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Moderators of the effects of meaning-centered group psychotherapy in cancer survivors on personal meaning, psychological well-being, and distress

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Abstract

Purpose There is evidence to support that meaning-centered group psychotherapy for cancer survivors (MCGP-CS) is an effective intervention for improving personal meaning and psychological well-being, as well as reducing psychological distress. In order to investigate which subpopulations MCGP-CS specifically benefits, this explorative study aims to analyze potential sociodemographic, clinical, and psychosocial factors that may moderate the effects.

Methods Cancer survivors (N = 114) were randomly assigned to MCGP-CS, or care as usual (CAU). Potential moderators included age, sex, relationship, education, employment, religion, cancer type, tumor stage, cancer treatment, time since treatment, anxiety, depression, other negative life events, and previous psychological treatment. Outcome measures were the Personal Meaning Profile (PMP), Scales of Psychological Well-Being (SPWB), and the Hospital Anxiety and Depression Scale (HADS). Assessment took place at baseline, post-intervention (short-term), and 3and 6-month follow-ups (long-term). For each moderator, separate short-term and long-term linear mixed models were built.

Results Short-term effect of MCGP-CS was moderated by (male) sex (on HADS-D; F(1,98) = 6.1, p = .015) and (a high level of) depressive symptoms at baseline (on SPWB; F(1,93) = 5.7, p = .019). Long-term effect of MCGP-CS was moderated by (not having received) previous psychological treatment (on HADS-total; F(3253) = 3.4, p = .017).

Conclusions Most sociodemographic and clinical characteristics do not appear to moderate the positive effect of MCGP-CS on personal meaning. However, MCGP-CS appears to reduce depressive symptoms, particularly in males, and to improve purpose in life of survivors with depressive symptoms. In the long-term, MCGP-CS appears to reduce psychological distress in survivors who had not received psychological treatment in the past year.

Relevance

This study is needed in order to shift from a one-size-fits-all approach to tailored psychosocial care for cancer survivors. In the future, the results of this study may contribute to developing a decision rule for clinical practice, which will help clinicians and patients find the optimal (existential) intervention.

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Keywords Cancer · Oncology · Psychotherapy · Meaning · Well-being · Moderator

Background

Due to ongoing cancer treatment innovations, the number of cancer survivors is steadily increasing [1]. Not only during but also after cancer, survivors may be confronted with challenges of experiencing a meaningful life, such as physical hindrances in achieving goals or existential concerns [2, 3]. After the initial shock of the diagnosis, and the often overwhelming treatment phase, survivors begin to reflect on what has happened. A meaning-focused coping strategy may be helpful to adjustment in the aftermath of cancer [4]. Meaning-centered group psychotherapy (MCGP) has been developed to sustain or enhance a sense of meaning in cancer patients' lives in order to cope with the consequences of cancer and improve their well-being [5, 6].

MCGP was initially developed for advanced cancer patients [5]. It has recently been adapted for cancer survivors who have completed curative treatment (MCGP-CS) [4, 7]. Adaptations include replacing topics about death with topics like carrying on in life despite limitations [8]. There is evidence to support that this intervention is effective in improving meaning and reducing distress in patients with advanced cancer [9], as well as in cancer survivors [8]. In a randomized controlled trial (RCT), MCGP-CS was compared to care as usual (CAU) and supportive group psychotherapy (SGP) among cancer survivors [8]. Compared to CAU, after MCGP-CS survivors improved more in terms of personal meaning (i.e., an individually constructed cognitive system, which endows life with significance [10]), goalorientedness, purpose in life, and positive relations, and compared to SGP, they improved more in terms of environmental mastery and personal growth. In the long-term, participants reported a decrease in depressive symptoms and distress following MCGP-CS. However, these overall effects do not contain information about which particular subgroups of survivors benefit most from MCGP-CS.

Moderator analyses may be used to identify subpopulations of cancer survivors that are differentially responsive to MCGP-CS. In previous RCTs and meta-analyses, several potential sociodemographic and clinical moderators of the effects of other types of psychosocial group interventions on psychological well-being among cancer patients have been identified [11–15], yielding inconsistent results. In some studies, younger [12] and higher educated [13] patients improved more, but in other studies this effect was not observed [11, 15]. Some studies suggest that particularly patients with a more advanced tumor stage benefit from longer interventions [16, 17], but this was not clearly supported in a meta-analysis [14]. Because of this lack of clarity, potential sociodemographic and clinical moderators of the effects of MCGP-CS are assessed in the present study.

A more consistent finding is that particularly patients with a higher level of distress and less psychological resources appear to benefit more from psychosocial group interventions [14, 18–22]. It is therefore expected that survivors with higher levels of distress, such as survivors with depressive and anxiety symptoms, who have experienced other negative life events, and who have received psychological treatment, will benefit more from MCGP-CS.

Since most studies on psychosocial group interventions were conducted either among cancer patients during medical treatment or in the palliative phase, the knowledge of group psychotherapy effects on cancer survivors is relatively limited. This is particularly the case for meaning-centered group psychotherapy, which has only recently been adapted and investigated for cancer survivors [2, 4]. The current study is a secondary analysis of the study on the efficacy of MCGP-CS [8] and aims to identify moderators of the effects of MCGP-CS on personal meaning, psychological well-being, and distress in cancer survivors who have completed curative treatment and who received their diagnosis in the last 5 years. Knowledge of which cancer survivor would benefit most from MCGP-CS is necessary in order to support survivors and their health care providers in selecting the optimal psychological treatment.

Methods

Study design and population

The current study is based on data from a multi-center RCT evaluating the efficacy of MCGP-CS. Detailed descriptions of the study procedures and primary results are published elsewhere [4, 8]. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center. The RCT had three conditions: MCGP-CS as the experimental intervention, SGP as an active control group, and a CAU control group. Because only MCGP-CS had a significant intervention effect compared to CAU on the primary outcome (personal meaning) of this RCT, the current analyses only include the MCGP-CS and CAU conditions.

Eligible participants were adult survivors of any type of cancer who had been diagnosed in the last 5 years, who had been treated with curative intent, and who had completed their main treatment (surgery, radiotherapy, and/or chemotherapy). Cancer stage could range from 0 (in situ) to IV, and cancer could be recurrent, as long as it could be treated curatively. Participants had to have an expressed need for psychological care, and at least one psychosocial complaint (e.g., depressed mood, anxiety, coping issues, relationship problems, or meaning-making difficulties). Exclusion criteria were severe cognitive impairment, current psychological treatment, and insufficient command of the Dutch language. Inclusion and exclusion criteria were assessed by a trained psychologist by means of a telephone interview.

Participants were recruited between August 2012 and September 2014 via four hospitals in the Netherlands and via advertisements in the public media. They received written information about the study and were asked to respond if they were interested in participating. Informed consent was obtained from all individual participants included in the study. After completing a baseline assessment, they were randomly assigned to one of the three conditions. Follow-up assessments were scheduled 1 week after the intervention, and 3 and 6 months thereafter.

Randomization and blinding

A computer-generated randomization table with random block sizes was prepared by an independent researcher and used to produce a list of sequentially numbered allocations. Participants were allocated to a group, and when a consecutive group had 7–10 participants, the independent researcher used the randomization list to assign the group to a condition. Participants and psychotherapists were then informed about the allocated condition, while data managers were blinded to the allocation.

Meaning-centered group psychotherapy for cancer survivors

MCGP-CS is an eight-week, manualized intervention that makes use of didactics, a workbook, group discussions, experiential exercises, and homework. Based on the results of a focus group study [2], MCGP was adapted for cancer survivors. The adaptations involved changes in terminology, replacing topics about death with topics relevant for survivors, and the addition of brief mindfulness exercises [8]. The following themes were addressed in MCGP-CS: sources of meaning, meaning before and after cancer, life story as a source of meaning (past), life story as a source of meaning (future), encountering life's limitations, creative sources of meaning, experiential sources of meaning, and representations of participants' life lessons [4]. Two psychotherapists with experience in treating patients with cancer each led about half of the intervention groups. Fidelity to the MCGP-CS protocol was ensured in several ways. Details are published elsewhere [8].

Care as usual

Cancer survivors assigned to the CAU condition did not participate in one of the group interventions. If a participant requested psychological care, he or she was referred to the physician general practitioner.

Potential moderators

Demographic characteristics

Demographic characteristics were collected at baseline using a self-report questionnaire. All variables were dichotomized: sex (male vs. female), age (younger vs. older than the median of 56 years), marital status (married or in a relationship vs. single), level of education (elementary and lower vocational education vs. higher secondary, higher vocational education and university), employment (employed vs. unemployed), and religious background (religious vs. non-religious).

Clinical characteristics

Clinical characteristics of survivors recruited in hospitals were retrieved from medical records. For survivors recruited via the public media (three persons), clinical characteristics were obtained via a self-report questionnaire. Cancer type was categorized as breast vs. colon. Because there was a small but diverse group of survivors from other cancer types, this category was not used in the analyses. Furthermore, tumor stage (0, I, II vs. III, IV), type of treatment (surgery vs. surgery combined with radiation and/or chemotherapy), and time since treatment (shorter vs. longer than 1 year) were collected.

Psychosocial characteristics

Psychosocial characteristics included baseline anxiety and depression score, measured using the Hospital Anxiety and Depression Scale (HADS) [23, 24]. For both the anxiety and depression subscale, a cutoff of ≥ 8 was used for dichotomization [25]. Furthermore, psychosocial characteristics included the occurrence of negative life events other than cancer in the past 2 years (yes vs. no). This was assessed using the question: "Have you been through a major negative experience during the past 2 years, besides cancer? (E.g. job loss, loss of a loved one, burn-out, divorce)" Finally, other psychological treatments (any treatment from a psychiatrist or psychologist) in the past year (yes vs. no) were assessed. All psychosocial characteristics were collected via self-report.

Outcome measures

Participants completed questionnaires on personal meaning, psychological well-being, and psychological distress. Only the (sub)scales that showed significant change after MCGP-CS compared to CAU in the previous efficacy study [8] were analyzed for potential moderators.

The Dutch version of the Personal Meaning Profile (PMP) was used to measure personal meaning. This 39-item measure comprises five subscales: relation with God, dedication to life, fairness of life, goal-orientedness, and relation with others. In the

present study, the total scale ($\alpha = .93$) and the 6-item subscale goal-orientedness ($\alpha = .89$) were used. Items were scored on a 7point Likert scale, ranging from 1 (not at all) to 7 (a great deal). The subscale scores were calculated as the mean item score, and the total score as the mean subscale score. A higher score indicated a stronger sense of personal meaning [26, 27].

Psychological well-being was measured with the Dutch version of Ryff's Scales of Psychological Well-Being (SPWB). In the present study, the 6-item subscale's positive relations with others ($\alpha = .81$) and purpose in life ($\alpha = .78$) were analyzed. Items were answered on a 6-point Likert scale, ranging from 1 (strongly disagree) to 6 (strongly agree). For the subscale scores, the mean item score was calculated, and a higher score indicated a greater sense of well-being [28, 29].

Psychological distress was measured using the continuous HADS-total score and depression using the HADS depression (HADS-D) subscale score. The HADS anxiety subscale was not used, since it showed no significant change in the previous efficacy study [8]. To avoid confounding, HADS-total and HADS-D were omitted as outcome measures, in models in which baseline anxiety and baseline depression were tested as potential moderators. The HADS-total score ($\alpha = .85$) ranges from 0 to 42 and the HADS-D score ($\alpha = .78$) from 0 to 21. A higher score reflected a higher level of distress or depression [23, 24].

Statistical analyses

Baseline characteristics are presented as numbers and percentages, as means, standard deviations, and range, or as median and range. Differences between MCGP-CS and CAU and all associations between the potential moderators were assessed using Chisquare and independent samples t-tests. In order to examine treatment response moderators, linear mixed models (LMM; intention-to-treat) were used with a random intercept for participant effects. Fixed effects for condition (MCGP-CS or CAU), time, moderator, all two-way interactions, and three-way interaction were included in the models. Time was treated as a categorical variable. Short-term effect was defined as the course of outcome measures from baseline until post-intervention. Long-term effect was defined as the course of the outcome measures from baseline to post-intervention, to 3- and 6-month follow-ups. Separate LMM models were constructed for each potential moderator, the short- and long-term, and each outcome measure, and the pvalue of the three-way interaction was assessed. This interaction term represents the difference in the change over time in the MCGP-CS and CAU condition between the different categories of the moderator, regardless of baseline values.

Post-hoc analyses via independent samples t tests with Bonferroni correction (corrected $\alpha = .05/2 = .025$) were carried out to assess whether change scores differed significantly between the MCGP-CS and CAU condition within each category of the significant moderator variables. Short-term change scores were calculated by subtracting baseline scores from post-intervention scores, and long-term change scores by subtracting baseline scores from 6-month follow-up scores. Between-group difference in effect sizes (Cohen's d) within the categories of the significant moderator variables was

 Table 1
 Participant characteristics

	MCGP-C (<i>N</i> = 57)	CS	CAU (N	= 57)	p^{a}
	Number	Percent	Number	Percent	
Age (M, SD, range)	59	11,	57	10,	.48
		81		83	
Sex (female)	40	70	51	90	.010*
Marital status (single)	12	21	13	23	.82
Level of education (high)	24	42	32	56	.13
Employment (paid work) ^b	26	70	31	76	.60
Religion					.19
Christian	23	40	30	53	
No religion	34	60	27	47	
Type of cancer					.053
Breast	30	53	42	74	
Colon	15	26	10	17	
Other	12	21	5	9	
Tumor stage					.45
0 (in situ)	3	5	2	4	
Ι	20	35	23	40	
II	22	39	15	26	
III	6	10	10	18	
IV	1	2	0	0	
Missing	5	9	7	12	
Type of treatment					
Surgery	57	100	56	98	.32
Surgery and radiation and/or chemotherapy	44	77	49	86	.23
Months since treatment (mdn, range)	19	6–58	18	3–55	.64
HADS anxiety $\geq 8^{\circ}$	24	42	20	36	.49
HADS depression ≥8 ^c	14	25	7	13	.10
Other negative life event	27	47	32	56	.35
Past psychological treatment ^d	12	21	7	12	.24

MCGP-CS meaning-centered group psychotherapy for cancer survivors, *CAU* care as usual

**p* < .05

^ap value of χ^2 test comparing numbers in MCGP-CS and CAU. Age means were compared using an independent samples t test, and the medians of months since treatment was compared using the Mann-Whitney U test

^b Only participants below retirement age were included in analyses using employment (MCGP-CS: N = 37, CAU: N = 41)

^c In CAU HADS anxiety and HADS depression: N = 56

^d In CAU psychological treatment: N = 55

Outcome measure	Moderator	Condition	Number	Baseline	Post- intervention	F(df) (3-way interaction LMM)	<i>p</i> (3-way interaction LMM)	<i>p</i> (post hoc <i>t</i> test)	Cohen's <i>d</i> (between groups)	R^2 of model without moderator	R^2 of model with moderator
Depression	Male	MCGP-CS	17	5.3	3.2	6.1 (1,98)	.015*	.020*	-1.5	.020	.12
(U-SUAH)		CAU	9	7.8	10.2						
	Female	MCGP-CS	40	5.0	3.9			.38	-0.31		
		CAU	51	4.0	3.7						
Purpose in life	Depression	MCGP-CS	43	4.3	4.6	5.7 (1,93)	.019*	.12	0.44	.027	.17
(SPWB)	(low)	CAU	50	4.4	4.4						
	Depression	MCGP-CS	14	3.4	3.9			.018*	1.5		
	(high)	CAU	7	4.0	3.7						

 $^{*}p < .05$

calculated by dividing the difference in change between MCGP-CS and CAU by the pooled standard deviation. To provide an estimation of the variance explained by the moderator, R^2 was calculated for the model without the moderator variable (time, condition, time × condition) and for the full model including the moderator variable [30]. For all analyses, SPSS 24 was used and p < .05 was considered to indicate statistical significance.

Results

Participant characteristics

Details of the participant flow and dropout were published elsewhere [8]. Of the total 170 participants, 57 were randomized into the MCGP-CS and 57 into the CAU condition. In the MCGP-CS condition, 50 participants completed the assessment post-intervention, and 45 at the 6-month follow-up. In the CAU condition, 47 completed assessment postintervention and 35 at the 6-month follow-up. Participant characteristics are displayed in Table 1. In MCGP-CS, 70% of the participants were female and they were on average 59 years old. Breast cancer was diagnosed in 53%, and colon cancer in 26% of MCGP-CS participants. All MCGP-CS participants had undergone surgery, and in addition, 77% had received radiation, chemotherapy, or both. The median time since their treatment completion was 19 months. CAU participants did not differ significantly from MCGP-CS participants, except that a higher percentage of females (90%) was randomly assigned to CAU.

Moderators of short-term MCGP-CS effect

Sex significantly moderated the effect of MCGP-CS on depressive symptoms (HADS-D; F(1,98) = 6.1, p = .015). Post hoc independent samples *t* tests with Bonferroni correction showed that males improved significantly more after MCGP-CS than in the CAU condition (d = -1.5). More specifically, males improved after MCGP-CS but deteriorated in the CAU condition. Improvement in females was not significantly greater when compared to CAU (d = -0.31) (Table 2, Fig. 1).

Depressive symptoms at baseline moderated the course of purpose in life (SPWB) after MCGP-CS (F(1,93) = 5.7, p = .019). Survivors with an elevated HADS-D score at baseline improved significantly more in the MCGP-CS group than in the CAU group (d = 1.5). Survivors with a low baseline HADS-D score improved after MCGP-CS, but their improvement did not differ significantly from survivors in the CAU group (d = 0.44).



Fig. 1 Moderator effects of sex (short-term), depressive symptoms at baseline (short-term), and psychological treatment in the year before participation (long-term). HADS-D hospital Anxiety and depression

scale, subscale depression; SPWB Ryff's Scales of Psychological Well-Being; MCGP-CS meaning-centered group psychotherapy for cancer survivors; CAU care as usual

Moderators of long-term MCGP-CS effect

Psychological treatment in the past year moderated the longterm effect of MCGP-CS (Table 3, Fig. 1). Survivors who had not received psychological treatment in the past year had a significantly better course of the HADS-total score during the 6-month follow-up period than survivors who had received psychological treatment in the past year (F(3253) = 3.4, p = .017). More precisely, only survivors who had not received psychological treatment in the past year improved during the 6 months after MCGP-CS, while participants who had received psychological treatment in the past year barely improved during the 6 months after MCGP-CS and got worse in the CAU condition.

However, the post hoc test did not show a significant difference in the HADS-total change score between MCGP-CS and CAU, neither did it in survivors who had received psychological treatment in the previous year (d = -0.91), nor in those who had not received psychological treatment in the previous year (d = -0.49).

None of the significant moderators were mutually associated.

Discussion

There is evidence to support that MCGP-CS is an effective intervention for cancer survivors, which enhances personal meaning and psychological well-being in the short term and reduces psychological distress in the longer term [8]. In this study, moderator analyses were conducted to identify subpopulations that may be particularly responsive to MCGP-CS. Fourteen potential sociodemographic, clinical, and psychosocial moderators of MCGP-CS efficacy on personal meaning, goal-orientedness, positive relations with others, purpose in life, distress, and depression were assessed postintervention and during the following 6 months. Most patient characteristics did not moderate any of the outcome variables. This may suggest that more statistical power is necessary in order to detect their moderating effects, or that MCGP-CS is equally effective for most sociodemographic and clinical cancer survivor subpopulations [11, 12]. However, sex did moderate MCGP-CS efficacy. The shortterm effect of MCGP-CS on depressive symptoms was greater for males than for females. As expected, baseline distress moderated the effect of MCGP-CS on purpose in life, but baseline anxiety and negative life events did not. Contrary to expectations, it was not survivors who had received previous psychological treatment, but those who had not received psychological treatment who benefitted more from MCGP-CS in terms of distress reduction.

Although female survivors are more likely to express the need for psychosocial support [31], this study suggests that male survivors may be more responsive to MCGP-CS. It is possible that for male survivors, losing work, physical health, social status, and masculinity due to cancer may trigger depressive symptoms [32]. An intervention focusing on finding the sources of meaning that they still have may be particularly suitable to help males alleviate depressive symptoms [6]. However, this finding only occurred on depressive symptoms, suggesting that both sexes responded in a comparable manner in the other outcomes (i.e., personal meaning, goal-orientedness, positive relations with others, purpose in life, and distress). Also, the literature shows no indications that male and female cancer patients respond differentially to other types of psychosocial group interventions [12, 13, 33]. The

Table 3 Estimate	ed marginal mean	outcome meas	ure sc	cores of sig	gnificant moderato	rs per moderator c	ategory and cond	lition from bas	eline to post-i	ntervention,	at 3- and 6-r	nonth FUs (lo	ng-term)
Outcome measure	Moderator	Condition	n l	Baseline	Post- intervention	Three-month FU	Six-month FU	F(df) (3-way interaction LMM)	<i>p</i> (3-way interaction LMM)	<i>p</i> (post hoc <i>t</i> test)	Cohen's d (between groups)	R ² of model with moderator	R ² of model with moderator
Distress (HADS-total)	Psychological treatment	MCGP-CS CAU	12	16 14	15 12	16 10	14 19	3.4(3253)	.017*	.26	-0.91	.035	.14
	Psychological treatment (no)	MCGP-CS CAU	50 50	11	8 11	8 10	7 11			.13	-0.49		
<i>HADS</i> hospital anx *p < .05	iety and depressio	n scale, <i>MCGI</i>	P-CS	meaning-c	entered group psy-	chotherapy for can	icer survivors, C	4U care as usu	al				

number of males in this study was low, which increased the possibility of a chance finding. Further research is needed into the potential differential effects of MCGP-CS for males and females.

The fact that MCGP-CS appears to be more effective in cancer survivors with depressive symptoms is in line with previous studies of other types of psychosocial interventions [14, 18, 19] and can possibly be explained by the fact that survivors with depressive symptoms have more room for improvement. However, following MCGP-CS, survivors with and without depressive symptoms responded equally well in terms of personal meaning, goal-orientedness, and positive relations with others. This suggests that the difference in improvement between depressed and non-depressed survivors should not be overestimated. Still, depressed people often find it hard to experience purpose in life [34, 35]. This study indicates that MCGP-CS may be particularly helpful for survivors with depressive symptoms in order to regain a sense of purpose in life.

While the moderating effects of sex and baseline depression faded in the long-term, during the long-term follow-up period, MCGP-CS became more effective in reducing psychological distress among cancer survivors who had not received psychological treatment in the past year than those who had. This is contrary to the expectations. Perhaps survivors who had received previous psychological treatment had already benefitted from their previous therapy and therefore had less room to improve due to MCGP-CS. However, this finding only occurred in one outcome measure, and the post hoc test did not show a significant difference in reduction of psychological distress between survivors with past psychological treatment following MCGP-CS and CAU. Further (qualitative) research is needed in order to obtain insight into previous psychological treatment as a moderator of the effect of MCGP-CS.

Study limitations

The strengths of this study are the long follow-up period and the relatively low dropout rate. A limitation is that this study was not designed for investigating potential moderators and thus had limited power for this type of analyses. A larger sample size is needed to adequately detect moderator effects. Because of this limitation, we included only a small set of potential psychosocial moderators, even though psychosocial characteristics may be promising moderators of MCGP-CS [21, 22]. Nevertheless, the inclusion of 14 potential moderators and six outcome measures, both short- and long-term, led to many separate models. Consequently, the observed effects might have been statistically significant only by chance. One could correct this for multiple testing, but there is no clear consensus on how to address this issue [36]. Furthermore, the small sample size in this study led to some moderator categories with just a few observations, which increases the chance that individual participants with relatively high or low scores may have influenced the p value of the three-way interaction term. Unfortunately, large sample sizes are hard to obtain due to financial and logistical reasons. Individual patient data meta-analysis, in which data sets of several group psychotherapy efficacy studies in cancer patients are combined, should be undertaken to attain more power [37].

Clinical implications

For clinical practice, it is important to gain more knowledge of what type of psychotherapy is beneficial for which patient. The results of the present study show several subgroups of survivors that responded particularly well to MCGP-CS. More studies on potential moderators of meaning-focused interventions should be conducted and combined with results from studies on the moderators of different types of psychosocial group interventions for cancer survivors in order to develop a clinical decision rule. Such a clinical decision rule will help clinicians and survivors find the optimal intervention tailored to the survivors' characteristics, capabilities, and preferences.

Conclusions

Most sociodemographic and clinical characteristics do not appear to moderate the positive effect of MCGP-CS on personal meaning. However, MCGP-CS appears to reduce depressive symptoms, particularly in males, and to improve purpose in life particularly for survivors with depressive symptoms. In the long-term, MCGP-CS reduces psychological distress, possibly especially in cancer survivors who had not received psychological treatment in the past year.

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Compliance with ethical standards The corresponding author has full control of all primary data and agrees to allow Supportive Care in Cancer to review the data if requested.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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