> = .29
Group allocation: intervention group – control group	8.59 (2.45 to 14.73) <i>P</i> = .007	8.70 (2.53 to 14.88) <i>P</i> = .007	7.23 (1.38 to 13.07) <i>P</i> = .02	10.71 (4.49 to 16.94) <i>P</i> < .001	10.71 (4.49 to 16.94) <i>P</i> < .001	10.71 (4.49 to 16.94) <i>P</i> < .001
Observations	129	117	129	95	95	95
DT (dependent variable: T2)						
DT (T1)	0.18 (0.01 to 0.35) <i>P</i> = .04	0.18 (0.01 to 0.35) <i>P</i> = .04	0.27 (0.11 to 0.43) <i>P</i> = .002	0.14 (–0.04 to 0.33) <i>P</i> = .14	0.14 (–0.04 to 0.33) <i>P</i> = .14	0.14 (–0.04 to 0.33) <i>P</i> = .14
Group allocation: intervention group – control group	–0.85 (–1.60 to –0.10) <i>P</i> = .03	–0.87 (–1.61 to –0.12) <i>P</i> = .03	–0.79 (–1.51 to –0.08) <i>P</i> = .04	–1.11 (–1.95 to –0.26) <i>P</i> = .02	–1.11 (–1.95 to –0.26) <i>P</i> = .02	–1.11 (–1.95 to –0.26) <i>P</i> = .02
Observations	129	117	129	95	95	95
HADS (dependent variable: T2)						
HADS (T1)	0.55 (0.43 to 0.67) <i>P</i> < .001	0.55 (0.43 to 0.67) <i>P</i> < .001	0.60 (0.49 to 0.72) <i>P</i> < .001	0.56 (0.43 to 0.68) <i>P</i> < .001	0.56 (0.43 to 0.68) <i>P</i> < .001	0.56 (0.43 to 0.68) <i>P</i> < .001
DT (T1) ≥ 5: true – false	0.70 (–1.45 to 2.84) <i>P</i> = .52	0.71 (–1.43 to 2.86) <i>P</i> = .51	0.57 (–1.45 to 2.59) <i>P</i> = .58	0.38 (–1.95 to 2.71) <i>P</i> = .75	0.38 (–1.95 to 2.71) <i>P</i> = .75	0.38 (–1.95 to 2.71) <i>P</i> = .75
Group allocation: intervention group – control group	–1.29 (–3.02 to 0.45) <i>P</i> = .15	–1.29 (–3.02 to 0.44) <i>P</i> = .15	–0.92 (–2.56 to 0.71) <i>P</i> = .27	–2.09 (–4.03 to –0.16) <i>P</i> = .04	–2.09 (–4.03 to –0.16) <i>P</i> = .04	–2.09 (–4.03 to –0.16) <i>P</i> = .04
Observations	129	117	129	95	95	95

NOTE. Results of analyses of covariance for postintervention scores (T2) with baseline scores (T1) as covariate, adjusted for stratification factor distress in FACIT-F and HADS but not in DT because this would result in model overspecification. First column (ITT/MI): primary analyses in the ITT population with MI for missing data. Other columns: sensitivity analyses in ITT and PP populations using MI, CC analyses, and LOCF analyses for missing data. Note that the models for the PP population are identical because there were no missing data.

Abbreviations: CC, complete case; DT, Distress Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; LOCF, last observation carried forward; MI, missing imputation; PP, per protocol.

Table A3. Sensitivity Analyses for Follow-Up Assessments

Measure	Mean (95% CI) <i>P</i>					
	ITT/MI	ITT/CC	ITT/LOCF	PP/MI	PP/CC	PP/LOCF
Follow-up intervention group						
FACIT-F (dependent variable: T3 – T2)	4.69 (–0.74 to 10.12) <i>P</i> = .09	4.69 (–0.86 to 10.25) <i>P</i> = .10	3.75 (–0.68 to 8.19) <i>P</i> = .10	2.19 (–4.10 to 8.48) <i>P</i> = .49	2.32 (–4.04 to 8.68) <i>P</i> = .47	2.26 (–3.93 to 8.45) <i>P</i> = .47
Observations	65	52	65	38	37	38
DT (dependent variable: T3 – T2)	–0.29 (–1.03 to 0.44) <i>P</i> = .43	–0.27 (–1.03 to 0.49) <i>P</i> = .49	–0.22 (–0.82 to 0.39) <i>P</i> = .48	–0.15 (–0.98 to 0.69) <i>P</i> = .73	–0.14 (–0.96 to 0.69) <i>P</i> = .75	–0.13 (–0.94 to 0.67) <i>P</i> = .75
Observations	65	52	65	38	37	38
HADS (dependent variable: T3 – T2)	–0.82 (–2.28 to 0.65) <i>P</i> = .27	–0.88 (–2.35 to 0.58) <i>P</i> = .24	–0.71 (–1.88 to 0.46) <i>P</i> = .24	–0.10 (–1.60 to 1.40) <i>P</i> = .90	–0.14 (–1.65 to 1.38) <i>P</i> = .86	–0.13 (–1.61 to 1.34) <i>P</i> = .86
Observations	65	52	65	38	37	38
Follow-up control group with delayed intervention						
FACIT-F (dependent variable: T3 – T2)	10.95 (6.18 to 15.71) <i>P</i> < .001	12.03 (7.39 to 16.68) <i>P</i> < .001	9.59 (5.72 to 13.46) <i>P</i> < .001	11.68 (6.83 to 16.53) <i>P</i> < .001	11.85 (7.12 to 16.58) <i>P</i> < .001	10.39 (6.14 to 14.65) <i>P</i> < .001
Observations	64	51	64	57	50	57
DT (dependent variable: T3 – T2)	–1.25 (–1.94 to –0.55) <i>P</i> < .001	–1.31 (–2.02 to –0.61) <i>P</i> < .001	–1.05 (–1.62 to –0.47) <i>P</i> < .001	–1.25 (–1.94 to –0.56) <i>P</i> < .001	–1.24 (–1.94 to –0.54) <i>P</i> < .001	–1.09 (–1.71 to –0.46) <i>P</i> < .001
Observations	64	51	64	57	50	57
HADS (dependent variable: T3 – T2)	–2.83 (–4.30 to –1.36) <i>P</i> < .001	–2.63 (–4.13 to –1.12) <i>P</i> < .001	–2.09 (–3.31 to –0.87) <i>P</i> = .002	–2.86 (–4.41 to –1.31) <i>P</i> < .001	–2.62 (–4.16 to –1.08) <i>P</i> = .002	–2.30 (–3.66 to –0.94) <i>P</i> = .002
Observations	64	51	64	57	50	57

NOTE: Results of paired *t* tests for 2-month follow-up scores (T3) with T2 scores as baseline. First column (ITT/MI); primary analyses in the ITT population with MI for missing data. Other columns: sensitivity analyses in ITT and PP populations using MI, CC analyses, and LOCF analyses for missing data.

Abbreviations: CC, complete case; DT, Distress Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; LOCF, last observation carried forward; MI, multiple imputation; PP, per protocol;

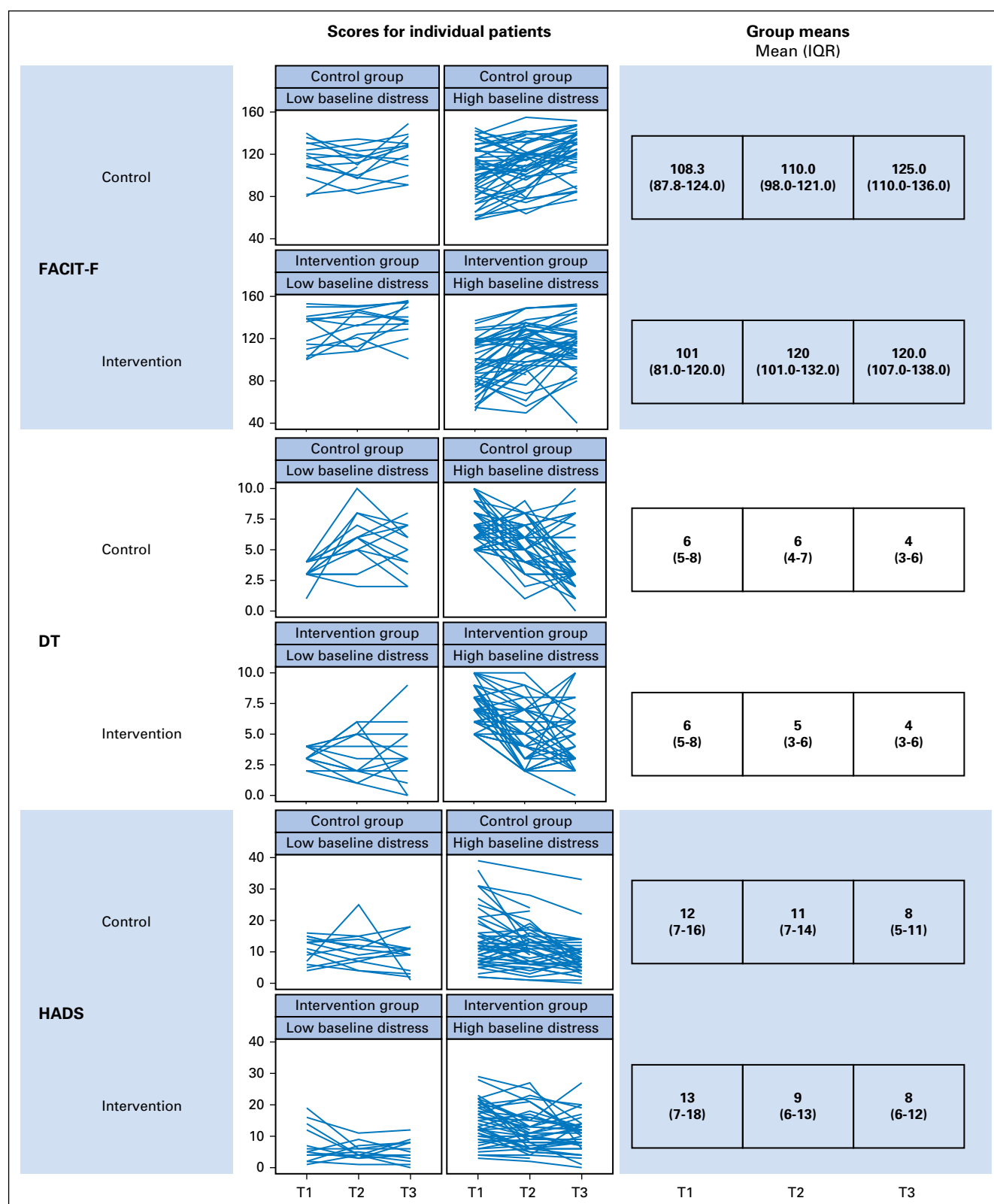


Fig A1. Individual patients' scores and group means for all time points. DT, Distress Thermometer; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue.