



**MAKING MEANING OF THE EFFECTS
OF MEANING-CENTERED GROUP PSYCHOTHERAPY
FOR CANCER SURVIVORS**

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**Making meaning of the effects
of meaning-centered group psychotherapy
for cancer survivors**

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VRIJE UNIVERSITEIT

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FOR CANCER SURVIVORS**

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie van de
Faculteit der Gedrags- en Bewegingswetenschappen
op maandag 30 november 2020 om 11.45 uur
in de aula van de universiteit,
De Boelelaan 1105

COLOFON

The research in this thesis was performed at the department of Clinical, Neuro- and Developmental Psychology, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam.

This thesis was accomplished with financial support from The Netherlands Organisation for Health Research and Development and by the Dutch Cancer Society (KWF).

Print by Gildeprint | www.gildeprint.nl

Cover & lay-out by Ilse Modder | www.ilsemodder.nl

ISBN: 978-94-6419-008-3

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1

GENERAL INTRODUCTION



GENERAL INTRODUCTION

The current thesis addresses psychological well-being in cancer survivors, with a special focus on meaning in life, posttraumatic growth and meaning-centered group psychotherapy for cancer survivors (MCGP-CS). The number of cancer survivors is rising. In 2018, over 114,000 individuals were diagnosed with cancer in the Netherlands¹ and an estimated 17 million new cases were diagnosed worldwide². The five-year survival percentage has increased from 33% in the 1960s to 66% among Dutch people diagnosed after 2010. It has been estimated that circa 5% of the population in western nations is currently living with or beyond cancer^{1,3}.

The World Health Organization defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”⁴. When curative treatment for cancer is completed, many survivors cannot simply return to the life they had before the diagnosis. Most are confronted with symptoms such as pain, fatigue and sleep disturbance (>60%)⁵⁻⁷. Furthermore, a substantial minority reports existential concerns or finds it harder to experience meaning in life⁸⁻¹¹. Due to the rising number of survivors, it is of the utmost importance to provide adequate psychosocial care, not only for those with a psychiatric disorder, but also for those who find it hard to adjust to life after cancer.

The definition of a cancer survivor used in this thesis is an individual who completed cancer treatment with curative intent and who has no signs of recurrence or a second cancer diagnosis^{3,12}. The present chapter describes the impact of having had cancer on one's psychological well-being and sense of meaning, introduces the ‘meaning-making model’ and MCGP-CS and discusses the contribution of this thesis to the field of psycho-oncology.

LIVING BEYOND CANCER

Psychological well-being, meaning, posttraumatic growth, distress and health-related quality of life were all assessed in the randomized controlled trial (RCT) this thesis is based on. These constructs are interrelated, play a role in the meaning-making model and may be affected by cancer.

Health-related quality of life

Health-related quality of life refers to an individual's level of functioning in the physical, psychological, social and spiritual domain¹³. Quality of life is not only influenced by cancer- and treatment-related symptoms and limitations, but also by an individual's

subjective evaluation of them. Not surprisingly, cancer patients report, on average, a lower quality of life than people in the general population^{14,15}. In the survivorship phase, quality of life often improves during the first years. Over time, it once again becomes largely comparable to that of the general population^{13,16,17}. At the same time, studies also show that in some individuals quality of life is enduringly affected by permanent or late effects of cancer and its treatment^{17,18}.

Distress

Distress can be described as an unpleasant emotional experience of a psychological, social or spiritual nature. It ranges from common feelings of sadness, fear and lack of joy to problems that interfere with daily functioning¹⁹. A high level of distress may indicate the presence of an anxiety or depressive disorder and warrants referral to psycho-oncological care²⁰. Physical symptoms and functional limitations due to cancer may form a source of distress. Vice versa, distressed survivors evaluate these symptoms and limitations more negatively²¹. Longitudinal studies indicate that many cancer patients (49-73%) either have a low level of distress or recover from distress when their treatment is completed²¹⁻²³. Some have low distress during treatment but begin to feel more distressed in the survivorship phase (8-38%). A minority (11-15%) has a stable high level of distress, both during treatment and in the survivorship phase. Especially when curative treatment has been finished, existential and meaning-related questions may come to the fore and become a major source of distress^{8,24-26}.

Psychological well-being

In this thesis, psychological well-being is not approached as the absence of distress, but as the presence of a number of aspects that contribute to a sense of well-being. According to Ryff and Singer, the two main ingredients of a ‘good’ life are having a sense of meaning in life and fulfilling bonds with others^{27,28}. In addition, having a positive attitude towards oneself, a sense of mastery and the perception of self-development over time all help strengthen one's psychological well-being^{29,30}. On average, cancer has a stronger negative impact on psychological well-being for younger people than for older people³¹. For younger adults, cancer may have come “off-time” and its consequences may interfere more with other aspects of their life, such as raising children and their career. Older survivors seem to have a level of psychological well-being that is, on average, comparable to the elderly in the general population³¹.

Meaning in life

A sense of meaning in life is not only seen as essential for psychological well-being, but also as a protective factor when facing stressful life events³²⁻³⁴. An individual's

personal sense of meaning can be defined as “the extent to which people comprehend, make sense of or see significance in their lives, accompanied by the degree to which they perceive themselves to have a purpose, mission or overarching aim in life”³⁵. People’s sense of meaning is generally stronger when they have commitments, goals and purpose in life, strong relations with others, perhaps a relationship with a deity and when they feel treated fairly by life³⁶. During a study conducted in the United States, for which 2,365 cancer survivors were followed over a period of nine years, four trajectories of meaning were identified: a stable high trajectory in which people consistently reported a high sense of meaning over these years (45-61%), a stable moderate trajectory (23-33%), a stable low trajectory (7-16%) and a declining trajectory (6-10%)¹¹. Although this study suggests that survivors’ sense of meaning is quite stable over time, many survivors experience changes in their perspective on what is meaningful in life^{10,37,38}. As a consequence of cancer, some sources of meaning may become harder to reach, while other sources become more important^{9,38}. Being able to navigate major life goals seems to be important when it comes to maintaining a sense of meaning in life after cancer³⁹.

Posttraumatic growth

As an unintentional outcome of attempting to cope with cancer, the majority of survivors seems to also experience positive psychological changes⁴⁰. Posttraumatic growth can be defined as an individual’s perception of positive psychological change as a result of the struggle with a traumatic event⁴¹. This growth may be experienced in the form of a greater appreciation of life, stronger relations with others, realizing one’s strength, spiritual changes or seeing new possibilities in life⁴².

Despite its clear definition, the nature of posttraumatic growth is highly debated. This may have to do with the inconsistent and puzzling findings regarding its association with distress^{43,44}. In many studies, no association was found; nevertheless, some studies associated posttraumatic growth with lower distress, while in other studies it was related to higher distress and especially to more symptoms of a posttraumatic stress disorder⁴⁵⁻⁴⁷. One explanation for these inconsistent findings is that this association is curvilinear^{48,49}. According to this theory, in one group of survivors, cancer did not invoke distress or initiate the coping processes that would otherwise result in posttraumatic growth. For a second group, cancer did invoke distress and the coping processes resulting in posttraumatic growth. In the third group, distress is so high that it inhibits posttraumatic growth. Another explanation for these puzzling findings is that posttraumatic growth is not only the outcome of a coping process, but also a coping strategy in itself^{43,44}. As such, it could be a positive coping strategy (e.g. helping to

maintain well-being) or a negative coping strategy (e.g. a way of avoiding the gravity of the situation)⁴³. Since posttraumatic growth is typically assessed cross-sectionally by self-report, often months or years after cancer, it is impossible for most studies to psychometrically distinguish genuine growth from the perception of growth as a positive or negative coping strategy⁵⁰.

Recently, a meta-analysis was published that included only longitudinal studies of psychological well-being in survivors of a traumatic event, preferably with the first assessment before the event and a control condition⁵¹. Positive changes in psychological well-being were regarded as posttraumatic growth. The results demonstrated an improvement in social relations after the traumatic event and a stronger sense of mastery, but less self-esteem. No changes were found in meaning and spirituality. The most common initial reaction to a traumatic event was no change in psychological well-being or an immediate decrease. Circa one to two years after this decline, individuals’ level of psychological well-being began to exceed their baseline level prior to the traumatic event, indicating posttraumatic growth^{46,51}.

THE MEANING-MAKING MODEL

The meaning-making model describes how making meaning of a stressful event can be connected to lower distress, better psychological well-being, posttraumatic growth and a better quality of life⁵². This model can be summarized in seven steps⁵³. (1) People possess an individually constructed cognitive system that provides a subjective sense of meaning or purpose in life, often called ‘global meaning’³⁶. (2) People continuously appraise situations they encounter, such as cancer-related symptoms and limitations, and assign meaning to them. (3) If the appraised meaning is discrepant with one’s global meaning, feelings of distress arise. (4) These feelings of distress initiate attempts to make meaning. (5) There are many ways to make meaning, including the perception of posttraumatic growth. (6) Through meaning-making, individuals seek to reduce the discrepancy between the appraised meaning of the situation and their global meaning. (7) This process is successful if meaning can be made of the situation. Made meanings can take many forms, including genuine growth, acceptance and a reappraised meaning of the stressor. Made meanings result in less distress, improved psychological well-being and a better quality of life.

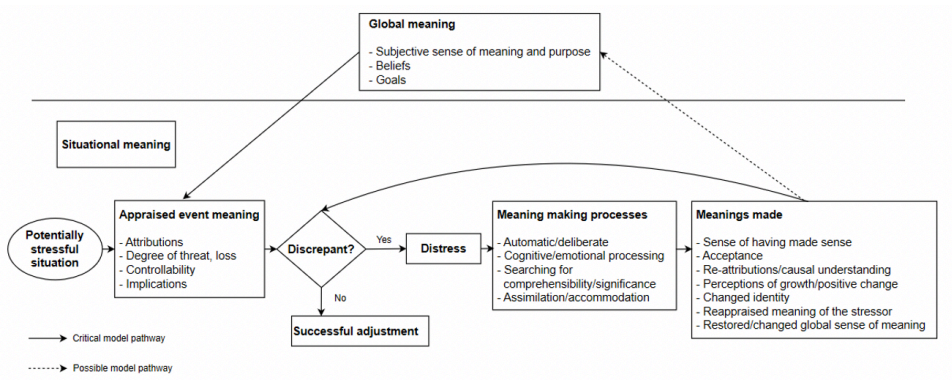


Figure 1. *The meaning-making model*
Note. This figure is adapted from Park, 2010.

MEANING-CENTERED GROUP PSYCHOTHERAPY FOR CANCER SURVIVORS

MCGP-CS was developed for cancer survivors with coping difficulties who feel distressed or have existential or meaning-related questions. MCGP-CS aims to enhance their sense of meaning in life, increase psychological well-being and decrease distress. Meaning-centered psychotherapy was initially developed in the United States to help advanced cancer patients who suffer from a loss of meaning^{54,55}. William Breitbart and his research team at Memorial Sloan Kettering Cancer Center studied Viktor Frankl’s ‘logotherapy’ – *logos* can be translated as meaning - to identify a set of principles and therapeutic techniques to help patients explore and become aware of their sources of meaning in life. In meaning-centered psychotherapy, patients are stimulated to identify a thread running through their life story, to learn from their past experiences and to adopt a courageous attitude in facing their disease. Frankl’s (1905-1997) logotherapy was highly influenced by his time spent in various concentration camps during the Holocaust, where he observed the importance of meaning to staying sane in these camps.

Essential principles adopted by MCGP-CS are that life never ceases to have meaning, that humans have an innate desire to find meaning and that a sense of meaning or purpose is a protective factor during hard times. Furthermore, people always have the freedom to choose their attitude in the face of suffering, when they encounter life’s limitations or when their life goals become unobtainable. According to Frankl, the attitude people adopt can even be a main source of meaning in itself. People also derive meaning from what they create, such as the works they accomplish in life or the legacy they leave for future generations, and from experiences, such as love or enjoying the beauty of nature or music. The role these sources of meaning

play always takes shape in an individual’s life story, which is embedded in a historical context. Within MCGP-CS, these principles were taken up in eight sessions, consisting of didactics, group discussions, experiential exercises and homework⁵⁴.

Table 1. *Session topics covered in MCGP-CS*

Session	Topic
1	Concept and sources of meaning
2	Meaning before and after cancer
3	The story of our life as a source of meaning: what made us who we are today?
4	The story of our life as a source of meaning: things we have done and what to do in the future
5	Attitudinal sources of meaning: encountering life’s limitations
6	Creative sources of meaning: responsibility, courage and creativity
7	Experiential sources of meaning
8	Termination: presentation of life lessons and goodbyes

Note. This table is adapted from van der Spek, Vos, van Uden-Kraan et al., 2017.

Evidence on the efficacy of MCGP-CS

There is scientific support for the efficacy of existential therapies in general, as well as for meaning-centered psychotherapy, both for advanced cancer patients and for cancer survivors (MCGP-CS). A meta-analysis of existential interventions revealed a large effect on meaning in life and a moderate effect on reducing psychopathology⁵⁶. In two RCTs, meaning-centered psychotherapy for advanced cancer patients was compared to supportive group psychotherapy^{57,58}. Meaning-centered psychotherapy resulted in stronger improvements of patients’ spiritual well-being and quality of life and a larger decrease of depressive symptoms and hopelessness^{57,58}. Furthermore, support has been found for the theoretical model underlying meaning-centered psychotherapy. The improvement in sense of meaning mediated better quality of life and the decrease of depressive symptoms two months later⁵⁹.

The Dutch RCT on the efficacy of MCGP-CS conducted by van der Spek and colleagues, forms the basis of the current thesis⁶⁰. In this RCT, MCGP-CS was compared to supportive group psychotherapy and care as usual. The main results showed that MCGP-CS leads to stronger improvements in personal meaning, goal-orientedness, purpose in life, positive relations and fighting spirit compared to care as usual⁶⁰. After three months, MCGP-CS participants also reported a larger decrease in hopelessness and, after six months, in distress and depressive symptoms, compared to participants who received care as usual. Compared to supportive group psychotherapy, MCGP-CS resulted in a stronger improvement of personal growth after three months and

environmental mastery after six months. A cost-utility study showed that MCGP-CS is also likely to be cost-effective⁶¹.

AIMS OF THIS THESIS

The main RCT results demonstrated the efficacy of MCGP-CS, but left many questions unanswered. To what extent do cancer survivors with distress experience posttraumatic growth? Are there subgroups of survivors who respond more strongly to MCGP-CS and therefore may be best referred to this intervention? Is there support for the underlying theoretical model of meaning-centered psychotherapy among cancer survivors? How long do the effects of MCGP-CS last? Lastly, the overlapping subscale themes of the patient-reported outcome measures (PROMs) of psychological well-being, meaning and posttraumatic growth raised the question of whether these constructs are distinct or overlapping and how we can measure positive mental health in a brief but comprehensive manner among cancer survivors.

The aim of this thesis is to contribute to the field of psycho-oncology by obtaining more insight into psychological well-being, meaning and posttraumatic growth in cancer survivors and to provide more detailed information about the effects of MCGP-CS. The study on posttraumatic growth is conducted using the baseline data of an RCT on stepped care in head and neck cancer patients with distress²⁰. The other studies are performed using data from the RCT on the efficacy of MCGP-CS described above⁶⁰.

- In **chapter 2**, the occurrence of posttraumatic growth among head and neck cancer patients with distress is investigated. Within this population, we also explore which sociodemographic, illness-related and psychological variables predict posttraumatic growth.
- In **chapter 3**, we investigate whether MCGP-CS is effective for cancer survivors in general or whether there are subgroups for whom MCGP-CS is especially beneficial.
- Support for the theoretical model underlying meaning-centered psychotherapy has been found among advanced cancer patients⁵⁹, but not yet among cancer survivors. **Chapter 4** addresses the question of whether enhanced meaning after MCGP-CS plays a role in the reduction of depressive symptoms later in time.
- The original RCT on the efficacy of MCGP-CS has been extended with follow-

up assessments conducted one and two years after the intervention. The long-term effects of MCGP-CS are investigated in **chapter 5**.

- Theoretically, the constructs psychological well-being, personal meaning and posttraumatic growth are not clearly distinguishable. Furthermore, their PROMs appear to overlap. **Chapter 6** addresses the question of whether these PROMs measure separate or overlapping constructs.
- In **chapter 7**, the main findings of this thesis are summarized and integrated into the relevant literature. This chapter ends with the clinical implications of these findings and future research perspectives.

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2

POSTTRAUMATIC GROWTH AMONG HEAD AND NECK CANCER SURVIVORS WITH PSYCHOLOGICAL DISTRESS

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ABSTRACT

OBJECTIVE

Information on posttraumatic growth (PTG) among HNC survivors with a high level of distress is limited. The aim of this cross-sectional study was to investigate the occurrence of PTG among distressed HNC survivors, and its association with anxiety, depressive, nicotine, and alcohol use disorders, and health-related quality of life.

METHODS

Seventy-four HNC survivors with psychological distress (HADS anxiety > 7 and/or HADS depression > 7) completed the Posttraumatic Growth Inventory, which comprises five subscales: Relating to others, New possibilities, Personal strength, Spiritual change, and Appreciation of life, and the EORTC Quality of Life Questionnaire. Anxiety, depressive, nicotine, and alcohol use disorders were measured using the Composite International Diagnostic Interview.

RESULTS

Moderate to high PTGI scores occurred in 10% of the HNC survivors with distress. The mean total PTGI score was 30.8 ($SD = 19.7$), with the highest mean score on the subscale Relating to others. A multivariate regression model consisting of tumor stage, anxiety disorder, alcohol use disorder, and social functioning predicted total PTGI score best ($F(4, 64) = 7.565, p < .000, R^2 = .321$).

CONCLUSIONS

The presence of PTG in this population of distressed HNC survivors was low. PTG occurred most in the domain of relating to others. Among distressed HNC survivors, higher PTG was associated with lower tumor stage, absence of an anxiety disorder, absence of an alcohol use disorder, and better social functioning.

BACKGROUND

It is increasingly acknowledged that adverse life events, like cancer, can lead to the experience of positive psychological changes. Various terms are used for these changes, such as posttraumatic growth (PTG)¹, benefit finding², stress-related growth³, and thriving⁴. Tedeschi and Calhoun, who coined the term PTG, consider these terms as roughly equivalent in meaning⁵. PTG is defined as psychological growth beyond previous levels of functioning, as a result of the struggle with a traumatic event⁵. The subjective appraisal of a life threatening illness generates psychological distress, which activates a coping process. Over time, this process may lead to PTG in several areas of life: relating to others, new possibilities, personal strength, spiritual change, and appreciation of life.

Head and neck cancer (HNC) survivors often have to deal with devastating consequences of this type of cancer and its treatment, such as pain, fatigue, problems with speech and swallowing, and changes in facial appearance. These effects negatively affect their health-related quality of life⁶, and over 25% of HNC survivors suffer from clinical levels of distress⁷. However, in this population moderate to high levels of PTG have consistently been found^{8–10}, which are comparable to levels of PTG in other cancer populations^{11–13}. In a systematic review including five studies, Harding and colleagues identified several factors that seem to be associated with PTG in HNC survivors: younger age at the time of diagnosis, relationship status, positive reframing, optimism, and hope¹⁴.

Little is known, however, about the occurrence of PTG specifically in HNC survivors with a high level of distress, and about the factors associated with it. Earlier studies in HNC survivors did not find a significant association between PTG and distress^{8,9,15}. According to Tedeschi and Calhoun distress and PTG can coexist. Some degree of distress is needed to initiate the struggle resulting in PTG, but PTG does not put an end to the distress caused by cancer⁵. Possibly, PTG in distressed HNC survivors may be moderate to high despite distress.

However, a meta-analysis on PTG in cancer and HIV patients showed that there is great variability in effect sizes between studies, but that overall there seems to be a small relation between increased negative aspects of mental health, including distress, and lower PTG¹⁶. A possible explanation for these inconclusive findings is that the association between PTG and distress is nonlinear, but has an inverted U shape, due to three groups of survivors¹⁷. One group of survivors may not have perceived cancer

as a severe or traumatizing illness, and is less distressed, but therefore not engaged in coping and PTG. Another group of survivors may experience more distress, but may cope adequately, and therefore experience higher levels of PTG. A third group may be so heavily burdened by comorbid psychiatric symptoms, such as anxiety and depression, that they experience PTG to a limited extent. Since the details of PTG in distressed HNC survivors are unknown, the focus in this study is specifically on PTG in this distressed survivor group.

Among distressed HNC survivors comorbid nicotine and alcohol use disorders may be highly prevalent¹⁸. Nicotine and alcohol use can function as maladaptive ways of coping with distress and may impede more healthy coping processes, leading to PTG^{19,20}. However, in two studies on HNC survivors, no association between substance use and benefit finding was found^{8,9}. It is possible that substance use only hampers the occurrence of PTG if it is substantial. Therefore, in the current study, survivors with a nicotine and alcohol use disorder were compared to survivors without these diagnoses.

The aim of the present study was to investigate the occurrence of PTG among HNC survivors with psychological distress, and to examine the associations of PTG with sociodemographic and clinical factors, nicotine and alcohol use disorders, anxiety and depressive disorders, and health-related quality of life. This study was designed to contribute to a better understanding of PTG in HNC survivors with psychological distress, and to answer the question whether it is a useful construct to address PTG in psychological care for HNC survivors.

METHODS

PARTICIPANTS

For this study, baseline data were used from a randomized controlled trial on a stepped care intervention program targeting psychological distress in HNC and lung cancer survivors²¹. This study has been approved by the Medical Ethical Committee of VU University Medical Center, Amsterdam, The Netherlands. HNC survivors were recruited between 2009 and 2013 at the Department of Otolaryngology-Head and Neck Surgery of VU University Medical Center. All patients visiting the department for follow-up consultation were screened for psychological distress. Inclusion criteria were: curative treatment for HNC (squamous cell carcinoma of the lip, oral cavity, oropharynx, hypopharynx, or larynx; all stages; all treatment modalities), treatment completed at least one month ago, and an increased level of psychological distress

as assessed by the Hospital Anxiety and Depression Scale (HADS anxiety > 7 and/or HADS depression > 7). Exclusion criteria were: cognitive dysfunction, high suicide risk, psychotic and/or manic signs, and too little knowledge of the Dutch language to fill out the questionnaires. Since the efficacy of stepped care was assessed in the intervention study, current psychological treatment, or treatment completed less than two months ago, were exclusion criteria, as well. Eligible survivors who provided informed consent, had a diagnostic telephone interview (Composite International Diagnostic Interview (CIDI))^{22,23} and received the baseline questionnaires. If the questionnaires were not returned, participants received one telephonic reminder.

OUTCOME MEASURES

Participants completed questionnaires on PTG (PTGI), anxiety and depressive symptoms (HADS), and health-related quality of life (EORTC QLQ-C30). Anxiety and depressive disorders, and nicotine and alcohol use disorders were measured using the World Mental Health Composite International Diagnostic Interview (WHO CIDI). Participants further filled out a study specific questionnaire on sociodemographic factors: age, gender, relationship status, number of years of education, and work situation. Illness-related information, including tumor location, tumor stage, type of treatment, and time since treatment, was obtained from medical records.

The PTGI is a 21-item measure of posttraumatic growth, validated in Dutch cancer patients. It has five subscales: relating to others, new possibilities, personal strength, spiritual change, and appreciation of life. A 6-point Likert scale was used with 0 = not at all, 3 = moderate, and 5 = very great degree of PTG. The total score ranges from 0 to 105. A higher score indicates a higher level of PTG^{1,24}. To investigate the prevalence of PTG participants were divided in two groups. Mean items scores of < 3 were considered as low PTG, and scores of ≥ 3 as moderate to high PTG²⁵. In the current study the PTGI had a Cronbach's alpha of .92.

A validated Dutch version of the HADS was used to assess psychological distress. The HADS is a 14-item self-assessment scale for measuring distress with two subscales: anxiety and depression. The total HADS score ranges from 0 to 42, the subscales from 0 to 21. A HADS anxiety or HADS depression score of > 7 indicates an increased risk for an anxiety or depressive disorder^{26,27}. Cronbach's alpha's were .77 for the HADS anxiety and .69 for the HADS depression subscale.

The 30-item EORTC QLQ-C30 (version 3.0) includes a global health-related quality of life scale and five functional scales: physical functioning, role functioning, emotional

functioning, cognitive functioning, and social functioning. There are three symptom scales: nausea and vomiting, fatigue, and pain, and six single items. The single item scales were not used in this study. The scores of the EORTC QLQ-C30 are linearly transformed to a scale of 0-100, with a higher score indicating a higher level of functioning or global health-related quality of life, or a higher level of symptoms or problems ^{28,29}. Cronbach's alpha's of the subscales ranged from .66 to .92.

The CIDI (basic version 1.0, 12 months) is a comprehensive, fully structured diagnostic interview of the presence of mental disorders in the last 12 months according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)^{22,23}. The disorders assessed in the present study were: depressive disorder, anxiety disorder (generalized anxiety disorder, panic disorder, agoraphobia, social and specific phobia), nicotine use disorder, and alcohol use disorder.

STATISTICAL ANALYSES

Descriptive statistics were used to describe the sociodemographic and illness-related characteristics of the study sample, the prevalence of PTG, and the scores on the measurement instruments. Univariate analyses were used to examine the association of PTG with sociodemographic and illness-related variables, the HADS, EORTC QLQ-C30, and CIDI diagnoses. Variables with $p < .10$ were tested for multicollinearity, using variance inflation factors and tolerance statistics, and were entered into a backward elimination regression analysis with the PTGI total score as outcome variable. Based on a power analysis, the number of determinants of the PTGI total score in the multiple regression was limited to a maximum of 7. In all analyses a $p \leq .05$ was considered statistically significant. IBM SPSS Statistics for Windows version 21 was used to perform all tests.

RESULTS

PARTICIPANTS

In total, 920 HNC survivors were screened, 162 (18%) survivors met all inclusion criteria, and 84 (52%) of them agreed to participate. Four participants (5%) could not be reached during the study, and six (7%) returned questionnaires with > 2 missing PTGI items and were excluded from analyses. Survivors who declined participation did not differ from participants in terms of gender and HADS score, but they were on average older ($M = 65.0$, $SD = 10.6$) than participants ($M = 61.2$, $SD = 8.5$) ($t(148) = -2.413$, $p < .05$). Participant characteristics of the remaining 74 survivors are shown in Table 1.

In summary, their mean age was 61 years, 58% was male, and 37% was working. They were on average 22 months after treatment, and 50% had tumor stage III or IV at diagnosis. Twelve percent had an anxiety disorder, 20% a depressive disorder, 23% a nicotine use disorder, and 14% was diagnosed with an alcohol use disorder.

Table 1. Sociodemographic and clinical characteristics of the study population (n=74)

Variable	n	%	M	SD	Range
Age (years)			61.2	8.5	41-83
Gender (female)	31	41.9			
Living situation (with partner)	52	70.3			
Years of education			11.5	3.4	5-21
Tumor location					
Lip/oral cavity/oropharynx	42	56.8			
Hypopharynx/larynx	20	27.0			
Other	12	16.2			
Tumor stage					
I and II	33	44.6			
III and IV	37	50.0			
Unknown	4	5.4			
Type of treatment					
Surgery	12	16.2			
Radiotherapy	27	36.5			
Chemoradiation	10	13.5			
Combination surgery and other	25	33.8			
Months since treatment			22.4	25.8	1-99
CIDI diagnosis					
Anxiety disorder (yes)	9	12.2			
Depressive disorder (yes)	15	20.3			
Nicotine use disorder (yes)	17	23.0			
Alcohol use disorder (yes)	10	13.5			

Note. CIDI: Composite International Diagnostic Interview.

POSTTRAUMATIC GROWTH (PTG)

Descriptive statistics of the PTGI total scale and subscales, the HADS, and EORTC QLQ-C30 are shown in Table 2. The mean PTGI score was 30.8 ($SD = 19.7$). The majority (90%) scored low (mean item score < 3) on this scale, and a minority of 10% reported moderate to high (mean item score ≥ 3) PTG. The highest growth was reported on the subscale Relating to others ($M = 13.1$, $SD = 7.7$), and the lowest on Spiritual change ($M = 1.4$, $SD = 2.2$).

UNIVARIATE ANALYSES OF ASSOCIATIONS WITH PTG

Univariate analyses (Table 3) showed that females had higher scores on the total PTGI

scale than males ($t(48.4) = -2.057, p < .05$). Age, living situation, number of years of education, and work situation were not significantly related to PTGI score.

Further, tumor stage was significantly associated with PTGI score ($t(51.0) = 2.490, p < .05$). Survivors with tumor stage I or II at diagnosis had a higher PTGI score than survivors with tumor stage III or IV. Tumor location, type of treatment, and time since treatment were not significantly related to PTGI score.

A lower score on depression (HADS depression; $r = -.331, p < .01$), and better social functioning ($r_s = .264, p < .05$) were associated with higher PTGI scores. Anxiety (HADS anxiety), other domains of health-related quality of life, diagnoses of depressive and anxiety disorders, and nicotine and alcohol use disorders were not significantly related to PTGI score.

Table 2. Descriptive statistics on patient reported outcomes

Measure	M	SD	Range
PTGI	30.8	19.7	0-90
Relating to others	13.1	7.7	0-30
New possibilities	5.8	5.2	0-20
Personal strength	5.1	4.7	0-19
Spiritual change	1.4	2.2	0-9
Appreciation of life	5.5	4.1	0-15
HADS anxiety	9.6	3.8	0-18
HADS depression	9.1	3.6	0-19
EORTC QLQ-C30			
Global quality of life	54.1	19.9	8-100
Physical functioning	69.6	20.5	13-100
Role functioning	60.6	26.5	0-100
Emotional functioning	52.0	25.8	0-100
Cognitive functioning	71.2	26.2	0-100
Social functioning	66.2	26.8	0-100
Fatigue	52.1	22.4	11-100
Nausea vomiting	10.8	17.8	0-100
Pain	38.7	29.5	0-100

Note. PTGI: Posttraumatic Growth Inventory; HADS: Hospital Anxiety and Depression Scale; EORTC QLQ-C30: European Organization Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30. $n = 74$ for all variables, except for Global quality of life. For this variable $n = 73$.

MULTIVARIATE ANALYSIS OF ASSOCIATIONS WITH PTG

A maximum of 7 variables with $p < .10$ were entered into a backward elimination regression analysis with the PTGI total score as outcome variable. These criteria were

met by: gender, tumor stage, HADS depression, CIDI diagnosis anxiety disorder, CIDI diagnosis alcohol use disorder, role functioning, and social functioning. The variance inflation factors and tolerance values indicated that multicollinearity was not a concern. Lower tumor stage, absence of an anxiety disorder, absence of an alcohol use disorder, and better social functioning were associated with a higher score on the PTGI ($F(4, 64) = 7.565, p < .000, R^2 = .321$) (Table 4).

Table 3. Univariate associations of sociodemographic, clinical and patient reported outcomes with PTG

Variable	Test statistic	p-value	R ²
Age	$r = -.013$.913	.000
Gender	$t(48.4) = -2.057$.041*	.065
Relationship status	$t(72) = 1.446$.153	.028
Years of education	$r = -.097$.411	.009
Employment	$t(72) = .614$.541	.005
Tumor location	$F(2, 71) = 2.480$.091	.065
Tumor stage	$t(51.0) = 2.490$.016*	.088
Type of treatment	$F(3, 70) = 1.159$.332	.047
Months since treatment	$r_s = -.187$.111	.026
HADS anxiety	$r = .014$.906	.000
HADS depression	$r = -.331$.004**	.109
EORTC QLQ-C30			
Global quality of life	$r = .201$.087	.041
Physical functioning	$r_s = -.035$.768	.000
Role functioning	$r_s = -.207$.077	.029
Emotional functioning	$r = .056$.638	.003
Cognitive functioning	$r_s = -.011$.926	.006
Social functioning	$r_s = .264$.024*	.049
Fatigue	$r_s = -.149$.206	.013
Nausea vomiting	$r_s = .020$.866	.002
Pain	$r_s = -.067$.573	.000
CIDI diagnosis			
depressive disorder	$t(72) = 1.019$.312	.014
anxiety disorder	$t(72) = 1.862$.067	.046
nicotine use disorder	$t(72) = -0.446$.657	.003
alcohol use disorder	$t(72) = 1.958$.054	.051

Note. PTG: Posttraumatic Growth; HADS: Hospital Anxiety and Depression Scale; EORTC QLQ-C30: European Organization Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; CIDI: Composite International Diagnostic Interview.

* $p < .05$

** $p < .01$

Table 4. Regression model of PTG in HNC survivors with psychological distress

Variable	B	SE B	Bêta	R ²	p-value
Tumor stage	-13.806	4.071	-0.355	.321	.001
Anxiety disorder (CIDI)	-19.847	6.739	-0.309		.004
Alcohol use disorder	-12.766	5.944	-0.221		.036
Social functioning	0.201	0.077	0.272		.011

Note. PTG: Posttraumatic growth; CIDI: Composite International Diagnostic Interview.

DISCUSSION

This study was conducted to investigate the occurrence of PTG, and factors associated with PTG among HNC survivors with psychological distress. Results showed that positive psychological changes do occur among distressed HNC survivors, albeit to a relatively small extent. Among these distressed HNC survivors, about 10% reported moderate to high PTG. In contrast, in two other studies on HNC survivors in general, 60-80% found a moderate to high amount of benefits after cancer, measured with the Benefit Finding Scale^{8,9}. Also, in the present study the overall PTGI level was significantly lower ($M = 30.8, SD = 19.7$) than, for example, in oral cavity cancer survivors ($M = 51.8, SD = 11.2, t(122) = -6.793, p < .05$)¹⁰, and in earlier studies on cancer survivors in general^{30,31}. An explanation may be that only HNC patients with a high level of distress were included in this study; survivors who do not perceive cancer as a severe illness, and therefore have both lower distress and PTG scores, were largely excluded. Distressed survivors may be so heavily burdened by symptoms of anxiety or depression, that they experience PTG only to a limited extent^{5,17}. These results suggest that distress and PTG can co-exist, but that higher levels of distress may inhibit coping processes resulting in PTG.

In line with the idea that there is a relation between perceived illness severity, distress and PTG, in the present study a higher tumor stage was associated with lower PTG. An association between a higher tumor stage and lower PTG was also reported by Ho and colleagues in oral cavity cancer patients¹⁰. Also, Tang and colleagues found much lower PTG in terminally ill cancer patients³². However, two other studies on HNC survivors did not find this association^{8,9}. In the present study, lower PTG was also associated with the presence of an anxiety disorder, which is in contrast with earlier studies³³. Further research is needed to explore in more detail the associations between tumor stage, perceived illness severity, distress, PTG, and anxiety disorders.

With respect to coping style, it is interesting that in the present study lower PTG was

associated with the presence of an alcohol use disorder. It may be that among HNC survivors with psychological distress, for some alcohol abuse functions as a maladaptive coping style, while PTG is the result of a more adaptive coping style for others. This association was reported earlier in HIV patients³⁴, but was absent in previous studies on HNC patients^{8,9}. Further, there is evidence that social support is positively associated with PTG in cancer patients³⁵. The association between better social functioning and higher PTG in the present study supports these findings. Also, the fact that the highest PTG was reported in the area of relations with others, underscores the importance of social relations for distressed HNC survivors. Perhaps, because HNC and its treatment can have effects that severely impede social functioning, more limitations in social functioning are associated with lower PTG among HNC survivors.

Limitations of this study were that the sample size was relatively small, all analyses were cross-sectional, which precludes causal inference, and only 32% of the variance in PTGI scores was explained. Several factors such as coping style, perceived illness severity and life threat, hope, and optimism were not assessed in this study, but could possibly explain an additional part of the variance^{11,13}. Future studies could give more insight in the role of these variables in experiencing PTG by distressed HNC survivors. Further, a debate is ongoing about the interpretation of PTGI scores³⁶. Tedeschi and Calhoun consider these scores as reflecting genuine psychological growth⁵, while others suggest that PTG is a subjective perception of reality, or a way of coping with a traumatic experience, in which no real growth takes place. Furthermore, some studies suggest that PTG might be predictive of negative psychological functioning³⁷. It may be that PTG functions as a coping style early after diagnosis, but becomes real growth after a longer period of time¹⁶. Since the passage of time may impact PTG, it is a limitation of the present study that the range in time since treatment was large. Also, for this study baseline data were used from an intervention study. Distressed survivors with a large suicide risk, or who already had psychological treatment, were not included, which hampers generalizability. Strengths of the present study were that it specifically targeted HNC survivors with psychological distress and that, in addition to patient reported anxiety and depressive symptoms, also depressive, anxiety, nicotine, and alcohol use disorders were investigated.

Prospective larger studies are needed to investigate the development and course of PTG from diagnosis to long-term follow-up in relation to possible moderators and mediators. Because in this study PTG occurred in only 10% of distressed HNC survivors, intervention studies are needed to investigate whether PTG can actually be stimulated by psychological interventions for distressed cancer survivors, and whether that

results in better psychological functioning. Because in this study social functioning was related to PTG, this may be particularly important to incorporate in such an intervention. However, experiencing PTG should not be regarded as something that cancer survivors should necessarily accomplish, but rather as a possibility clinicians should be aware of and may facilitate³⁸. Based on the findings in the present study, PTG could possibly be better facilitated if anxiety disorders and alcohol use disorders are addressed, as well as social functioning.

CONCLUSIONS

PTG occurred among HNC survivors with psychological distress, albeit to a lesser extent compared to (HNC) cancer survivors in general. A sense of improved relations with others was the strongest domain of PTG. Among distressed HNC survivors, more PTG was experienced by survivors with a lower tumor stage, no anxiety or alcohol use disorder, and better social functioning.

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3

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

OBJECTIVE

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 analyse 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, gender, 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 three and six month follow-up (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) gender (on HADS-D; $F(1,98)=6.1$, $p=.015$) and (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; $F(3,253)=3.4$, $p=.017$).

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.

BACKGROUND

Due to ongoing cancer treatment innovations, the number of cancer survivors is steadily increasing¹. 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 cancer⁴. 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 patients⁵. 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 limitations⁸. There is evidence to support that this intervention is effective in improving meaning and reducing distress in patients with advanced cancer⁹, as well as in cancer survivors⁸. In a randomised controlled trial (RCT) MCGP-CS was compared to care as usual (CAU) and supportive group psychotherapy (SGP) among cancer survivors⁸. 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 significance¹⁰), goal-orientedness, 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 younger¹² and

higher educated¹³ 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-analysis¹⁴. 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 survivors²⁴. The current study is a secondary analysis of the study on the efficacy of MCGP-CS⁸, 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 five years. Knowledge of which cancer survivors 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 five 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 baseline assessment, they were randomly assigned to one of the three conditions. Follow-up assessments were scheduled one week after the intervention, and three and six months thereafter.

RANDOMISATION AND BLINDING

A computer-generated randomisation 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)

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 study² 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 exercises⁸. 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 lessons⁴. 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 elsewhere⁸.

CARE AS USUAL (CAU)

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 dichotomised: gender (male vs. female), age (younger vs. older than the median of 56 years), marital status (married or 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 (3 persons) clinical characteristics were obtained via a self-report questionnaire. Cancer type was categorised 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 one 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 cut-off of ≥ 8 was used for dichotomisation²⁵. Furthermore, psychosocial characteristics included the occurrence of negative life events other than cancer in the past two 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 treatment (any treatment from a psychiatrist or psychologist) in the past year (yes vs. no) was 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 study⁸ were analysed 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 7-point 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^{10,26}.

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 subscales positive relations with others ($\alpha=.81$) and purpose in life ($\alpha=.78$) were analysed. 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^{27,28}.

Psychological distress was measured using the continuous HADS-total score, and depression using the HADS depression subscale (HADS-D) score. The HADS anxiety subscale was not used, since it showed no significant change in the previous efficacy study⁸. 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 0-42, and the HADS-D score ($\alpha=.78$) from 0-21. 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 chi-square 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, the moderator,

all two-way interactions, and the 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 three and six months follow-up. Separate LMM models were constructed for each potential moderator, the short and long-term, and each outcome measure, and the p-value 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 six months follow-up scores. Between-group difference in effect sizes (Cohen's d) within the categories of the significant moderator variables were 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 variable²⁹. 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 drop-out were published elsewhere⁸. Of the in total 170 participants, 57 were randomised into the MCGP-CS and 57 into the CAU condition. In the MCGP-CS condition, 50 participants completed assessment post-intervention, and 45 at six months follow-up. In the CAU condition, 47 completed assessment post-intervention and 35 at six months 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%) were randomly assigned to CAU.

Table 1. Participant characteristics

	MCGP-CS (N=57)		CAU (N=57)		<i>p</i> ^a
	<i>n</i>	%	<i>N</i>	%	
Age (<i>M, SD, range</i>)	59	11, 32-81	57	10, 37-83	.48
Gender (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 (<i>in situ</i>)	3	5%	2	4%	
I	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 (<i>Mdn, range</i>)	19	6-58	18	3-55	.64
HADS anxiety $\geq 8^c$	24	42%	20	36%	.49
HADS depression $\geq 8^c$	14	25%	7	13%	.10
Other negative life event	27	47%	32	56%	.35
Past psychological treatment ^d	12	21%	7	12%	.24

Note. MCGP-CS: meaning-centered group psychotherapy for cancer survivors; CAU: care as usual.
^a*p*-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.
^bOnly participants below retirement age were included in analyses using employment (MCGP-CS: N=37, CAU: N=41).
^cIn CAU HADS anxiety and HADS depression: N=56.
^dIn CAU Psychological treatment: N=55.
**p*<.05

MODERATORS OF SHORT-TERM MCGP-CS EFFECT

Gender 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).

Table 2. Estimated marginal mean outcome measure scores of significant moderators per moderator category, and condition from baseline to post-intervention (short term)

Outcome measure	Moderator	Condition	<i>n</i>	Baseline	Post-intervention	<i>F</i> (<i>df</i>) (3-way interaction LMM)	<i>p</i> (3-way interaction LMM)	<i>p</i> (post-hoc t-test)	Cohen's <i>d</i> (between groups)	<i>R</i> ² of model without moderator	<i>R</i> ² of model with moderator		
depression (HADS-D)	male	MCGP-CS	17	5.3	3.2	6.1(1,98)	.015*	.020*	-1.5	.020	.12		
		CAU	6	7.8	10.2								
	female	MCGP-CS	40	5.0	3.9							.38	-0.31
		CAU	51	4.0	3.7								
purpose in life (SPWB)	depression (low)	MCGP-CS	43	4.3	4.6	5.7(1,93)	.019*	.12	0.44	.027	.17		
		CAU	50	4.4	4.4								
	depression (high)	MCGP-CS	14	3.4	3.9							.018*	1.5
		CAU	7	4.0	3.7								

Note. HADS-D: hospital anxiety and depression scale; SPWB: scales of psychological well-being; MCGP-CS: meaning-centered group psychotherapy for cancer survivors; CAU: care as usual. * $p < .05$

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 ($d=0.44$).

MODERATORS OF LONG-TERM MCGP-CS EFFECT

Psychological treatment in the past year moderated the long-term 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 six months follow-up period than survivors who had received psychological treatment in the past year ($F(3,253)=3.4, p=.017$). More precisely, only survivors who had not received psychological treatment in the past year, improved during the six months after MCGP-CS, while participants who had received psychological treatment in the

past year barely improved during the six months after MCGP-CS, and got worse in the CAU condition.

Table 3. Estimated marginal mean outcome measure scores of significant moderators per moderator category, and condition from baseline to post-intervention, at three and six months FU (long-term)

Outcome measure	Moderator	Condition	<i>n</i>	Baseline	Post-intervention	Three month FU	Six month FU	<i>F</i> (<i>df</i>) (3-way interaction LMM)	<i>p</i> (3-way interaction LMM)	<i>p</i> (post-hoc t-test)	Cohen's <i>d</i> (between-groups)	<i>R</i> ² of model with moderator	<i>R</i> ² of model with moderator
distress (HADS-total)	psychological treatment (yes)	MCGP-CS	12	16	15	16	14	3.4(3,253)	.017*	.26	-0.91	.035	.14
		CAU	7	14	12	10	19						
	psychological treatment (no)	MCGP-CS	45	11	8	8	7						
		CAU	50	11	11	10	11						

Note. HADS: hospital anxiety and depression scale; MCGP-CS: meaning-centered group psychotherapy for cancer survivors; CAU: care as usual. * $p < .05$

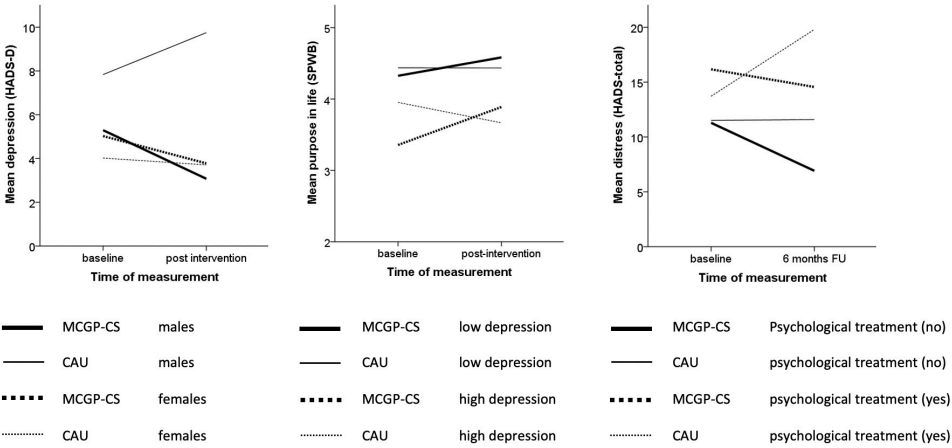


Figure 1. Moderator effects of gender (short-term), depressive symptoms at baseline (short-term), and psychological treatment in the year before participation (long-term)

Note. 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

However, the post-hoc test did not show a significant difference in the HADS-total change score between MCGP-CS and CAU, neither 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 term⁸. 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 post-intervention and during the following six 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, gender did moderate MCGP-CS efficacy. The short-term 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 support³⁰, 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 symptoms³¹. An intervention focusing on finding the sources of meaning that they still have may be particularly suitable to help males alleviate depressive symptoms⁶. 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^{12,13,32}. The 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^{33,34}. 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 gender 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 drop-out 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 fourteen 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 issue³⁵. 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 datasets of several group psychotherapy efficacy studies in cancer patients are combined, should be undertaken to attain more power³⁶.

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 to 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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4

DOES ENHANCED MEANING AFTER MEANING-CENTERED GROUP PSYCHOTHERAPY MEDIATE A REDUCTION IN DEPRESSIVE SYMPTOMS IN CANCER SURVIVORS?

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ABSTRACT

OBJECTIVE

After meaning-centered group psychotherapy for cancer survivors (MCGP-CS), depressive symptoms tend to decrease. Based on MCGP-CS' working model, an enhanced sense of meaning may play a mediating role in this decrease. This study's aim, is to assess whether personal meaning, and other meaning-related factors, are mediators of the relation between MCGP-CS and depressive symptoms.

METHODS

Cancer survivors ($n=114$) were randomly allocated to MCGP-CS or care as usual (CAU). Assessments were scheduled at baseline, post-intervention, at three and six months follow-up. Assessed mediators were personal meaning, goal-orientedness, purpose in life and positive relations. Mediation models were estimated based on structural equation modeling. Subsequently, we computed the indirect effects of MCGP-CS on depressive symptoms at three and six months follow-up, through the mediators, respectively post-intervention and at three months follow-up.

RESULTS

A small but significant indirect effect of MCGP-CS on depressive symptoms at three months follow-up was found through personal meaning post-intervention ($b=-0.29$, 95% bootstrap CI $(-0.63, -0.034)$). There were no significant indirect effects through the other meaning-related factors. Also, no significant indirect effects occurred analyzing the effect of MCGP-CS on depression at six months follow-up.

CONCLUSIONS

This study tentatively supports MCGP-CS' working model that an enhanced sense of meaning as a result of MCGP-CS mediates a reduction in depressive symptoms. Personal meaning mediated a small effect of MCGP-CS on depressive symptoms, but the other meaning-related factors did not. The longitudinal mediation effect of personal meaning occurred within a time period of three months after MCGP-CS.

BACKGROUND

Meaning-centered psychotherapy aims to enhance a sense of meaning in life, in order to reduce symptoms of depression and to improve cancer patients' quality of life¹. Several studies show its effects on meaning, depressive symptoms, and quality of life²⁻⁴. That meaning-making plays a central role in adjustment to difficult life circumstances, is a widely accepted notion among existential philosophers and psychologists⁵⁻⁹. Meaning-centered psychotherapy is based on Frankl's *logotherapy*¹⁰, and was initially developed to treat despair and demoralization in advanced cancer patients¹. Van der Spek et al. adapted meaning-centered psychotherapy for survivors of cancer¹¹. In the survivorship phase active cancer treatment is completed, but people may encounter newly arising and sometimes unexpected limitations^{12,13}. Meaning-centered group psychotherapy for cancer survivors (MCGP-CS) aims to enhance a sense of meaning in order to help survivors adjust to living after cancer.

The idea that a stronger sense of meaning leads to a decrease in depressive symptoms is also incorporated into Park's meaning-making model^{15,14}. According to this model, people continuously appraise and assign meaning to the situations they encounter. If the assigned meaning is discrepant with their global sense of meaning, feelings of distress arise. Meaning-making coping can be a way to reduce this discrepancy. If meaning-making coping leads to finding meaning and subsequent adaptation of one's global meaning, people can better account for the situation. This is expected to result in better adjustment and a reduction in depressive symptoms.

This study aims to assess whether personal meaning and other meaning-related factors are mediators of the relation between MCGP-CS and depressive symptoms later in time. Better understanding of *how* and *when* MCGP-CS affects its outcomes is necessary to be able to improve its effectiveness¹⁵⁻¹⁷. In a randomized controlled trial (RCT) among advanced cancer patients, enhanced meaning after meaning-centered psychotherapy mediated a reduction in depressive symptoms two months later¹⁸. A comparable mediation effect was found after life review therapy¹⁹. Also, longitudinal studies observing the influence of meaning on depressive symptoms over time mostly suggest that finding meaning leads to better adjustment^{14,20-24}.

This study is a secondary analysis of an RCT on the efficacy of MCGP-CS³. The outcomes revealed an improvement in meaning and other meaning-related factors, such as goal-orientedness, purpose in life, and positive relations post-intervention, as well as a reduction in depressive symptoms six months later. The present study

will investigate whether this reduction in depressive symptoms is (partly) due to the increase in meaning and other meaning-related factors, as a result of MCGP-CS. Because little is known about the timescale in which to expect an influence of meaning on depression¹⁴ the effects on both the three and six months follow-up measures are analyzed. This is the first study that investigates these potential mediation effects in the context of an RCT among cancer survivors.

METHODS

STUDY DESIGN AND POPULATION

Information on the study design, sample size calculation, randomization procedure, blinding and the primary and secondary outcomes were published in more detail previously^{3,11}. The original RCT had three conditions: MCGP-CS, supportive group psychotherapy, and care as usual (CAU), and participants were allocated in a 1:1:1 ratio. In the present study, data from MCGP-CS and CAU were analyzed, because MCGP-CS' effects on meaning and depression were clearest compared to CAU. Measurements were completed at baseline, post-intervention, and at three and six months follow-up.

Participants were recruited in four hospitals in the Netherlands. Participants were adult cancer survivors who had been diagnosed in the last five years, treated with curative intent, and who had completed their main treatment (i.e. surgery, radiotherapy, and/or chemotherapy). They had to have an expressed need for psychological care, and at least one psychosocial or meaning-related complaint. Exclusion criteria were severe cognitive impairment, current psychological/psychiatric treatment elsewhere, and insufficient command of Dutch. This RCT was approved by the Medical Ethics Committee of the Leiden University Medical Center and registered in the Netherlands Trial Register (NTR3571). Informed consent was obtained from all individual participants included in the study.

MEANING-CENTERED GROUP PSYCHOTHERAPY FOR CANCER SURVIVORS (MCGP-CS)

MCGP-CS consists of eight weekly two-hour sessions, including didactics, group discussions, experiential exercises and homework, led by a psychotherapist. Central themes are: exploration of one's identity before and after cancer; participants' life story; the things they learned during their life that can help them cope with the aftermath of cancer; creativity and the role of responsibility and courage in creating a meaningful life; and experiential sources of meaning that make one feel connected with life, such

as love and humor²⁵.

CARE AS USUAL

Cancer survivors in the CAU study arm did not participate in the group interventions. Their mental health care uptake was monitored.

OUTCOME

Depressive symptoms

The Hospital Anxiety and Depression Scale (HADS) was used to measure distress^{26,27}. The HADS is a 14-item questionnaire consisting of the subscales depression and anxiety, validated among Dutch patients²⁶. In this study the depression subscale ($\alpha=.78$) was used, because this was affected by MCGP-CS³. Items were scored on a 4-point Likert scale and a higher score reflects more symptoms of depression.

MEDIATORS

Meaning and goal-orientedness

The Dutch version of the Personal Meaning Profile (PMP) was used to measure one's sense of meaning^{28,29}. This is a 39-item measure comprising five subscales, validated in Dutch cancer patients²⁸. In this study the total personal meaning scale ($\alpha=.93$) and the goal-orientedness subscale ($\alpha=.89$) were investigated as mediators. Their scores were transformed to a scale of 0 to 100. Higher scores indicated a stronger sense of meaning in life or goal-orientedness.

Purpose in life and positive relations

Ryff's Scales of Psychological Well-Being (SPWB)^{30,31} measure psychological well-being. The Dutch version of the SPWB consists of 49 items in eight subscales and was validated in a Dutch sample³¹. In this study the subscales purpose in life ($\alpha=.78$) and positive relations ($\alpha=.81$) were investigated as mediators. Items were scored on a 6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree). Subscale scores were calculated as the mean item score and higher scores indicated a greater sense of purpose in life and more positive relations.

CONFOUNDERS

Several patient characteristics could potentially influence the effect of meaning-centered psychotherapy on meaning^{1,32}. Sociodemographic characteristics were assessed by self-report: age, gender, education, household composition, and religion. Illness-related characteristics were retrieved from medical records: type of cancer, type of treatment, and months since last cancer treatment.

STATISTICAL METHODS

Differences in participant characteristics between MCGP-CS and CAU were tested with independent samples t-tests, chi-square tests, Fisher's exact tests and Mann-Whitney U tests. Characteristics that differed significantly between these conditions, were assessed as confounders in all mediation models. If the potential confounder changed the indirect effect >10%, it was kept in the model.

Participants with missing assessments were compared to complete cases with regard to sociodemographic and clinical characteristics and baseline mediator and outcome scores. Based on these analyses, it was assumed that data were missing at random (MAR). In the longitudinal mediation analyses full information maximum likelihood estimation (FIML) was used, so participants with missing assessments were still included.

Longitudinal mediation analysis was performed based on cross-lagged panel models, estimated with structural equation modelling (SEM) (Figure 1)¹⁷. Both the mediator and the outcome were measured at four points in time (baseline, post-intervention, three and six months follow-up). All post-intervention and follow-up scores were controlled for scores one time point earlier. The total effect of MCGP-CS on depression was measured in a model with only paths from the intervention to each post-intervention and follow-up measure of depression (c-paths). In the mediation model, paths were added from the mediator scores at baseline, post-intervention and 3 months follow-up to depression scores one point later in time (b-paths). The effect of the intervention in the mediation model was represented by paths from the condition (MCGP-CS or CAU) to each post-intervention and follow-up score of the mediator (a-paths) and outcome (c'-paths).

Within each model two mediation paths were analysed: (1) from the condition to the mediator post-intervention (a1), to the outcome three months later (b2) and (2) from the condition to the mediator three months later (a2), to the outcome six months later (b3). The longitudinal indirect effects were calculated as $a1*b2$ and as $a2*b3$, and accompanied by 95% percentile bootstrap confidence intervals based on 5000 bootstrap samples³³.

Two sensitivity analyses were conducted. First, all analyses were repeated using a sample with participants with complete data on all follow-up assessments. The second sensitivity analysis was conducted to acquire more insight into the timing of the mediation effect. In this analysis cross-sectional paths from the mediator

to depression at the same time were added to the model. Stata statistical software (version 16, StataCorp) was used for SEM and IBM SPSS Statistics (version 24) for all other analyses. A p -value <.05 was considered statistically significant.

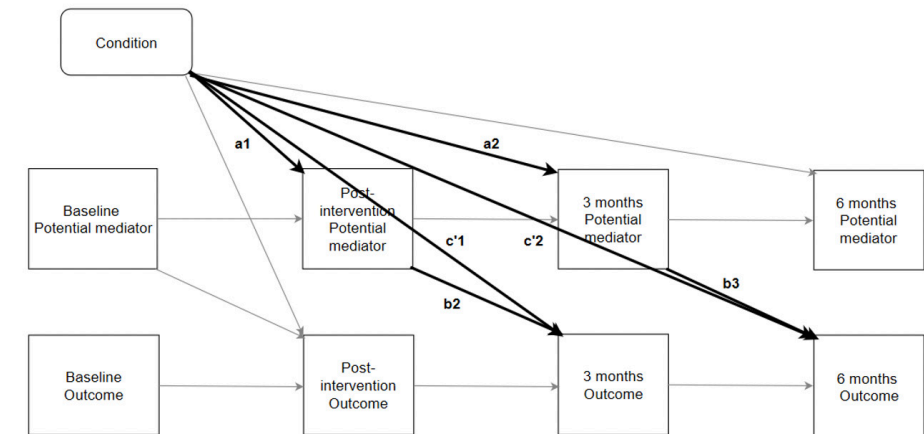


Figure 1. Cross-lagged panel model used to test longitudinal indirect effects of enhanced meaning after MCGP-CS at depressive symptoms

RESULTS

PARTICIPANT CHARACTERISTICS

In total, 2200 survivors received an invitation, 419 responded, and 170 were eligible, signed informed consent and filled in the baseline questionnaire. Details of the participant flow were published previously³. In the present study, data was used of 114 participants, randomly allocated to MCGP-CS (n=57) or CAU (n=57). In the MCGP-CS condition 42 (74%) participants completed all follow-up assessments and in the CAU condition 29 (51%). Most participants were female (76%) and they were on average 59 (SD: 11) years old. The majority lived with a partner (48%), was treated for breast cancer (60%) and 44% still had hormone therapy (Table 1).

There were significantly more females randomized into CAU (89%) than into MCGP-CS (70%), but gender did not change the indirect effects >10%. There were no significant differences between complete cases and those who missed follow-up assessments, except for number of MCGP-CS sessions attended. Participants who attended >5 sessions, were more likely to have completed all assessments ($\chi^2(2)=17.10$, $p<0.001$). These results supported the assumption that data were MAR.

Table 1. *Participant characteristics*

	MCGP-CS (n=57)	CAU (n=57)	p
Age, mean (SD), range	59 (11), 32-81	57 (10), 37-83	0.48
Gender			0.010
Female	40, 70%	51, 89%	
Male	17, 30%	6, 11%	
Level of education			0.46
Low	18, 32%	17, 30%	
Medium	20, 35%	15, 26%	
High	19, 33%	25, 44%	
Household composition			0.60
Alone	10, 18%	11, 19%	
With partner	28, 49%	21, 37%	
With children	2, 3%	3, 5%	
With partner and children	17, 30%	22, 39%	
Religion			0.13
Yes	23, 40%	31, 54%	
No	34, 60%	26, 46%	
Type of cancer			0.053
Breast	30, 53%	42, 74%	
Colon	15, 26%	10, 17%	
Other	12, 21%	5, 9%	
Type of treatment			
Surgery	57, 100%	56, 98%	1.00
Chemotherapy	26, 46%	36, 63%	0.060
Radiation	31, 54%	33, 58%	0.71
Hormone therapy	22, 39%	30, 53%	0.13
Months since last cancer treatment, median (range)	19 (6-58)	18 (3-55)	0.83
Number of MCGP-CS sessions completed			
< 3	9, 16%		
3-5	4, 7%		
> 5	44, 77%		

Note. MCGP-CS: meaning-centered group psychotherapy for cancer survivors; CAU: care as usual.

TOTAL EFFECTS

Participants in the MCGP-CS group had a significantly lower depression score than in CAU post-intervention ($b = -1.18$, $p < 0.05$, 95% CI (-2.14, -0.23)), and after six months of follow-up ($b = -1.57$, $p < 0.05$, 95% CI (-2.89, -0.25)). After three months, the depression scores of MCGP-CS and CAU were comparable ($b = 0.040$, $p > 0.05$, 95% CI (-0.94, 1.02)).

LONGITUDINAL MEDIATION EFFECTS

Personal meaning

Compared to CAU, MCGP-CS resulted in a significantly higher personal meaning score post-intervention (a1-path, $b = 5.67$, $p < 0.001$) (Table 2, Figure 2). Subsequently,

higher personal meaning post-intervention significantly reduced the depression score three months later (b2-path, $b = -0.052$, $p < 0.05$). Also, the indirect effect of MCGP-CS on depression after three months through personal meaning post-intervention was significant (a1*b2, $b = -0.29$, 95% bootstrap CI (-0.63, -0.034)). This means that compared to CAU, MCGP-CS participants reported on average a 0.29 points lower HADS-depression score, through a higher personal meaning score. The direct effect of MCGP-CS on depression after three months (c'1-path) was not significant, but after six months it was (c'2-path, $b = -1.61$, $p < 0.05$). Both the effect of MCGP-CS on personal meaning three months later (a2-path), as well as the effect of personal meaning on depression six months later (b3-path), were not significant. Nor was the indirect effect of MCGP-CS on depressive symptoms after six months through personal meaning after three months (a2*b3).

The mediation models of the meaning-related factors followed a comparable pattern as the mediation model of personal meaning.

Goal-orientedness

Compared to CAU, MCGP-CS resulted in a significant improvement of goal-orientedness post-intervention (a1-path), which significantly reduced depression three months later (b2-path). The indirect effect of MCGP-CS on depression through goal-orientedness (a1*b2), however, was not significant. The effect of MCGP-CS on goal-orientedness three months later (a2-path) was not significant. Nor was the effect of goal-orientedness three months later on depression six months later (b3-path), and their indirect effect (a2*b3). The direct effect of MCGP-CS on depression six months later was significant (c'2-path).

Purpose in life

MCGP-CS significantly improved purpose in life post-intervention (a1-path), which subsequently reduced depression three months later (b2-path). The indirect effect (a1*b2), however, was not significant. Also, the effect of MCGP-CS on purpose in life after three months (a2-path), the effect of purpose in life after three months on depression after six months (b3-path), and their indirect effect (a2*b3), were not significant. The direct effect of MCGP-CS on depression after six months (c'2-path) was significant.

Positive relations

The effect of MCGP-CS on positive relations post-intervention (a1-path) was significant, but the effect of positive relations post-intervention on depression three months later (b2-path), and the indirect effect (a1*b2) were not significant. Further, the effect of

MCGP-CS on positive relations three months later (a2-path) was not significant, nor was the effect of positive relations on depression after six months (b3-path), and their indirect effect (a2*b3). The direct effect of MCGP-CS on depression after six months (c'2-path) was significant.

Table 2. Indirect effects of the mediators between the condition (MCGP-CS or CAU) and depressive symptoms

Mediator	From	Condition (baseline)	Mediator (post-intervention)	Condition (baseline)	Indirect effect (95% bootstrap CI)
	To	Mediator (post-intervention)	Depression (3 months)	Depression (3 months)	
		a1 (b)	b2 (b)	c' (b)	
Personal meaning		5.67***	-0.052**	0.22	-0.29 (-0.63, -0.034)
Goal-orientedness		13.64***	-0.034*	0.39	-0.46 (-0.98, 0.010)
Purpose in life		0.29**	-0.68*	0.075	-0.20 (-0.57, 0.067)
Positive relations		0.27*	-0.27	0.025	-0.073 (-0.34, 0.13)
	From	Condition (baseline)	Mediator (3 months)	Condition (baseline)	
	To	Mediator (3 months)	Depression (6 months)	Depression (6 months)	
		a2 (b)	b3 (b)	c' (b)	
Personal meaning		-0.75	0.035	-1.61*	-0.026 (-0.21, 0.13)
Goal-orientedness		-4.66	0.015	-1.62*	-0.072 (-0.43, 0.16)
Purpose in life		6.2×10^{-3}	0.15	-1.58*	-9.2×10^{-4} (-0.17, 0.17)
Positive relations		-0.091	-0.52	-1.67*	0.047 (-0.12, 0.18)

*p<.05
**p<.005
***p<.001

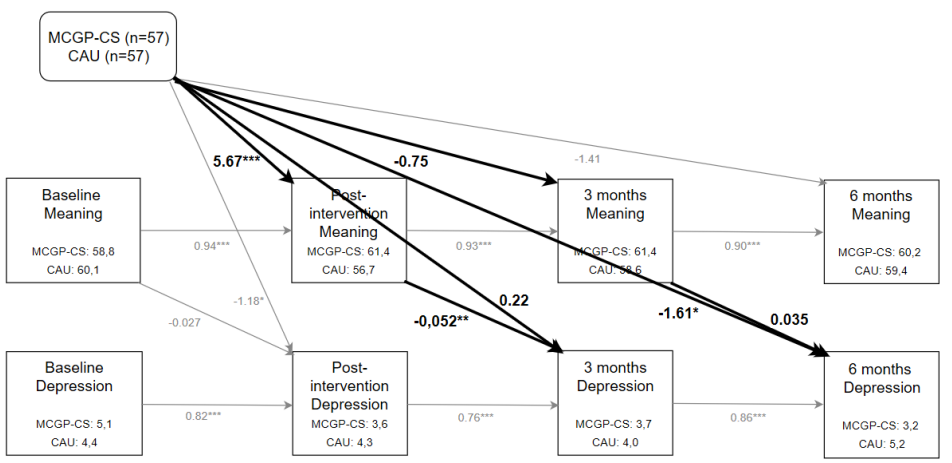


Figure 2. Cross-lagged panel model displaying longitudinal mediation effects using unstandardized path coefficients, and mean scores of meaning and depressive symptoms

Note. MCGP-CS: meaning-centered group psychotherapy for cancer survivors; CAU: care as usual.

*p<.05
**p<.005
***p<.001

COMPLETE CASES

Among complete cases religion differed between both conditions, but only needed to be kept in the mediation model of positive relations. The total effect of MCGP-CS on depression was only significant after six months ($b=-1.56, p<0.05, 95\% \text{ CI } (-2.91, -0.22)$). The outcomes of the longitudinal mediation analyses gave comparable regression coefficients as the intention-to-treat analyses (Table 3). A notable difference was that among complete cases the indirect effect of MCGP-CS on depressive symptoms three months later through goal-orientedness post-intervention ($a1*b2$) reached statistical significance ($b=-0.61, 95\% \text{ bootstrap CI } (-1.21, -0.098)$), alongside the significant indirect effect through personal meaning.

CROSS-SECTIONAL MEDIATION EFFECTS

The cross-sectional associations between personal meaning and depression were significant at all time points (Figure 3). The cross-sectional indirect path from the intervention to depression post-intervention through meaning post-intervention was significant ($b=-0.63, p<0.05, 95\% \text{ CI } (-1.25, -0.15)$), but the cross-sectional indirect paths from the intervention to depression after three and six months through meaning were not. Among the other meaning-related factors no significant cross-sectional indirect effects emerged.

Table 3. Indirect effects of the mediators between the condition (MCGP-CS or CAU) and depressive symptoms, analysing complete cases

Mediator	From	Condition (baseline)	Mediator (post-intervention)	Condition (baseline)	Mediation effect (95% bootstrap CI)
	To	Mediator (post-intervention)	Depression (3 months)	Depression (3 months)	
		a1 (b)	b2 (b)	c' (b)	
Personal meaning		4.09*	-0.058**	0.50	-0.29 (-0.54, -0.0051)
Goal-orientedness		12.00***	-0.051***	0.68	-0.61 (-1.21, -0.098)
Purpose in life		0.22	-1.02*	0.29	-0.22 (-0.68, 0.045)
Positive relations ¹		0.38*	-0.33	0.033	-0.12 (-0.54, 0.16)
	From	Condition (baseline)	Mediator (3 months)	Condition (baseline)	
	To	Mediator (3 months)	Depression (6 months)	Depression (6 months)	
		a2 (b)	b3 (b)	c' (b)	
Personal meaning		-1.57	0.038	-1.56*	-0.060 (-0.30, 0.10)
Goal-orientedness		-3.73	0.016	-1.62*	-0.060 (-0.38, 0.16)
Purpose in life		-0.019	0.089	-1.63*	-1.7×10^{-3} (-0.20, 0.17)
Positive relations ^a		-0.22	-0.50	-1.52*	0.11 (-0.11, 0.34)

¹Religion was included as a confounder in the mediation model.

*p<.05
**p<.005
***p<.001

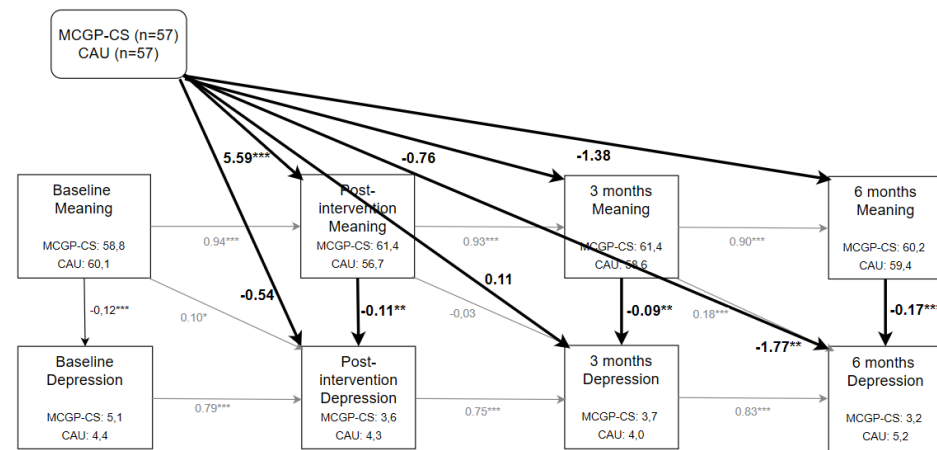


Figure 3. Cross-lagged panel model displaying cross-sectional mediation effects using unstandardized path coefficients, and mean scores of meaning and depressive symptoms

Note. MCGP-CS: meaning-centered group psychotherapy for cancer survivors; CAU: care as usual.

* $p < .05$

** $p < .005$

*** $p < .001$

DISCUSSION

The aim of this study was to assess whether personal meaning and other meaning-related factors can be considered as mediators of MCGP-CS' effect on symptoms of depression. The results tentatively support the working model underlying MCGP-CS¹. The longitudinal, intention-to-treat mediation analyses among cancer survivors indicated that improvement in meaning directly after MCGP-CS, compared to CAU, led to a small reduction in depressive symptoms three months later. Although personal meaning emerged as a mediator, the meaning-related factors purpose in life and positive relations did not. Their improvement after MCGP-CS had a smaller, non-significant effect on depressive symptoms. In contrast, among complete cases goal-orientedness emerged as a mediator, alongside personal meaning.

These findings are in line with Rosenfeld et al.'s study in which a comparable mediation effect was found within two months after meaning-centered psychotherapy, among advanced cancer patients¹⁸. Although meaning-making is typically described as a process that may lead to better adjustment over time¹⁴, it seems that when meaning-making is facilitated by psychotherapy, enhanced meaning may play a role in reducing depressive symptoms quite soon. In the present study, meaning mediated depressive

symptoms immediately post-intervention, as well. This may mean that enhanced meaning influences depressive symptoms simultaneously, and that this effect lingers on for a period of about three months.

No evidence was found that MCGP-CS continues to increase meaning three months later, and thereby would continue to play a role in further reduction of depression. Such a mediation effect, however, was found in a study on the mediating role of enhanced meaning after life review therapy on depressive symptoms six months later¹⁹. The outcomes of the present longitudinal mediation analysis seem to be in line with the interpretation that after three months a new balance has been found²², with a slightly higher sense of meaning and less depressive symptoms than before MCGP-CS. The reduction in depressive symptoms six months after MCGP-CS³, could not be explained by enhanced meaning, and should be confirmed in a future study.

The results in the first months after MCGP-CS are compatible with Park's meaning-making model¹⁴. Applying this model, we could hypothesize that (1) MCGP-CS stimulated survivors to make meaning of their cancer experience, (2) that they were generally able to make meaning, (3) that this resulted in an enhanced global meaning, which can better account for the stressors cancer survivors encounter, (4) resulting in less harmful or more benign reappraisals, (5) invoking less depressive symptoms. In the present study only step 3 and 5 were measured, but support for this route has also been found in other studies^{7,9,21,23,34}. However, the indirect effects observed in this study were small, indicating that this process is one among other factors affecting survivors' symptoms of depression.

STUDY LIMITATIONS

Strengths of this study were the sophisticated cross-lagged panel model and the robust intention-to-treat approach. A limitation is that the longitudinal statistical associations do not prove a causal relation between meaning and depressive symptoms. Future studies should investigate whether these findings can be explained by alternative factors causing changes in both variables, and whether a dose-response relationship can be demonstrated^{35,36}. A second limitation is that possibly survivors in different stages of searching for and finding meaning were included. Some did perhaps search for meaning, while others possibly already found meaning or did not feel the need to search for meaning³⁷. The effect of enhanced meaning on depressive symptoms may have been stronger for survivors searching for meaning and weaker for the other groups²¹. Lastly, there was an interval of three months between the follow-up measures. More follow-up measures with a shorter time interval may give more insight

in the timescale of this mediation effect.

CLINICAL IMPLICATIONS

For clinical practice, it is useful not only to know whether an intervention is effective, but also to be able to rely on an empirically supported working model, and to know at what timescale effects could be expected. This study suggests that meaning enhanced by MCGP-CS is a pathway to a reduction in depressive symptoms. However, MCGP-CS is foremost an intervention to enhance a sense of meaning in cancer survivors, and not solely to treat depressive symptoms.

CONCLUSIONS

This study tentatively supports MCGP-CS' working model that enhanced meaning mediates a reduction in depressive symptoms. Personal meaning mediated a small effect of MCGP-CS on depressive symptoms, but the other meaning-related factors did not. The longitudinal mediation effect of personal meaning occurred within a time period of three months after MCGP-CS.

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5

LONG-TERM EFFICACY OF MEANING-CENTERED GROUP PSYCHOTHERAPY FOR CANCER SURVIVORS: 2-YEAR FOLLOW-UP RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

OBJECTIVE

Meaning-centered group psychotherapy for cancer survivors (MCGP-CS) is an effective intervention to improve personal meaning, psychological well-being and depressive symptoms until six months after the intervention. In this study the long-term effects of MCGP-CS (i.e. at one and two years follow-up) on meaning, psychological well-being and posttraumatic growth were assessed, in comparison to supportive group psychotherapy (SGP) and care as usual (CAU).

METHODS

Cancer survivors ($n=170$) were randomized into MCGP-CS, SGP or CAU. Assessments were scheduled at baseline, one week, three months, six months, one year, and two years post-intervention. Outcome measures were the Personal Meaning Profile (PMP), Ryff's Scales of Psychological Well-Being (SPWB), the Posttraumatic Growth Inventory (PTGI), and their subscales. Linear mixed models (LMM) were used and results were both reported on an intention-to-treat (ITT) basis, as well as for intervention completers only.

RESULTS

LMM and post-hoc analyses with Bonferroni correction revealed that MCGP-CS participants reported more improvement on positive relations (subscale of SPWB) than CAU participants two years post-intervention (ITT analysis, Cohen's $d=.82$). Completers also reported more personal growth (subscale of SPWB) after MCGP-CS than after SGP one year post-intervention (Cohen's $d=.94$). No long-term effects were found on the other outcome measures.

CONCLUSIONS

In the two years after MCGP-CS the short-term significant effects on personal meaning and most positive effects related to psychological well-being faded. However, MCGP-CS had a long-term positive effect on positive relations with others and on survivors' sense of personal growth.

BACKGROUND

Many cancer survivors encounter physical hindrances and are confronted with psychosocial and existential problems, also years after curative treatment is completed^{1,2}. There is growing evidence that meaning-focused coping is a viable way to successfully adjust to the aftermath of cancer², especially if meaning can be made from the cancer experience^{3,4}. Breitbart and colleagues developed meaning-centered group psychotherapy (MCGP) to improve psychological well-being in patients with advanced cancer^{5,6}. This intervention is grounded in the work of the psychiatrist Viktor Frankl⁷, founder of logotherapy (i.e. meaning therapy). MCGP was adapted for cancer survivors (MCGP-CS) by Van der Spek et al.⁸. MCGP-CS focuses on enhancing a sense of meaning in life by addressing issues like: how to carry on in life despite limitations, choosing one's attitude towards suffering, and discussing sources of meaning in life.

There is evidence that MCGP and MCGP-CS are effective in enhancing a sense of meaning, psychological well-being, and reducing depressive symptoms^{5,8-10}. MCGP-CS is likely to be cost-effective, as well¹¹. In a randomized controlled trial (RCT) among advanced cancer patients, MCGP was more effective than supportive group psychotherapy (SGP) in improving quality of life, spiritual well-being and reducing depression and hopelessness. These improvements were sustained during the two months follow-up period⁵. Van der Spek et al.⁹ found in an RCT among cancer survivors that MCGP-CS had larger treatment effects than CAU on personal meaning, goal orientedness, purpose in life, positive relations (all post intervention) and depressive symptoms (follow-up). Compared to SGP, MCGP-CS participants improved more on personal growth and environmental mastery (follow-up). This RCT on MCGP-CS suggests that most positive post-intervention effects fade away, but that some effects occur only several months later. Since cancer survivors often live for years with limitations in several areas of life, it is important to know whether MCGP-CS's positive effects are maintained in the long-term.

Several other types of existential interventions have been developed¹²⁻¹⁶, and a few studies reported on the long-term effects of these interventions. In four RCT's on experiential-existential¹⁷, cognitive-existential¹³, or supportive expressive group psychotherapy^{18,18}, participants improved over the one year follow-up period, but not more than after a non-meaning-focused type of group psychotherapy^{16,17} or the care as usual condition^{12,18}. In an RCT on cognitive existential couple therapy, couples did better after the existential therapy compared to care as usual, and these results were maintained during the nine months follow-up period¹⁹.

The aim of this study is to investigate the long-term follow-up results of the RCT on the efficacy of MCGP-CS by Van der Spek et al.⁹. Survivors' sense of personal meaning, as well as psychological well-being and posttraumatic growth were compared for MCGP-CS, SGP and CAU until two years after the intervention, both for all participants (intention-to-treat), and only for those who completed the intervention. Because many other things can also influence one's sense of meaning over the course of two years, in additional sensitivity analyses psychological treatment and cancer recurrence during these two years were taken into account. Insight into the long-term MCGP-CS effects reveals whether this intervention supports survivors enduringly to experience a sense of meaning, well-being and growth, despite the limitations of having had cancer.

METHODS

STUDY DESIGN AND POPULATION

This study is an extension of a multi-center RCT on the efficacy of MCGP-CS compared to SGP and CAU with three follow-up assessments: post-intervention and at three and six months follow-up. In the present study, assessments were added at one and two years follow-up. To limit participant burden, only personal meaning, psychological well-being, and posttraumatic growth were assessed at long-term follow-up. The study protocol and extension were approved by the Medical Ethics Committee of the Leiden University Medical Center and the trial was registered in the Netherlands Trial Register (NTR3571).

Details of the study procedure can be found in the previous report on the efficacy of MCGP-CS⁸. In brief, eligible patients were adult cancer survivors who were diagnosed in the last 5 years and who had completed treatment with curative intent. Participants had to have an expressed need for psychological care and at least one psychosocial complaint. Exclusion criteria were severe cognitive impairment, current psychiatric or psychological treatment elsewhere, and insufficient mastery of the Dutch language. Informed consent was obtained from all individual participants included in the study.

RANDOMISATION AND BLINDING

An independent researcher prepared a computer-generated randomisation table with random block sizes and made a list of sequentially numbered allocations. Participants were placed in a group, and when a consecutive group had 7-10 participants, the independent researcher allocated the group to a study arm.

INTERVENTIONS

Meaning-centered group psychotherapy for cancer survivors

MCGP-CS is a manualized intervention consisting of eight weekly two-hour sessions²⁰. The following themes were addressed: sources of meaning, meaning before and after cancer, past and future life stories as sources of meaning, participants attitude towards life's limitations, creative sources of meaning, and experiential sources of meaning. In addition, important existential concepts played a role in MCGP-CS, such as identity, existential guilt, isolation, and freedom.

Supportive group psychotherapy

SGP is a manualized intervention that aims to help survivors cope better with the cancer-related difficulties²¹. Like MCGP-CS, this intervention consists of eight weekly two-hour sessions. The themes addressed were: need for support, communicating with health care providers, coping with medical tests, with family and friends, with vocational issues, body image, limitations in physical functioning, and coping with the future. Fidelity to both treatment protocols was ensured in several ways²².

OUTCOME MEASURES

The primary outcome measure was personal meaning, measured as the total score of the Personal Meaning Profile (PMP)^{23,24}. The PMP has 39 items ($\alpha=.92$) and five subscales: relation with God ($\alpha=.86$), dedication to life ($\alpha=.89$), fairness of life ($\alpha=.78$), goal-orientedness ($\alpha=.88$), and relation with others ($\alpha=.85$). All items were scored on a 7-point Likert scale from 1 (not at all) to 7 (a great deal). The total and subscale scores were transformed to a scale of 0-100. Higher scores indicate a stronger sense of meaning. The PMP was validated in Dutch cancer patients and showed good internal consistency and construct validity²⁴.

The 49-item Dutch version of the Ryff's Scales of Psychological Well-Being (SPWB) was used to measure psychological well-being^{25,26}. This measure has no total score. The original scale consists of six subscales: positive relations ($\alpha=.83$), autonomy ($\alpha=.84$), environmental mastery ($\alpha=.77$), personal growth ($\alpha=.71$), purpose in life ($\alpha=.79$), and self-acceptance ($\alpha=.81$). In the Dutch version two subscales of spiritual well-being were added: inner strength ($\alpha=.75$) and higher power ($\alpha=.91$)²⁶. Items were scored on a 6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree). Subscale scores were calculated as the mean item score and higher scores indicated greater well-being.

Posttraumatic growth was measured using the total score of the Posttraumatic Growth Inventory (PTGI)^{27,28}. This 21-item measure ($\alpha=.91$) has five subscales: relating to others

($\alpha=.85$), new possibilities ($\alpha=.80$), personal strength ($\alpha=.80$), spiritual change ($\alpha=.70$), and appreciation of life ($\alpha=.75$). Items were rated from 0 (not at all) to 5 (very great degree). The total score was calculated as the sum of all items and a higher score represented more posttraumatic growth.

A study-specific questionnaire was used to obtain sociodemographic characteristics. Clinical characteristics were retrieved from medical records. Uptake of psychological treatment was measured at baseline and all follow-up assessments, except post-intervention, using the items about psychiatric and psychological treatment of the Treatment Inventory of Costs in Patients with psychiatric disorders (TiC-P)²⁹.

STATISTICAL METHODS

Linear mixed models (LMM) with fixed effects for study arm, time, and their two-way interaction, as well as a random intercept for subjects, were used to investigate differences in the course of the outcome measures over time in the three study arms. Patient characteristics with significant baseline differences across study arms were corrected for. Also, analyses were corrected for baseline scores of outcome measures in case of significant differences between study arms at baseline. Results were reported on an intention-to-treat (ITT) basis and for participants who attended six, seven or all therapy sessions (completers).

If the course of an outcome measure differed significantly over time between the study arms, post-hoc analyses were performed to assess which two groups differed significantly, using LMM, and between which points in time, using independent-samples t-tests. Post-hoc analyses were corrected for multiple testing by Bonferroni's correction. Cohen's *d* effect sizes were calculated by dividing the difference in change since baseline between the study arms by the pooled standard deviation, calculated at all separate follow-up time points. Effect sizes of 0.2 were categorized as small, 0.5 as medium and 0.8 as large.

As sensitivity analyses, all analyses were repeated without participants (1) who received psychological treatment during follow-up and (2) who faced cancer recurrence during follow-up. Analyses were performed in SPSS 24 and a two-sided *p*-value <0.05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATION

Basic information about the participant flow during the recruitment period and drop-out in various phases of the study can be found in Figure 1, and is published in more detail elsewhere⁸. Fifty-seven survivors were randomly allocated to MCGP-CS, 56 to SGP, and 57 to CAU. After two years 39 (68%) of the MCGP-CS participants filled out the follow-up questionnaire, 41 (73%) of the SGP participants and 35 (61%) of the CAU participants.

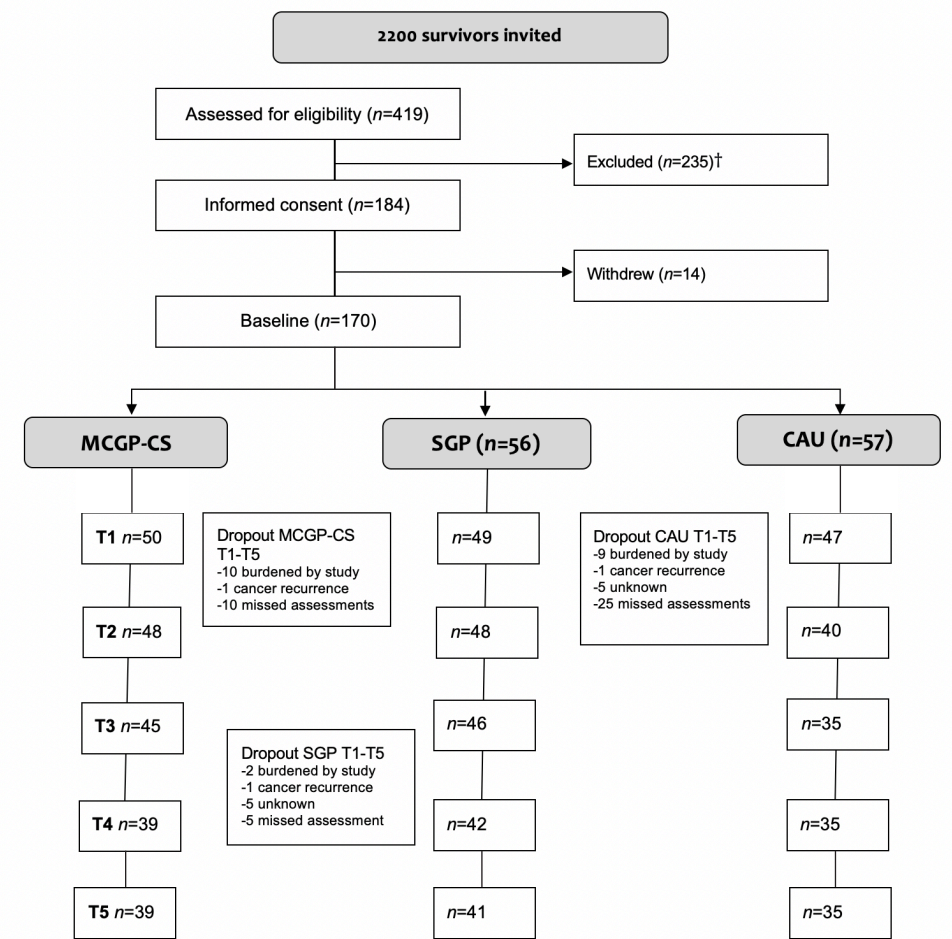


Figure 1. CONSORT diagram

Note. MCGP-CS: Meaning-centered group psychotherapy for cancer survivors; SGP: Supportive group psychotherapy; CAU: care as usual
†More details can be found in Van der Spek et al. (2017).

Sociodemographic and clinical participant characteristics are displayed in Table 1. Overall, most participants were female, in a relationship, and diagnosed with early stage breast cancer. Most completed the main cancer treatment about 1.5 year ago, and 80 (47%) still had hormonal therapy. In total, 29 (23%) participants received additional psychological treatment during follow-up, 13 (8%) participants faced cancer recurrence and 3 (2%) participants died.

Table 1. Participant characteristics

	MCGP (n=57)		SGP (n=56)		CAU (n=57)		p
	n	%	n	%	n	%	
Age (M, SD, range)	59	11 (32-81)	56	9 (41-80)	57	10 (37-83)	.34
Gender (female)	40	70%	49	88%	51	90%	.012*
Marital status (single)	12	21%	9	16%	13	23%	.65
Level of education							.16
Low	18	32%	9	16%	17	30%	
Medium	20	35%	25	45%	15	26%	
High	19	33%	22	39%	25	44%	
Religion							.18
Christian	23	40%	32	57%	30	53%	
No religion	34	60%	24	43%	27	47%	
Past psychological treatment							.53
In the last year	12	21%	11	20%	7	13%	
>1 year ago	21	37%	21	37%	17	31%	
Never	24	42%	24	43%	31	56%	
Psychological treatment during follow-up	12	21%	9	16%	8	14%	.61
Other negative life event in past 2 years (yes)	27	47%	31	55%	32	56%	
Type of cancer							.071
Breast	30	53%	40	71%	42	74%	
Colon	15	26%	12	21%	10	18%	
Other	12	21%	4	7%	5	9%	
Type of treatment							
Surgery	57	100%	56	100%	56	98%	.37
Radiation	31	54%	32	57%	33	58%	.92
Chemotherapy	26	46%	34	61%	36	63%	.12
Hormonal therapy	22	39%	28	50%	30	53%	.28
Months since last cancer treatment (median, range)	19	6-58	16	5-52	19	3-55	.97
Cancer recurrence	3	5%	5	9%	5	10%	.70
Mortality	1	2%	2	4%	0	0%	

Note. MCGP: Meaning-centered group psychotherapy; SGP: Supportive group psychotherapy; CAU: care as usual.

* $p < .05$

LONG-TERM EFFICACY OF MCGP-CS

Significant differences between the three study arms in the course of the outcome measures over the period of two years follow-up were found on the primary outcome: personal meaning (PMP; $F(10, 587)=2.01, p=.030$), and on the following secondary outcome measures: goal-orientedness (PMP; $F(10, 610)=3.27, p<.001$), positive relations (SPWB; $F(10, 612)=2.10, p=.022$), and purpose in life (SPWB; $F(10, 588)=2.04, p=.028$) (Table 2 and Supporting Information).

Post-hoc LMM analyses with Bonferroni correction did not show a significant difference between two of the study arms in the course of personal meaning (PMP total score) and purpose in life (SPWB) from baseline to two years follow-up (Table 3). Stronger long-term treatment effects of MCGP-CS compared to CAU were found on goal-orientedness (PMP; $F(5, 392)=4.97, p<.001$) and positive relations (SPWB; $F(5, 388)=3.43, p=.025$).

Between group Cohen's d effect sizes of MCGP-CS compared to CAU on goal-orientedness (PMP) were large and significant ($d=1.07, p<.001$) when comparing the post-treatment assessment with baseline assessment, but not on the longer-term assessments. Effect sizes of MCGP-CS compared to CAU on positive relations (SPWB) remained medium to large during the two year follow-up period and were significant when comparing the post-intervention (T1; $d=.59, p=.008$) and two years follow-up (T5; $d=.82, p=.005$) assessment with baseline.

COMPLETERS

For completers, the results were largely comparable (Table 2). Significant differences between study arms in the course of the outcome measure were found for personal meaning (PMP total score), goal-orientedness (PMP), positive relations (SPWB), and purpose in life (SPWB). An additional significant result was found for personal growth (SPWB; $F(10, 551)=2.03, p=.029$).

Post-hoc analyses with Bonferroni correction did not reveal significant differences between two of the study arms for personal meaning (PMP total score) and purpose in life (SPWB). However, both MCGP-CS participants ($F(5, 368)=5.22, p<.001$) and SGP participants ($F(5, 381)=3.30, p=.030$) scored significantly higher on goal-orientedness (PMP) than CAU participants over the course of two years. Furthermore, MCGP-CS participants scored significantly better on positive relations (SPWB) than CAU participants ($F(5, 359)=3.43, p=.025$) and reported significantly more personal growth (SPWB) than SGP participants ($F(5, 378)=3.55, p=.020$) (Table 3).

Table 2. Baseline, post-intervention and long-term results of linear mixed models analysing treatment outcome†

	Short-term						Long-term						p com- pleters
	Baseline (T0)			1-week post-intervention (T1)			1-year (T4)			2-years (T5)			
	M (SD)	SGP	CAU	M (SD)	SGP	CAU	M (SD)	SGP	CAU	M (SD)	SGP	CAU	
PMP													
Total score	59 (16)	61 (13)	59 (12)	62 (16)	63 (13)	57 (14)	59 (15)	61 (14)	58 (13)	59 (17)	63 (12)	58 (11)	.011*
Relation with God	32 (25)	39 (23)	30 (20)	36 (26)	40 (26)	29 (23)	34 (26)	41 (24)	32 (23)	32 (28)	42 (22)	31 (21)	.094
Dedication to life	67 (19)	66 (16)	68 (15)	69 (18)	67 (15)	65 (17)	67 (17)	65 (16)	66 (17)	67 (19)	66 (15)	65 (15)	.43
Fairness of life	56 (16)	55 (15)	55 (15)	60 (16)	59 (17)	54 (17)	58 (16)	58 (16)	58 (13)	60 (16)	60 (17)	57 (13)	.48
Goal-orientedness	69 (20)	71 (17)	72 (17)	74 (20)	72 (16)	63 (23)	66 (17)	69 (18)	66 (18)	66 (20)	73 (17)	68 (16)	<.001*
Relation	73 (24)	77 (22)	77 (19)	74 (24)	80 (20)	76 (20)	73 (24)	76 (22)	75 (22)	73 (25)	79 (20)	72 (21)	.36
SPWB													
Positive relationst	4.1 (1.0)	4.5 (1.0)	4.5 (.83)	4.4 (1.0)	4.7 (.95)	4.4 (.93)	4.4 (1.1)	4.6 (1.0)	4.5 (1.0)	4.4 (1.1)	4.6 (1.1)	4.3 (1.1)	.022*
Autonomy‡	4.2 (.85)	4.3 (.83)	4.3 (.72)	4.4 (.80)	4.5 (.76)	4.3 (.76)	4.4 (.84)	4.4 (.85)	4.4 (.59)	4.4 (.80)	4.4 (.87)	4.4 (.70)	.51
Environmental mastery	4.2 (.74)	4.3 (.71)	4.4 (.72)	4.5 (.75)	4.3 (.79)	4.4 (.67)	4.3 (.78)	4.3 (.76)	4.4 (.71)	4.4 (.82)	4.3 (.83)	4.4 (.72)	.053
Personal growth	4.2 (.75)	4.4 (.59)	4.3 (.60)	4.4 (.68)	4.4 (.56)	4.3 (.62)	4.4 (.75)	4.3 (.57)	4.3 (.71)	4.2 (.72)	4.3 (.58)	4.3 (.66)	.061
Purpose in life	4.1 (.89)	4.3 (.77)	4.4 (.62)	4.4 (.89)	4.3 (.80)	4.3 (.65)	4.2 (.84)	4.3 (.81)	4.4 (.66)	4.3 (.74)	4.3 (.88)	4.3 (.61)	.028*
Self-acceptance	4.0 (.87)	4.2 (.80)	4.3 (.64)	4.2 (.82)	4.3 (.83)	4.3 (.63)	4.2 (.77)	4.1 (1.0)	4.3 (.72)	4.2 (.84)	4.1 (.85)	4.3 (.66)	.53
Inner strength	4.0 (.69)	4.1 (.80)	4.1 (.66)	4.3 (.80)	4.2 (.74)	4.1 (.78)	4.2 (.90)	4.3 (.84)	4.2 (.65)	4.3 (.78)	4.3 (.71)	4.0 (.72)	.12
Higher power	2.8 (1.4)	3.1 (1.3)	2.8 (1.2)	3.0 (1.3)	3.2 (1.3)	2.7 (1.2)	3.0 (1.4)	3.2 (1.2)	2.6 (1.1)	2.9 (1.4)	3.1 (1.2)	2.9 (1.2)	.28
PTGI	42 (21)	48 (17)	46 (18)	48 (20)	53 (17)	49 (19)	44 (24)	50 (17)	50 (21)	45 (21)	50 (19)	47 (20)	.77
													.46

Note. MCGP: meaning-centered group psychotherapy; SGP: supportive group psychotherapy; CAU: care as usual; PMP: Personal Meaning Profile; SPWB: Scales of Psychological Well-Being; PTGI: posttraumatic growth inventory; ITT: intention-to-treat.

†Corrected for baseline scores.

‡Corrected for

*p< .05

Table 3. Post-hoc analyses: linear mixed models analysing difference between two study arms, and treatment effect post-intervention and at long-term follow-up

	LMM analyses			Short-term		Long-term					2-years follow-up vs. baseline	
	From baseline to 2-years follow-up			Post-intervention vs. baseline		1-year follow-up vs. baseline					MCGP-SGP	
	MCGP-SGP	MCGP-CAU	SGP-CAU	MCGP-SGP	MCGP-CAU	MCGP-SGP	MCGP-CAU	Cohen's d, p	Cohen's d, p	Cohen's d, p	Cohen's d, p	Cohen's d, p
Intention-to-treat												
PMP												
Total score	1.00	.12	.17									
Goal-orientedness	1.00	<.001**	.055		1.07, <.001**		.12, 1.00					
SPWB												
Positive relationst	1.00	.025*	.91		.59, .008*		.41, .21					
Purpose in life	.22	.080	1.00									
Completers												
SPWB												
Personal growth	.020*	.28	1.00		.65, .012*		.94, .007*				.34, .68	

Note. MCGP: meaning-centered group psychotherapy; SGP: supportive group psychotherapy; CAU: care as usual; PMP: Personal Meaning Profile; SPWB: Scales of Psychological Well-Being.

†LMM analyses are corrected for baseline score.

*p< .05

**p<.005

Compared with ITT analyses, effect sizes of MCGP-CS on goal-orientedness (PMP) and positive relations (SPWB) were slightly larger. Effect sizes comparing the change in personal growth between baseline and the assessments post-intervention ($d=.65$, $p=.012$), three months follow-up ($d=.64$, $p=.017$) and one year follow-up ($d=.94$, $p=.007$) were medium to large in favor of MCGP-CS.

SENSITIVITY ANALYSES

Both long-term effects of MCGP-CS on positive relations (SPWB; T5; $d=.86$, $p=.010$; compared to CAU) and personal growth (SPWB; T4; $d=.76$, $p=.007$; compared to SGP) remained significant when repeating the analyses without participants who received psychological treatment in the period from four weeks preceding the study to two years follow-up. In addition, at two years follow-up MCGP-CS participants reported more inner strength (SPWB) than CAU participants ($d=.91$, $p=.007$). No significant long-term effects were found when repeating the analysis without participants who faced cancer recurrence during follow-up.

DISCUSSION

In the present study, the effects of MCGP-CS on personal meaning, psychological well-being, and posttraumatic growth over a period of two years, were compared to the effects of SGP and CAU. A previous study⁸ had shown that MCGP-CS was effective in improving personal meaning, goal-orientedness, positive relations and purpose in life post-intervention. The present study indicated that most of these effects fade one and two years after the intervention, including MCGP-CS's positive effect on personal meaning. However, two years after MCGP-CS occurred a medium to large positive effect on positive relations (compared to CAU). When analyzing completers only, MCGP-CS had a large effect on personal growth one year later, as well (compared to SGP). These long-term results favored MCGP-CS over the other conditions.

It is striking that none of the sources of meaning investigated in this study (e.g. goal-orientedness) were significantly affected by MCGP-CS in the long-term. The few long-term effects that were identified, all occurred on the measure of psychological well-being (SPWB). It is possible that the SPWB is more sensitive for change than the measure that was used for personal meaning (PMP). An alternative explanation may be that the long-term improvements in the area of psychological well-being were not strong enough to be translated into an enhanced sense of meaning. MCGP-CS's few long-term effects on psychological well-being were slightly stronger when analyzing

completers only and without participants who received other psychological treatment during the follow-up period. No long-term effects were found when participants who faced cancer recurrence during follow-up were left out. Further research is not only needed to validate these long-term findings, but should also address the question how these long-term intervention effects interact with other major events in life.

The long-term results of MCGP-CS seem to be in line with the results of previous studies on long-term effects of existential interventions. Overall, these effects seem to be quite modest. However, while some other studies did not find significant differences between the long-term effects of an existential intervention and a non-meaning-focused intervention^{16,17} or care as usual^{13,30} the present study did find stronger improvement on some outcomes at long-term follow-up.

CLINICAL IMPLICATIONS

MCGP-CS is a useful addition to the current mental health care available in the oncology field. It is a brief intervention that is effective and cost-effective^{8,11}. Some of its effects linger on for one or even two years. Relatively easy adaptations could be made to stimulate stronger long-term improvements of psychological well-being and personal meaning. Meta-analyses show that long term effects could be stimulated by more contact hours³¹, possibly in the form of booster sessions³². MCGP-CS could also be extended with an online component, which can facilitate participants to remind and practice the skills they have learned³³.

STUDY LIMITATIONS

A strength of this study is its conservative ITT analyses with Bonferroni correction. The statistical methods decrease the chance of false positive findings, lending more credibility to the effects that were found. Yet, the possibility of chance findings could not be ruled out and the significant long-term effects should be interpreted tentatively. Especially because some results appeared to be inconsistent. MCGP-CS participants reported better positive relations (SPWB) at long term, but did not report that these relations became a stronger source of personal meaning (PMP) for them. Furthermore, personal growth was better after MCGP-CS compared to SGP, but not compared to CAU, and only for completers of the intervention. In addition, there are no clear criteria for minimal important difference (MID) on the outcome measures used in this study, so it is unknown to what extent the significant differences are clinically meaningful.

Another limitation of this study is the omission of a measure of depressive symptoms at one and two years follow-up. The decision about which outcome measures to

maintain at follow-up, was made before the short-term results became available. However, when these results became available, an interesting finding was that symptoms of depression were significantly decreased after MCGP-CS compared to CAU, but only at six months follow-up. Unfortunately, in the present long-term study we could not confirm whether this effect remained after one and two years.

CONCLUSIONS

In the two years after MCGP-CS there was a decay of the short-term positive effect on personal meaning and most positive effects related to psychological well-being. However, MCGP-CS had a long-term positive effect on positive relations with others and on survivors' sense of personal growth.

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6



POSITIVE MENTAL HEALTH AMONG CANCER SURVIVORS: OVERLAP IN PSYCHOLOGICAL WELL-BEING, PERSONAL MEANING, AND POSTTRAUMATIC GROWTH

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ABSTRACT

OBJECTIVE

Positive mental health involves theoretical constructs like psychological well-being, personal meaning, and posttraumatic growth. This study aims to provide empirical insight into possible overlap between these constructs in cancer survivors.

METHODS

Within the context of a randomized controlled trial, 170 cancer survivors completed the patient reported outcome measures (PROMs) Ryff's Scales of Psychological Well-Being (SPWB), Personal Meaning Profile (PMP) and Posttraumatic Growth Inventory (PTGI). Exploratory factor analysis (EFA) on the subscales of these PROMs, as well as structural equation modeling (SEM) were used to explore overlap in these three constructs.

RESULTS

The EFA resulted in a three factor solution with an insufficient model fit. SEM led to a model with a high estimated correlation (.87) between SPWB and PMP, and lower estimated correlations with PTGI (respectively .38 and .47). Furthermore, the estimated correlation between the subscales Relation with God (PMP) and Spiritual change (PTGI) was high (.92). This model had adequate fit indices ($\chi^2(93)=144$, $p=.001$, RMSEA=.059, CFI=.965, TLI=.955, SRMR=.061).

CONCLUSIONS

The constructs psychological well-being and personal meaning overlap to a large extent in cancer survivors. Posttraumatic growth can be seen as a separate construct, as well as religiosity. These findings facilitate researchers to select the appropriate PROM(s) when testing the effect of a psychosocial intervention on positive mental health in cancer survivors.

RELEVANCE

An increasing number of psychosocial intervention trials for cancer survivors use positive mental health outcomes. These constructs are often multifaceted and overlapping. Knowledge of this overlap is important in designing trials, in order to avoid the pitfalls of multiple testing and finding artificially strengthened associations.

BACKGROUND

Patient reported outcome measures (PROMs) in psychosocial intervention trials targeting cancer survivors generally focus on psychological distress and quality of life¹. However, absence of distress does not necessarily lead to positive mental health^{2,3}. Positive mental health involves factors such as psychological well-being⁴, experiencing a sense of meaning in life⁵, posttraumatic growth⁶, self-compassion⁷, and flourishing⁸. Evidence on the importance of positive mental health for a successful adjustment to life after cancer is growing^{9–11}. Studies show that positive mental health protects cancer survivors against distress and demoralization¹² and that it plays a role in mental recovery after the treatment phase¹³.

In the field of positive mental health research, constructs are often not clearly demarcated from each other, which can be observed in their often extensive descriptions^{5,14,15}. Although the theories of constructs like psychological well-being¹⁶, meaning in life^{5,17} and posttraumatic growth¹⁸ are rooted in different research traditions, the multifaceted descriptions of these constructs tend to overlap considerably. This hinders their operationalization into adequately distinguishable constructs, which is imperative for carrying out rigorous randomized controlled trials (RCTs) investigating the effects of interventions that aim to improve positive mental health in cancer survivors.

Not surprisingly, the overlap between psychological well-being, meaning, and posttraumatic growth is reflected in medium to strong correlations between these constructs in cancer survivors^{11,19,20}, although correlations with posttraumatic growth tend to be lower^{11,21–24}. Furthermore, the overlap is noticeable when these constructs are operationalized into measurement instruments. Three frequently used PROMs in psycho-oncology (Ryff's Scales of Psychological Well-Being (SPWB)¹⁶, the Personal Meaning Profile (PMP)¹⁷, and the Posttraumatic Growth Inventory (PTGI)²⁵) were recently used in a randomized controlled trial (RCT) on the efficacy of meaning-centered group psychotherapy (MCGP) for cancer survivors²⁶. All three measurement instruments contain a subscale on relations with other people. Overlap between the measures of psychological well-being and personal meaning can further be found in the areas of pursuing worthwhile goals, having a sense of mastery or dedication, and a sense of being at peace with oneself. Posttraumatic growth by definition comprehends positive psychological *change* in response to an adverse event, in contrast to psychological well-being and personal meaning. Yet the measurement instrument of posttraumatic growth has overlap with the measurement instruments of psychological well-being and meaning in all its facets, including growth, finding new possibilities in life, and

spirituality. An overview of the overlap between these measurement instruments is displayed in Table 1.

As a result of the overlap between these instruments, it is difficult to gain insight into what exactly is affected by interventions that aim to improve positive mental health. Furthermore, the question rises which (subscales of) instruments are suited best to be used as primary outcome measure in RCTs investigating these interventions. Therefore, the aim of the present study was to investigate empirically the overlap between measurement instruments of psychological well-being, personal meaning, and posttraumatic growth among cancer survivors. Factor analysis was conducted on the subscales of the Dutch versions of these well-validated PROMs (i.e. SPWB, PMP and PTGI), as filled out in the context of the RCT evaluating MCGP²⁶. It was presumed that factor analysis would not result in three separate factors representing psychological well-being, personal meaning, and posttraumatic growth. It was expected that a different factor structure would appear, crossing through these measurement instruments and revealing areas of overlap. The results will contribute to better understanding of the overlap of these positive mental health constructs, which is highly needed to develop core outcome sets to measure cancer survivors' positive mental health in the future.

METHODS

PATIENTS

For this study, baseline data were used from an RCT on the efficacy of MCGP for cancer survivors²⁶. Ethical approval for this study was provided by the Medical Ethical Committee of Leiden University Medical Center (NL34814.058.10). Information about the study protocol, participants, and primary outcomes has been published previously^{26,27}.

Participants were recruited between August 2012 and September 2014. Inclusion criteria were: cancer diagnosis in the last five years, treated with curative intent, main treatment completed (i.e. surgery, radiotherapy, chemotherapy), presence of an expressed need for psychological support, and at least one psychosocial complaint. Exclusion criteria were: severe cognitive impairment, current psychological or psychiatric treatment elsewhere, and an insufficient mastery of the Dutch language. All criteria were ascertained during a telephonic screening interview.

Informed consent was obtained from all individual participants included in the study. Demographic characteristics were obtained by self-report: age, gender, marital status,

education level, employment, religious background, other negative life events, and past psychological treatment. Illness-related characteristics included: type of cancer, tumor stage, type of treatment, and time since treatment, and were retrieved from medical records or by self-report, if medical records were unavailable.

Table 1. Overview of overlap between measures of psychological well-being, personal meaning and posttraumatic growth.

Measure	Scales of Psychological Well-Being (SPWB)	Personal Meaning Profile (PMP)	Posttraumatic Growth (PTGI)
Subscale Description	Purpose in life Goals and purpose in life, directedness, meaning to present and past life, aims and objectives for living.	Goal-orientedness Life goals, worthwhile objectives, valuable pursuits, purpose, meaning and direction in life, actualize his/her potentials.	Appreciation of life Priorities in life, appreciation for his/her own life, appreciates each day.
	Environmental mastery Mastery and competence in managing the environment, complex array of external activities, effective use of opportunities, creates contexts suitable to personal needs and values.	Dedication to life Contributes to well-being of others, values and is committed to his/her work, contribution to society, initiatives, likes challenges, persistent and resourceful, makes full sense of his/her abilities, personal growth, does not give up, altruistic and helpful.	Personal Strength Self-reliance, knows he/she can handle difficulties, accepts the way things work out, discovered that he/she is stronger than he/she thought he/she was.
	Personal growth Continued development, growing and expanding, open to experiences, sense of realizing his/her potential, improvement in self and behavior, changing in ways that reflect more self-knowledge and effectiveness.		New possibilities New interests, new path for life, does better things with his/her life, new opportunities which wouldn't have been available otherwise, changes things which need changing.
	Self-acceptance Positive attitude toward the self, acknowledges and accepts multiple good and bad aspects of self, positive about past life.	Fairness of life Treated fairly by life and others, at peace with past self, accepts his/her limitations, receives fair share of opportunities and rewards, justice in this world, accepts what cannot be changed, at peace with him/her self.	
	Autonomy Self-determined, independent, resists social pressures, regulates behavior from within, evaluates self by personal standards.		
	Positive relations Warm, satisfying, trusting relationships, concerned about others; capable of strong empathy, affection and intimacy, understands give and take of human relationships.	Relation with other people Mutually satisfying relationship, found someone he/she loves deeply, someone to share intimate feelings with, good family life, confidants to give him/her emotional support, relates well to others. Relation with God / higher order In peace with God, beliefs in afterlife, seeks to do God's will and glorifies God, personal relationship with God, sense of mission or calling, order and purpose in the universe, seeks higher values.	Relating to others Counts on people, closeness with others, willing to express his/her emotions, compassion, putting efforts in relationships, learned about how wonderful people are, accepts needing others. Spiritual change Understanding of spiritual matters, a stronger religious faith.

OUTCOME MEASURES

Psychological well-being was measured using the Dutch version of the SPWB²⁸. This is a 39-item measure consisting of six subscales: self-acceptance ($\alpha=.81$), positive relations with others ($\alpha=.83$), autonomy ($\alpha=.84$), environmental mastery ($\alpha=.76$), purpose in life ($\alpha=.79$), and personal growth ($\alpha=.71$). Items were answered on a 6-point Likert scale, ranging from 1 (strongly disagree) to 6 (strongly agree). Subscale scores were calculated as the mean item score. Higher scores indicated greater well-being. The Dutch version has the same six subscales as the original version, although several items had to be removed to reach adequate fit. The Dutch version showed sufficient internal consistency and good construct validity²⁸.

The Dutch version of the PMP was used to measure personal meaning^{17,29}. This 39-item measure has five subscales: dedication to life ($\alpha=.89$), fairness of life ($\alpha=.77$), goal-orientedness ($\alpha=.89$), relations with other people ($\alpha=.85$) and relation with God ($\alpha=.86$). Items were scored on a 7-point Likert scale from 1 (not at all) to 7 (a great deal). A higher score reflects a more important source of meaning. This measure was validated in Dutch cancer patients and showed good internal consistency and construct validity. Its number of items and factor structure differed from the original Canadian version. Of the originally 57 items 18 had to be removed in the Dutch version, because of low or double loadings and the original factors 'relations' and 'intimacy' formed one factor in the Dutch version, as well as 'fair treatment' and 'self-acceptance'²⁹.

Posttraumatic growth was measured using the Dutch translation of the PTGI^{25,30}. This 21-item measure has five subscales: relating to others ($\alpha=.85$), new possibilities ($\alpha=.80$), personal strength ($\alpha=.79$), spiritual change ($\alpha=.70$), and appreciation of life ($\alpha=.75$). Items were rated from 0 (not at all) to 5 (very great degree). Subscale scores were calculated as mean item scores and a higher score suggests stronger growth. A psychometric study of the PTGI in Dutch cancer patients showed good internal consistency, construct validity and factorial validity. The Dutch version contains the same factors as the original version³⁰.

STATISTICAL METHODS

Exploratory maximum likelihood factor analysis (EFA) with varimax rotation on all subscales of the SPWB, PMP and PTGI was conducted to explore possible areas of overlap between psychological well-being, personal meaning and posttraumatic growth. The number of factors to retain was based on the eigenvalues (>1.0), the slope of the scree plot and parallel analysis. To assess the goodness-of-fit of the resulting model, this model was entered into a confirmatory maximum likelihood factor analysis

(CFA) using the same sample. The following goodness-of-fit indices and thresholds were used: the χ^2 -test ($p<0.05$), the root mean square error of approximation (RMSEA, <0.06), the comparative fit index (CFI, ≥ 0.90), the Tucker-Lewis index (TLI, ≥ 0.90), and the standardized root mean square (SRMS, <0.08). Missing data were presumed to be missing completely at random (MCAR).

When the model resulting from the EFA would not show adequate fit, two additional models would be considered. (1) In order to compare the result of the EFA with the null model (i.e. a model in which the subscales load on a factor that represents their own measurement instrument, revealing no areas of overlap) the goodness-of-fit indices would be calculated for this null model, as well, using CFA. (2) In order to explore the overlap between the SPWB, PMP and PTGI further, structural equation modeling (SEM) would be used. Beginning with the null model, in which each measurement instrument formed a latent variable, represented by its subscales as manifest variables, the path with the highest modification index would be added to the model and the goodness-of-fit indices would be re-calculated. This procedure would be repeated until the model had an adequate fit. Correlations in the models were considered as low (<0.5), moderate (≥ 0.5 and <0.7) or high (≥ 0.7). All analyses were performed in IBM SPSS Statistics 24 or R 3.4.0, package Lavaan.

RESULTS

PARTICIPANT CHARACTERISTICS

In total 2192 cancer survivors received an invitation letter for this study, 419 survivors responded positively, 184 met all inclusion criteria, and 170 completed the outcome measures at baseline. Participants were on average 57 years old and 82% was female. Eighty percent was married or in a relationship, 39% was higher educated, and 53% was employed. Breast cancer was diagnosed in 66% of the participants, 70% had tumor stage II or lower. All participants but one had surgery and 81% had additional radiation or chemotherapy. Participants were median 18 months post treatment. Other negative life events were reported by 53% of the participants, and 18% had psychological treatment in the last year (Table 2). More details on the participant flow and drop-out can be found elsewhere²⁶.

Table 2. Participant characteristics (N=170)

	N	%	range
Age (M, SD, range)	57	10	32-83
Gender (female)	140	82	
Marital status (single)	34	20	
Education level			
Low	23	13	
Medium	81	48	
High	66	39	
Employment (yes) ^a	88	53	
Religion			
Christian	85	50	
No religion	85	50	
Type of cancer			
Breast	112	66	
Colon	37	22	
Other (esophagus, stomach, pancreatic, lung, endometrial, ovarian, melanoma, lymphoma)	21	12	
Tumor stage			
0 (in situ)	10	6	
I	57	34	
II	51	30	
III	28	16	
IV	3	2	
Missing	21	12	
Type of treatment			
Surgery	169	99	
Surgery combined with radiation and/or chemotherapy	138	81	
Months since treatment (Mdn, range) ^b	18		3-58
Negative life event in last two years (other than cancer)	90	53	
Previous psychological treatment ^c			
< 1 year ago	30	18	
> 1 year ago	59	35	
Never	79	47	

Note.

^aN=165

^bN=159

^cN=168

EXPLORATORY FACTOR ANALYSIS

Based on the scree plot and the eigenvalues three factors should be extracted. The parallel analysis, however, indicated a solution of two factors. The eigenvalue of the third factor (1.355) was below the parallel analysis eigenvalue at the 95th percentile (1.420). However, it was higher than the average parallel analysis eigenvalue of the third factor (1.347). Because both the scree plot and the eigenvalues indicated a three factor solution, and the parallel analysis 'almost' indicated a three factor solution, this solution was retained (Table 3; see

Figure 1 for a graphical representation of these factors). The three factor solution explained 59% of the variance. The first factor consisted of all SPWB and PMP subscales, except the PMP subscale relation with God. The second factor consisted of all PTGI subscales, except spiritual change. The third factor consisted of the subscales relation with God (PMP) and spiritual change (PTGI). The goodness-of-fit indices of this three factor solution were unsatisfactory ($\chi^2(101)=314$, $p<.001$, RMSEA=.115 (95% CI: .100-.129), CFI=.854, TLI=.827, SRMR=.085), meaning that the model did not fit well with the data.

Table 3. Rotated (varimax) component matrix

Subscales	Measurement Instrument	Loadings		
		1	2	3
Self-acceptance	SPWB	0.85		
Purpose in life	SPWB	0.85		
Environmental mastery	SPWB	0.82		
Dedication to life	PMP	0.74		
Goal-orientedness	PMP	0.69		0.32
Positive relations	SPWB	0.63		
Autonomy	SPWB	0.61		
Fairness of life	PMP	0.61		
Relation with other people	PMP	0.57		
Personal growth	SPWB	0.53	0.35	
Personal strength	PTGI		0.83	
Appreciation of life	PTGI		0.77	
New possibilities	PTGI		0.73	
Relating to others	PTGI		0.67	
Relation with God	PMP			0.98
Spiritual change	PTGI		0.32	0.63

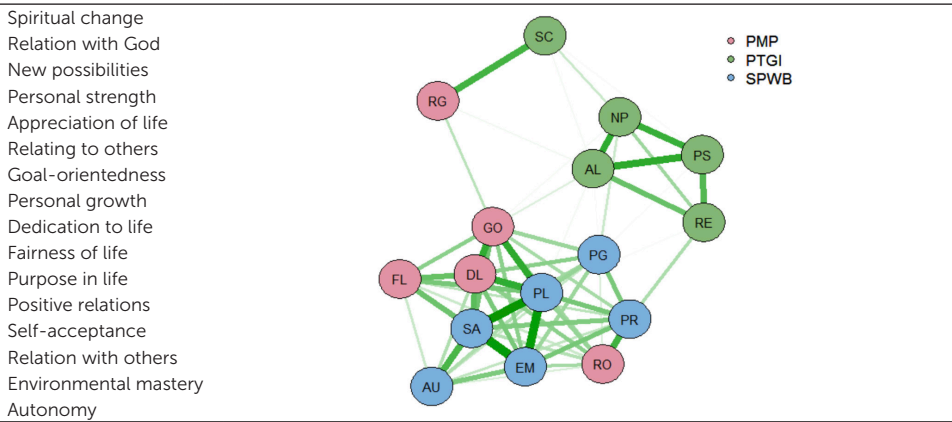


Figure 1. Graphical representation of the correlations between the subscales of the Personal Meaning Profile (PMP), Ryff's Scales of Psychological Well-Being (SPWB) and Posttraumatic Growth Inventory (PTGI)

Note. Factor loadings <.30 are suppressed.

N=161

ADDITIONAL ANALYSES

Since the above described three factor solution did not have an adequate fit, the question arose whether a model in which each measurement instrument formed a separate factor (null model) would better fit with the data. The results of this CFA showed that the goodness-of-fit indices of the null model were slightly worse ($\chi^2(101)=357, p<.001$, RMSEA=.126 (95% CI: .112-.140), CFI=.825, TLI=.792, SRMR=.094).

When pathways were subsequently added to the null model using SEM, based on the modification indices, the fit improved ($\chi^2(93)=144, p=.001$, RMSEA=.059 (95% CI: .039-.077), CFI=.965, TLI=.955, SRMR=.061). In the resulting model the latent variables SPWB and PMP had an estimated correlation of .87, SPWB and PTGI of .38 and PMP and PTGI of .47 (Fig 1). Furthermore, a path was added between the subscales relation with God (PMP) and spiritual change (PTGI) and between spiritual change (PTGI) and personal growth (SPWB). The subscale positive relations with others (SPWB) formed paths with relations with other people (PMP), relating to others (PTGI) and personal growth (SPWB). The subscale personal growth (SPWB) also loaded on the PTGI. The subscale relation with God (PMP) loaded negatively on the SPWB, as well. Finally, a negative pathway had to be added between the SPWB subscales autonomy and purpose in life. Since the fit of this model was adequate, it was considered as the main outcome of this study.

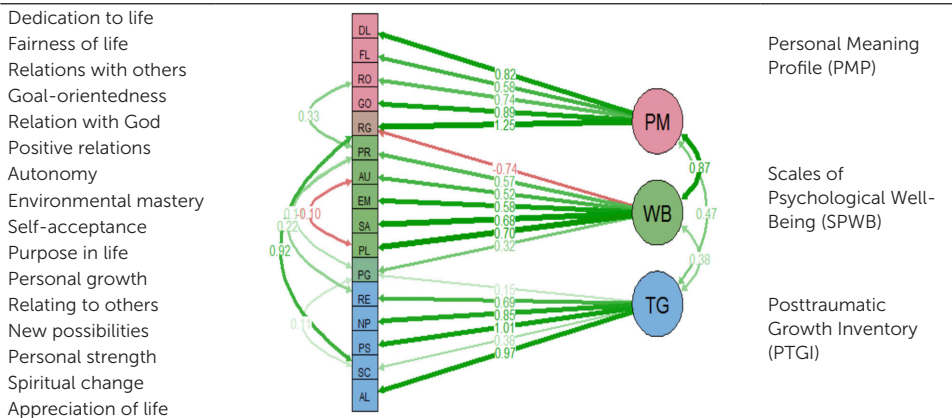


Figure 2. Model resulting from adding pathways to the null model in which each measurement instrument formed a latent variable, represented by its subscales as manifest variables
Note. N=161

DISCUSSION

The empirical baseline data of cancer survivors participating in an RCT, supported the expectation that measurement instruments of psychological well-being, personal meaning, and posttraumatic growth do share areas of overlap. The resulting model was complex, but three main conclusions can be drawn. (1) The scores on psychological well-being (SPWB) and personal meaning (PMP) were highly correlated (as latent variables), which suggests that both PROMs measure similar or very closely related aspects of positive mental health. (2) Their estimated correlation with the posttraumatic growth measure (PTGI), as latent variable, was lower, suggesting that posttraumatic growth is a related, but distinct construct. (3) A high estimated correlation was found between the subscales relation with God (PMP) and spiritual change (PTGI), while their loadings on their respective measurement instruments deviated from the other subscale loadings. This supports the idea that religiosity is distinct from psychological well-being, personal meaning, and posttraumatic growth.

These results have clear implications for the use of the SPWB, PMP and PTGI in trials that investigate the effect of psychosocial interventions targeting cancer survivors. The overlap implies that if an intervention aims to improve both psychological well-being and personal meaning, in fact, the same phenomena or behaviors, feelings, cognitions, goals and convictions may have changed. Measuring these constructs separately means that these specific phenomena are measured double³¹. Previous studies showed similar results in the operationalization of spirituality and well-being^{32,33}. It may be more efficient and less burdensome for cancer survivors to measure these phenomena just once.

In addition, taking this overlap into account may help to avoid various pitfalls in designing a trial. The overlap between these measures will artificially increase the strength of their association³², so one may wrongly conclude that personal meaning leads to psychological well-being or vice versa. Furthermore, measuring both constructs increases the problem of multiple testing, because the same phenomena are measured more often. Further psychometric research is needed to select those items from the SPWB and PMP that measure these overlapping phenomena in the most parsimonious way with the largest sensitivity for change.

The results of this study do not mean that psychological well-being and meaning are entirely exchangeable concepts. Their connotations are different¹⁵, these concepts are rooted in different literary and research traditions, and their measures will not

invariably give similar outcomes. What this study does show however, is that when it comes to operationalization, these constructs overlap in many ways. Better insight into cancer survivors' positive mental health is served by acknowledging this overlap.

Despite the conceptual overlap between posttraumatic growth, psychological well-being and personal meaning, the results of this study suggest that mainly psychological well-being and personal meaning overlap, while posttraumatic growth falls farther outside. This is in agreement with several studies that did not find a significant association between posttraumatic growth and well-being^{18,34}. An alternative explanation for this outcome is that the PTGI requires a different type of item response than the SPWB and PMP. Survivors are not asked to rate how they feel at the moment, but how their feelings differ from before cancer. Scales with a different type of item response may artificially influence SEM results.

Finally, the results support the idea that religiosity can be seen as distinct from psychological well-being, personal meaning and posttraumatic growth. Perhaps, especially in a secular country like The Netherlands there is a large variability in the role religion plays in people's lives, ranging from absent to prominent and from negative to positive. This finding is in line with previous studies in The Netherlands²⁸, as well as in the United States³⁵. Hence, it seems that religiosity is a domain that should be measured separately in cancer survivors.

This study had several limitations. First, the number of participants was relatively small, females and breast cancer survivors were overrepresented, and all analyses were conducted using the same sample. Second, only three of the many available, albeit frequently used measures of well-being, meaning and posttraumatic growth were examined. It is possible that other measures show less overlap. Third, psychological well-being, personal meaning and posttraumatic growth do not cover the full spectrum of positive mental health¹⁶. To identify the domains of a core outcome set for cancer survivors' positive mental health, future studies should include a broader variety of measurement instruments³⁶. Such a core outcome set of positive mental health in cancer survivors can be used routinely to document and compare effects of psychosocial intervention on survivors' positive mental health.

The majority of cancer survivors have no clinical level of distress, but there is a large differentiation in their level of positive mental health². Since a growing number of survivors will live for an increasing number of years³⁷, it becomes important that high quality psychosocial interventions are available that stimulate positive mental health

and help survivors adjust to the aftermath of cancer. The efficacy of interventions can only be evaluated when their effects can be monitored properly. This study contributes to the understanding of positive mental health in cancer survivors and to develop a core outcome set.

CONCLUSIONS

Psychological well-being and personal meaning overlap to a large extent in cancer survivors, while posttraumatic growth and religiosity can be seen as distinguished constructs. These findings facilitate researchers to select the appropriate PROMs when testing the effect of a psychosocial intervention on positive mental health in cancer survivors.

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7

GENERAL DISCUSSION



GENERAL DISCUSSION

The aim of this thesis was to obtain more insight into psychological well-being, meaning and posttraumatic growth in cancer survivors and to provide more detailed information about the effects of MCGP-CS. We explored posttraumatic growth in distressed survivors (chapter 2), the patient groups for whom MCGP-CS may be especially beneficial (chapter 3), whether there is support for its theoretical model (chapter 4), how long its effects last (chapter 5) and to what extent psychological well-being, meaning and posttraumatic growth overlap in cancer survivors (chapter 6). In this final chapter, the main findings of this thesis are integrated into the relevant literature and their implications for clinical practice and future research are discussed.

DO HEAD AND NECK CANCER SURVIVORS WITH DISTRESS EXPERIENCE POSTTRAUMATIC GROWTH?

Reporting posttraumatic growth may reflect genuine growth, but also a positive or negative way of coping. All these aspects have different associations with distress. In chapter 2, the occurrence of posttraumatic growth was assessed in a sample of distressed head and neck cancer survivors.

The results suggest that only 10% of the head and neck cancer survivors with distress experience moderate to high posttraumatic growth. This is notably lower than the 60-80% of head and neck cancer survivors that report posttraumatic growth in general¹⁻⁴. This also means that 90% of the distressed head and neck cancer patients seem to perceive little or no posttraumatic growth and that it plays a small role in this group. Less posttraumatic growth was best predicted by a model consisting of a higher tumor stage, the presence of an anxiety and alcohol use disorder and more limitations in social functioning. In addition, less posttraumatic growth was associated with more distress. These results seem to be mostly in line with the theory of a curvilinear association between distress and posttraumatic growth^{5,6}, because within this distressed sample, posttraumatic growth was higher among those with relatively low distress. Perhaps those with a high tumor stage at diagnosis (50%), an anxiety disorder (12%) and alcohol use disorder (14%) and more limitations in social functioning were so heavily burdened that this inhibited their posttraumatic growth. Although it is not possible to distinguish between genuine growth and posttraumatic growth as a coping strategy in this study, because posttraumatic growth was assessed cross-sectionally and by self-report⁷⁻⁹, it seems less likely that posttraumatic growth was primarily used as a negative coping strategy. In that case, one would have expected posttraumatic growth to be associated with higher distress. Still, it is possible that those reporting posttraumatic growth use it

as a positive coping strategy in such a way as described in the meaning-making model.

Posttraumatic growth usually occurs unintentionally, but according to Tedeschi and Calhoun, it can be facilitated in psychotherapy¹⁰. Posttraumatic growth was assessed as a secondary outcome in the RCT on the efficacy of MCGP-CS, but its improvement was not significantly different from the change in the control conditions¹¹. The results of chapter 2 suggest that the posttraumatic growth reported among head and neck cancer survivors with distress is genuine growth, but that the level of posttraumatic growth is low. This may be taken as a signal that these survivors could benefit from an intervention that (also) facilitates posttraumatic growth.

MAKING MEANING OF THE EFFECTS OF MCGP-CS

Which subgroups of cancer survivors respond best to MCGP-CS?

After MCGP-CS, personal meaning, goal-orientedness, purpose in life and positive relations were enhanced and distress and depression diminished six months later, compared to the care as usual condition¹¹. The study presented in chapter 3 is the first study that investigates which subgroups of cancer survivors respond best to MCGP-CS. This knowledge may be used to inform a clinical decision rule, to be developed in the future. Such a rule can help healthcare providers refer patients to the psycho-oncological intervention that is most suitable for them¹²⁻¹⁵.

Of the fourteen demographical, illness-related and psychosocial survivor characteristics examined, three moderated a short- or long-term effect of MCGP-CS: (1) males showed a greater reduction in depressive symptoms, (2) survivors with depressive symptoms at the start of MCGP-CS experienced more purpose in life afterwards and (3) survivors who did not have psychological treatment in the past year reported less distress six months later. In the behavioral medicine literature, there are no firmly established demographical or illness-related patient characteristics that generally influence response to a particular psycho-oncological intervention or to psycho-oncological interventions in general¹⁶. That males responded well in this study does not mean that females did not respond to MCGP-CS; it merely indicates that males responded more strongly, particularly when compared to males in the care as usual condition. In an independent patient data meta-analysis of the efficacy of psychosocial interventions for cancer patients, gender did not moderate the effects of these interventions¹⁷. It is possible that males are particularly responsive to MCGP-CS¹⁸, but it would be premature to draw this conclusion based on the present study. Future research may confirm or disprove this finding.

There are psychosocial characteristics that more consistently seem to influence response to psycho-oncological interventions. In general, patients with more symptoms of distress tend to show a stronger response^{14,16,17,19}. The finding that survivors with more depressive symptoms at the start respond better to MCGP-CS is in agreement with these studies. We also expected survivors who already received psychological or psychiatric treatment in the past year to respond better to MCGP-CS, because they are more likely to have more symptoms of distress. Contrary to this expectation, survivors without psychological treatment showed the largest reduction of distress six months after MCGP-CS. Perhaps survivors who already received psychological or psychiatric treatment had more psychiatric comorbidity, which may have limited their capacity to benefit from MCGP-CS. However, these interpretations should be taken cautiously, especially because the number of participants who already received psychological or psychiatric treatment was low. The outcomes of this exploratory study may be used to generate hypotheses for future research on subgroups responsive to meaning-centered psychotherapy and could be combined with future studies in order to develop a clinical decision rule.

Does enhanced meaning as a result of MCGP-CS play a role in a reduction of depressive symptoms?

While personal meaning is enhanced immediately after MCGP-CS, depressive symptoms diminished six months later in the original RCT¹¹. According to the theoretical model underlying meaning-centered psychotherapy, an enhanced sense of meaning plays a role in the reduction of depressive symptoms²⁰. However, in order to prove that enhanced meaning after MCGP-CS mediates a reduction in depressive symptoms, several criteria should be met: there has to be a temporal relation between the mediator and the outcome, a dose-response association and evidence that no other variable(s) cause change in the mediator or the outcome²¹.

In chapter 4, the hypothesized effect of MCGP-CS on depressive symptoms through enhanced meaning was modelled over time. A small but significant mediation effect of MCGP-CS on depressive symptoms three months later, through enhanced meaning immediately after the intervention, was found. Additional analyses suggest that this mediation effect starts immediately after the intervention and seems to last a few months. This mediation effect was not found longer than three months after MCGP-CS and did not explain the reduction of depressive symptoms after six months. Comparable mediation effects could not be demonstrated for goal-orientedness, purpose in life and positive relations with others, although their regression coefficients followed the same pattern.

This study supports the emerging evidence that meaning enhanced by psychotherapy appears to play a role in reducing depressive symptoms over time²²⁻²⁹. When we apply the meaning-making model³⁰, we could hypothesize that this enhanced sense of meaning better enables cancer survivors to account for the cancer-related stressors they encounter, which may result in less threatening or more benign appraisals that invoke fewer depressive symptoms. However, the study in chapter 4 only addressed the temporal relation between enhanced meaning and a reduction in depressive symptoms. It did not look into a possible dose-response association and it is still possible that other variables affect both meaning and depressive symptoms or that they share a common etiology.

What are the long-term effects of MCGP-CS?

After curative treatment for cancer, many survivors still have a long road ahead of them. Studies into the long-term effects of psycho-oncological interventions are scarce³¹. Furthermore, there is no consensus about how long we want these effects to last. The few studies presenting long-term follow-up results suggest that these effects are quite modest³²⁻³⁶. To gain more insight into the long-term efficacy of MCGP-CS, follow-up assessments of psychological well-being, personal meaning and posttraumatic growth were conducted one and two years after the intervention.

A single long-term effect was found: the improvement of relations with others after MCGP-CS remained stable over the course of two years. The positive effects of MCGP-CS on personal meaning, goal-orientedness, and purpose in life faded after a few weeks or months. Additional analyses suggest that this long-term outcome is not entirely robust. When participants who faced cancer recurrence during follow-up were omitted, no long-term effects emerged at all. However, participants who completed more than five sessions of MCGP-CS showed improvements with regard to their relations with others (compared to care as usual) and personal growth (compared to supportive group psychotherapy). When omitting participants who received psychological care during follow-up - a group that might be less responsive to MCGP-CS, as suggested in chapter 2 - a third effect occurred as well. Participants without additional psychological care also reported more inner strength after one year. Compared to the number of outcomes tested, only a few long-term results emerged, but all results favored MCGP-CS over one of the control conditions. These results indicate that additional measures should be taken if we wish to prolong the effects of MCGP-CS. Based on the literature, more session hours, booster sessions or an additional online component may help to enhance survivors' sense of meaning for a longer period of time^{19,37,38}.

DO THE CONSTRUCTS OF PSYCHOLOGICAL WELL-BEING, PERSONAL MEANING, AND POSTTRAUMATIC GROWTH OVERLAP IN CANCER SURVIVORS?

MCGP-CS was expected to strengthen positive mental health. Psychological well-being, personal meaning and posttraumatic growth were therefore used as PROMs in the original RCT. Constructs in the field of positive mental health are often extensively described, but poorly demarcated³⁹. This can also be observed when these constructs are operationalized into PROMs. This apparent overlap may mean that we (also) measure something else, instead of or in addition to that which we actually intend to measure. This hampers our understanding of how these constructs are related. Furthermore, this may impose an unnecessary burden on survivors who complete these (usually long) PROMs.

The results presented in chapter 6 suggest that the PROMs of psychological well-being and personal meaning measure similar or very closely related aspects of positive mental health. Posttraumatic growth seems to be a more distinct, albeit related, construct. Furthermore, religiousness came forward as a separate construct. Notably, the subscales about relations did not clearly stand out from the other psychological well-being and meaning subscales. Perhaps pursuing goals and social relations are very closely intertwined. A recent study among 7,452 older adults showed that changes in perceived social support and sense of purpose over time are quite strongly associated with each other⁴⁰. This close intertwinement of meaning and social relations could offer an explanation for the enduring effect of MCGP-CS on patients' relations with others. For instance, pursuing meaningful goals may foster committed relations with others. Future research could explore whether therapeutically enhanced meaning facilitates better relations with others and vice versa.

The large overlap between the PROMs of psychological well-being and personal meaning can mean two things. On the one hand, we should revisit these questionnaires in order to reduce their overlap. On the other hand, we should conduct further research into the question of whether it is possible to empirically distinguish between these constructs. Perhaps one's sense of psychological well-being and meaning in life boils down to the same thing once translated into measurable behavior. Chapter 6 did not cover the full spectrum of positive mental health, so this single study cannot provide a conclusive answer to the question of what we should measure if we want to measure positive mental health in cancer survivors. However, the preliminary answer is that psychological well-being and meaning can be measured as one, while posttraumatic growth and religiosity should be measured separately. These results call for the development of a brief but comprehensive core outcome set of positive mental

health in the survivorship phase⁴¹.

STRENGTHS AND LIMITATIONS

A strength of this thesis is that it is based on two large RCTs, which provided data on, respectively, 74 and 170 cancer survivors^{11,42}. Due to the randomization process, all outcomes on moderators of the effects of MCGP-CS (chapter 3), its theoretical model (chapter 4) and its long-term effects (chapter 5) were compared to the natural course over time of the outcomes in the care as usual condition and could be attributed to the intervention. All these secondary analyses of the effects of MCGP-CS were conducted in a conservative manner, applying the intention-to-treat principle and taking into account that we performed multiple tests by using linear mixed-model analyses⁴³ and applying Bonferroni correction on all post-hoc analyses (chapter 3 and 5).

However, the fact that this thesis is based on secondary analyses also presents limitations. Firstly, the inclusion criteria of the RCT on the efficacy of MCGP-CS, such as the criterion to have a psychosocial complaint and need for help, were relevant for the RCT, but hampered the generalizability of the study on overlap between psychological well-being, meaning and posttraumatic growth (chapter 6). Secondly, the sample size calculation of the original RCT did not account for the assessment of moderators (chapter 3), analyzing long-term assessments (chapter 5) and exploratory and confirmatory factor analysis (chapter 6). As a result, the number of participants was small for these analyses and the outcomes should be seen as exploratory. Thirdly, although all outcome measures used in this thesis are validated and commonly applied, there is little knowledge about the responsiveness of the measures of personal meaning, psychological well-being and posttraumatic growth. There are also no clear norm scores available. The clinical relevance of the statistically significant findings therefore remains unclear. Furthermore, some significant improvements after MCGP-CS were accompanied by a deterioration in the control condition. In the context of an RCT, both changes can be attributed to the presence or absence of the intervention, but it is unlikely that all changes are exclusively due to the intervention. Moreover, the efficacy of an intervention found in an RCT is often an overestimation of its effectiveness in real life⁴⁴. Lastly, this thesis relies solely on a statistical approach. A mixed-methods approach, which combines quantitative and qualitative research methodologies, can offer a more comprehensive perspective. For that reason, several qualitative studies of meaning-centered psychotherapy and meaning making in cancer survivors were used as background information for this thesis⁴⁵⁻⁴⁸.

IMPLICATIONS FOR CLINICAL PRACTICE

In clinical practice, it is preferable to use evidence-based interventions. MCGP-CS is an evidence-based intervention for cancer survivors with psychosocial or meaning-related issues that is designed to enhance their sense of meaning and improve their psychological well-being¹¹. This thesis adds useful knowledge about psychological well-being, meaning and posttraumatic growth in cancer survivors and the effects of MCGP-CS. Firstly, this thesis suggests that posttraumatic growth is hardly present in distressed head and neck cancer survivors. Therapists may therefore consider the option of exploring potential positive changes with their clients (chapter 2). Next, this thesis shows that MCGP-CS could be recommended to all subgroups of cancer survivors. Stronger improvements can be expected in survivors with more depressive symptoms, but perhaps not in survivors with psychiatric comorbidity. Furthermore, MCGP-CS may be particularly suitable for males (chapter 3). Enhancing a sense of meaning in life can be a therapy goal in itself, but the results of chapter 4 indicate that an enhanced sense of meaning also plays a positive role in coping with depressive symptoms. Therapists should be aware that most positive effects of MCGP-CS seem to fade away in the first months after the intervention (chapter 5). These results may urge therapists and researchers to find ways to maintain these effects over a longer period of time. Furthermore, psychological well-being and personal meaning seem to be almost empirically indistinguishable from each other in cancer survivors (chapter 6). In particular, the experience of well-being and meaning can be put into words in various ways, so carefully listening is required when communicating about it in psychotherapy.

RECOMMENDATIONS FOR FUTURE RESEARCH

This thesis makes it clear that there are many venues for future research. Firstly, to unravel the intertwinement between posttraumatic growth and depressive symptoms in cancer survivors, we need to distinguish between genuine positive psychological change and the mere perception of change. Currently, the only way to capture real growth is to prospectively measure positive psychological constructs over time⁷. The ways in which genuine growth, perceived growth and depressive symptoms are interrelated should therefore be assessed in a longitudinal study, preferably with a baseline measurement conducted prior to the cancer diagnosis and with a control condition.

Secondly, a core outcome set should be developed to create more unity in measuring positive mental health in cancer survivors and to be able to compare outcomes across studies. This core outcome set preferably covers the entire scope of positive mental health and has subdomains that, at minimum, overlap with each other. Furthermore,

the responsiveness of this core outcome set should be mapped to determine how changes in cores on this core outcome set correspond to clinically meaningful change.

Thirdly, we know remarkably little about how psycho-oncological interventions achieve their effects and, related to that question, for whom they work best. To gain insight into the working mechanisms of MCGP-CS, we not only need to study enhanced meaning, but also factors common to other psycho-oncological interventions, such as the therapeutic relation and the expectancy of change²¹. Preferably, such an RCT has assessments several times during the intervention and during follow-up in order to examine the timing of these effects. The dose-response relationship may be investigated in separate studies. If we better understand the working mechanisms, it may be easier to formulate hypotheses about which survivors will respond to an intervention. At the same time, we may conduct an independent patient data meta-analysis of RCTs on meaning-centered group psychotherapy to investigate which subgroups of patients respond best. Furthermore, the protocol of MCGP-CS may be modified in minor ways to make its effects last longer. The effects of these modifications may be studied in a new RCT, preferably one with inclusion criteria that mirror the patients receiving MCGP-CS in clinical practice⁴⁴.

FINAL CONCLUSION

MCGP-CS is an evidence-based intervention that enhances a sense of meaning and psychological well-being in cancer survivors. Cancer survivors with psychological distress hardly seem to experience posttraumatic growth after cancer. This thesis indicates that MCGP-CS is an effective intervention for cancer survivors in general and that an enhanced sense of meaning appears to play a role in a reduction of depressive symptoms. Most of MCGP-CS positive effects fade in the first months after the intervention, but some seem to persist for two years. Extensive future research should be conducted into well-being, meaning and posttraumatic growth of cancer survivors, how to measure it and how to improve it in the long run.

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A

SUMMARY

DUTCH SUMMARY - SAMENVATTING

ACKNOWLEDGEMENTS - DANKWOORD

ABOUT THE AUTHOR

LIST OF PUBLICATIONS



SUMMARY

The general introduction (**chapter 1**) notes that cancer survivors may encounter numerous physical, psychological, social and existential challenges as a consequence of their disease and its treatment, which may cause distress. At the same time, many survivors also perceive posttraumatic growth. Meaning-centered group psychotherapy for cancer survivors (MCGP-CS) was developed to enhance survivors' psychological well-being and sense of meaning in life. The meaning-making model describes how meaning can be related to adjustment to difficult life circumstances, less distress and a better quality of life. The results of a randomized controlled trial (RCT) suggest that MCGP-CS is effective in enhancing personal meaning, goal-orientedness, purpose in life and positive relations with others immediately after the intervention. MCGP-CS also reduced symptoms of distress and depression six months later. However, these overall effects leave many questions unanswered. The aim of this thesis was therefore to obtain more insight into psychological well-being, meaning and posttraumatic growth in cancer survivors and to provide more detailed information about the effects of MCGP-CS.

In **chapter 2**, the occurrence of posttraumatic growth was assessed among 74 head and neck cancer survivors with psychological distress. A moderate to high level of posttraumatic growth was reported by 10% of these head and neck cancer survivors, while 90% reported little or no posttraumatic growth. Relating to others was the life domain in which strongest growth was reported, while survivors perceived, on average, the least growth in the domain of spirituality. The mean score on the Posttraumatic Growth Inventory (mean = 30.8, standard deviation = 17.9) was significantly lower than what was found among non-distressed head and neck cancer survivors in other studies. Stronger posttraumatic growth was best predicted by a lower tumor stage, the absence of an anxiety and alcohol use disorder and better social functioning.

MCGP-CS was developed for survivors with coping or meaning-making issues in the aftermath of cancer. In **chapter 3**, data from the original RCT were re-analyzed in order to identify patient subpopulations for whom MCGP-CS was particularly beneficial, in comparison to the care as usual condition. Six demographical, four illness-related and four psychosocial patient characteristics which could potentially moderate the effects of MCGP-CS on personal meaning, goal-orientedness, purpose in life, positive relations, distress and depressive symptoms were analyzed. Three patient characteristics did moderate one of the effects of MCGP-CS. Firstly, males in particular reported fewer depressive symptoms after MCGP-CS. Secondly, particularly survivors with depressive symptoms reported stronger personal growth after MCGP-CS. Thirdly, particularly patients who did not receive psychological or psychiatric treatment in the

past year reported a reduction in distress over six months after MCGP-CS. However, most of the investigated patient characteristics did not moderate any of the effects of MCGP-CS. Based on these analyses, the tentative conclusion is that MCGP-CS is generally effective for cancer survivors with coping and meaning-making issues and could be recommended to all such patients.

In **chapter 4**, we assessed whether the improvement of personal meaning after MCGP-CS mediated a reduction in depressive symptoms three or six months later, in comparison with the care as usual condition. Additionally, goal-orientedness, purpose in life and positive relations with others were assessed as potential mediators of the effect of MCGP-CS on depressive symptoms. The outcomes of the data analysis indeed showed that an enhanced sense of meaning after MCGP-CS played a mediating role in the reduction of depressive symptoms three months later. Improvements in goal-orientedness seemed to play a similar role, but this effect only became significant among participants who completed all follow-up measures. These effects only occurred within the first few months after the intervention and not later in time.

The strongest improvements to personal meaning and psychological well-being after MCGP-CS were measured in the week after the intervention. However, some effects only occurred three or six months later. **Chapter 5** described the extension of all three study arms of the original RCT with follow-up measures after one and two years. MCGP-CS's positive effects on personal meaning, goal-orientedness and purpose in life, compared to care as usual, faded in the first months after the intervention. However, the improvement in positive relations with others remained stable over the course of these two years. Among the subgroup of participants who completed the intervention, the improvement in personal growth after MCGP-CS also remained stable over one year, compared to supportive group psychotherapy. To summarize, although most effects of MCGP-CS seem to fade out in the months after the intervention, some effects appear to persist in the years after MCGP-CS.

Constructs in the field of positive mental health, including psychological well-being, meaning and posttraumatic growth, are often extensively described, but poorly demarcated. This can also be observed when these constructs are operationalized into PROMs. This raised the question to what extent these constructs can be distinguished from each other empirically. It is important to be able to distinguish between these concepts in order to rigorously study the effects of psychological interventions. The confirmatory factor analysis in **chapter 6** showed that a model in which each subscale loaded on 'its own' total scale (as latent factor) did not fit well with the data. Additional

paths were added to this model until an adequate fit had been realized. From the resulting model, three main conclusions could be drawn: (1) the PROMs on personal meaning and psychological well-being appear to measure similar or very closely related aspects of positive mental health, (2) posttraumatic growth seems to be a related but distinct construct and (3) religiosity seems to be distinct from psychological well-being, personal meaning and posttraumatic growth.

In the general discussion (**chapter 7**) these results are taken together and integrated into the psycho-oncology literature. This thesis indicates that distressed cancer survivors hardly experience posttraumatic growth. MCGP-CS is an evidence-based intervention for survivors with coping or meaning-related difficulties. This intervention seems to be effective for survivors in general and an enhanced sense of meaning appears to play a role in a reduction of depressive symptoms. Most of MCGP-CS positive effects fade in the first months after the intervention, but some seem to persist for two years. Extensive future research should be conducted into well-being, meaning and posttraumatic growth of cancer survivors, how to measure it and how to improve it in the long run.

DUTCH SUMMARY – SAMENVATTING

In de algemene inleiding (**hoofdstuk 1**) wordt beschreven dat mensen die kanker hebben overleefd, als gevolg van deze ziekte en de behandeling, te maken kunnen krijgen met uiteenlopende klachten op fysiek, psychologisch, sociaal en existentieel gebied. Deze klachten kunnen distress oproepen. Tegelijkertijd geven veel overlevers aan dat ze ook positieve psychologische veranderingen ervaren door kanker. Dit wordt posttraumatische groei genoemd. De psychologische interventie 'meaning-centered group psychotherapy - cancer survivors' (MCGP-CS), in Nederland ook bekend onder de namen zingevinggerichte psychotherapie en 'Kanker en persoonlijke zingeving', is ontwikkeld om het psychologisch welzijn en het gevoel van zingeving van overlevers van kanker te versterken. In het 'meaning-making model' beschrijft Crystal Park hoe zingeving een rol kan spelen bij het aanpassen aan moeilijke omstandigheden in het leven. Zingeving speelt volgens dit model een rol bij het verminderen van distress en het verbeteren van de kwaliteit van leven. In een gerandomiseerde, gecontroleerde studie (RCT) werd MCGP-CS vergeleken met een sociale steungroep en een controlegroep die alleen de gebruikelijke zorg kreeg. De resultaten van deze RCT duiden erop dat MCGP-CS persoonlijke zingeving (iemand's gevoel dat zijn of haar leven zinvol is) en doelgerichtheid versterkt. Ook verschillende aspecten van psychologisch welzijn, waaronder het hebben van een doel en richting in het leven en positieve relaties met anderen werden versterkt door MCGP-CS. In deze RCT leide MCGP-CS bovendien tot een afname van distress en depressieve klachten zes maanden na afloop van de interventie. Deze algemene effecten van MCGP-CS vertellen echter maar een deel van het verhaal. De doelstelling van dit proefschrift is om meer inzicht te verwerven in het psychologisch welzijn, zingeving en posttraumatische groei bij overlevers van kanker en om de effecten van MCGP-CS hierop gedetailleerder in kaart te brengen.

In **hoofdstuk 2** is de prevalentie van posttraumatische groei onder overlevers van hoofd-halskanker met een verhoogde mate van distress onderzocht. Van de 74 deelnemers aan deze studie gaf 10% aan een matig tot hoge mate van posttraumatische groei te ervaren. Dit betekent dat 90% weinig tot geen posttraumatische groei lijkt te ervaren. Relaties met anderen was het gebied waarop de meeste groei werd gerapporteerd. Op het gebied van spiritualiteit werd de minste groei gerapporteerd. De gemiddelde score op de Posttraumatic Growth Inventory (gemiddelde = 30.8, standaarddeviatie = 17.9) was significant lager dan de gemiddelde score in eerdere studies onder hoofd-halskanker patiënten, waarin patiënten niet geselecteerd waren op een verhoogde mate van distress. Sterkere posttraumatische groei werd voorspeld door een model van vier variabelen: een lager tumorstadium, de afwezigheid van een angststoornis en de afwezigheid van een stoornis in het gebruik van alcohol en minder beperkingen in het sociaal functioneren.

MCGP-CS is bedoeld voor overlevers van kanker die moeilijk kunnen omgaan met de gevolgen van deze ziekte of te maken krijgen met levensvragen die (existentiële) distress oproepen. In **hoofdstuk 3** zijn de data van de originele RCT opnieuw geanalyseerd om te achterhalen of er verschillende subgroepen van overlevers te onderscheiden zijn voor wie MCGP-CS vooral effectief is. De effecten van MCGP-CS voor een bepaalde subgroep werden in deze analyses telkens vergeleken met het beloop van de uitkomstmaten (persoonlijke zingeving, doelgerichtheid, doel/richting in het leven, positieve relaties met anderen, distress en depressieve klachten) in de controlegroep. In totaal zijn zes demografische, vier ziektegerelateerde en vier psychosociale eigenschappen geanalyseerd. Drie van deze veertien eigenschappen bleken het beloop van een uitkomstvariabele te modereren. Ten eerste bleken vooral mannelijke deelnemers minder depressieve klachten te hebben gekregen na MCGP-CS. Ten tweede bleken deelnemers die met meer depressieve klachten begonnen aan de interventie sterkere persoonlijke groei te ervaren na afloop van de interventie. Als laatste bleken deelnemers die in het jaar voorafgaand aan de interventie geen andere psychologische of psychiatrische behandelingen hadden gehad, minder distress te ervaren zes maanden na afloop van MCGP-CS. Deze moderatie-effecten werden telkens gevonden op één van de zes uitkomstmaten en de overige elf eigenschappen leidden niet tot gedifferentieerde effecten van deze interventie. Op grond hiervan is de voorlopige conclusie getrokken dat MCGP-CS effectief is voor overlevers van kanker in het algemeen en niet specifiek effectiever voor bepaalde subgroepen.

In **hoofdstuk 4** staat de vraag centraal of een versterking van persoonlijke zingeving na MCGP-CS een mediërende rol speelde in de afname van depressieve klachten, zowel drie als zes maanden na de interventie. Ook doelgerichtheid, doel/richting in het leven en positieve relaties met anderen zijn onderzocht als mediators van het effect van MCGP-CS op depressieve klachten. In al deze analyses is gecontroleerd voor het natuurlijke beloop van de mediator en de uitkomstmaat in de controlegroep. De uitkomsten wezen er inderdaad op dat een sterkere mate van zingeving na MCGP-CS een rol speelt in de afname van depressieve klachten drie maanden later, al is deze rol klein. Versterking van doelgerichtheid na MCGP-CS leek een vergelijkbare rol te spelen, maar dit mediatie-effect werd alleen significant in de subgroep van deelnemers die alle metingen hadden ingevuld. Dit mediatie-effect leek alleen aanwezig te zijn in de eerste maanden na de interventie. De afname van depressieve klachten zes maanden na MCGP-CS kon niet worden verklaard door een toename van zingeving. Uit de originele RCT bleek dat de sterkste verbeteringen van psychologisch welzijn en persoonlijke zingeving plaatsvonden in de week na MCGP-CS, al bleken sommige

effecten pas drie tot zes maanden later naar voren te komen. Voor **hoofdstuk 5** zijn er nametingen toegevoegd aan alle drie condities van de originele RCT. Zowel één als twee jaar later werden de effecten van MCGP-CS op psychologisch welzijn, zingeving en posttraumatische groei opnieuw gemeten. De positieve effecten van MCGP-CS op persoonlijke zingeving, doelgerichtheid en doel/richting in het leven namen af in de eerste maanden na de interventie. Wel bleef de verbetering van positieve relaties met anderen in vergelijking met de controlegroep stabiel over de gehele looptijd van twee jaar. Onder de deelnemers die minimaal zes van de acht sessies van MCGP-CS of de sociale steungroep hadden bijgewoond kwam nog een tweede lange-termijn effect naar voren. Deelnemers ervoeren een sterkere verbetering van persoonlijke groei tot één jaar na MCGP-CS in vergelijking met de sociale steungroep. Dus hoewel de meeste effecten van MCGP-CS afnamen in de maanden na de interventie, lijken enkele effecten nog te blijven bestaan in het jaar of de jaren daarna.

Positieve psychologische constructen, zoals psychologisch welzijn, persoonlijke zingeving en posttraumatische groei, worden in de literatuur uitgebreid omschreven, maar nauwelijks afgegrensd van andere constructen. Ook als deze constructen geoperationaliseerd worden als patiënt-gerapporteerde uitkomstmaten (PROMs) wordt deze ogenschijnlijke overlap zichtbaar. Dit roept de vraag op in hoeverre psychologisch welzijn, persoonlijke zingeving en posttraumatische groei empirisch van elkaar te onderscheiden zijn. Het is van belang om deze constructen te kunnen onderscheiden van elkaar, onder andere om de effecten van psychologische interventies goed in kaart te kunnen brengen. De confirmatieve factoranalyse in **hoofdstuk 6** liet zien dat een model waarin elke subschaal hoort bij 'zijn eigen' PROM niet goed bij de data paste. In een exploratieve analyse werden vervolgens paden aan dit model toegevoegd, totdat het model wel goed bij de data paste. Op grond van het uiteindelijke model konden drie conclusies getrokken worden: (1) de PROMs van psychologisch welzijn en zingeving lijken gelijke of zeer sterk aan elkaar gerelateerde aspecten van mentale gezondheid te meten, (2) posttraumatische groei lijkt een afzonderlijk construct te zijn, dat wel gerelateerd is aan psychologisch welzijn en zingeving en (3) religiositeit lijkt naar voren te komen als een construct dat losstaat van psychologisch welzijn, zingeving en posttraumatische groei.

In de algemene discussie (**hoofdstuk 7**) zijn deze resultaten samengenomen en geïntegreerd in de psycho-oncologische literatuur. Dit proefschrift laat zien dat overlevers van kanker met distress weinig posttraumatische groei ervaren. MCGP-CS is een wetenschappelijk onderbouwde interventie voor overlevers van kanker met levensvragen of die moeilijk kunnen omgaan met de gevolgen van de ziekte

en de behandeling. MCGP-CS lijkt effectief te zijn voor overlevende van kanker in het algemeen en een versterkt gevoel van zingeving door deze interventie lijkt een rol te spelen in de afname van depressieve klachten. De meeste effecten van MCGP-CS nemen af in de eerste maanden na de interventie, maar sommige effecten blijven nog tot twee jaar later bestaan. Uitgebreid onderzoek is nodig om meer inzicht te krijgen in psychologisch welzijn, zingeving en posttraumatische groei bij overlevende van kanker, om deze constructen beter te kunnen meten en om ze langduriger te kunnen versterken.

ACKNOWLEDGEMENTS - DANKWOORD

Veel mensen hebben een onmisbare bijdrage geleverd aan dit proefschrift, of aan mijn leven tijdens het schrijven van dit proefschrift. Nu is het moment aangebroken om jullie persoonlijk te bedanken.

Allereerst alle overlevers van kanker die meegewerkt hebben aan een screeningsgesprek, één van de studiearmen en de vele nametingen. De meeste deelnemers heb ik verschillende malen telefonisch gesproken. Jullie verhalen hebben diepe indruk op me gemaakt.

Dit proefschrift had hier niet gelegen zonder prof. dr. Irma Verdonck-de Leeuw. Een sterke vrouw met een optimistische blik die altijd de weg vooruit ziet. Irma, je bent niet alleen mijn promotor, maar ook de rode draad sinds ik begonnen ben bij de VU. Je bent bij iedere stap die ik gezet heb in de academische wereld aanwezig geweest. Ontzettend veel dank hiervoor.

Naast Irma had ik me geen prettigere promotor kunnen wensen dan prof. dr. Pim Cuijpers. Pim, feilloos heb je telkens sterkere en zwakkere punten van mijn papers uitgelicht. Maar ook persoonlijk heb ik me altijd gesteund gevoeld door de manier waarop je luistert en meedenkt.

Mijn copromotor dr. Nadia van der Spek heeft de basis gelegd voor dit proefschrift. Nadia, bedankt dat je een plekje voor mij gecreëerd hebt op je onderzoeksproject. Jij zette me ertoe aan om telkens weer tot een nieuwere en betere versie van mijn werk te komen. Bedankt ook voor alle fijne gesprekken door de jaren heen.

Graag wil ik de promotiecommissie bedanken, bestaande uit prof. dr. Annemieke van Straten, dr. Grieteke Pool, dr. Eline Aukema, prof. dr. Ernst Bohlmeijer, prof. dr. Gaby Jacobs en prof. dr. Mirjam Sprangers. Ik heb veel bewondering voor jullie werk. Verschillende aspecten daarvan hebben invloed gehad op dit proefschrift of op andere projecten waar ik aan werk.

Speciaal wil ik Eline Aukema, Vincent Willemsen en Kitty Knipscheer bedanken. Eline, de samenwerking met het Ingeborg Douwes Centrum heeft niet alleen dit proefschrift voortgebracht, maar ook andere mooie onderzoeksprojecten. Jouw enthousiasme en energie werken aanstekelijk. Vincent en Kitty, bedankt voor de fijne samenwerking op het gebied van zingevingstherapie.

I am also very thankful to prof. dr. William Breitbart, the initiator of meaning-centered

psychotherapy and co-author of most papers in this dissertation. Dear dr. Breitbart, I am grateful for your support of this study and of the new research proposals that arose from it.

Voor dit onderzoeksproject heb ik vele dagen doorgebracht in verschillende ziekenhuizen. Graag wil ik de artsen bedanken die de studies in mijn proefschrift mogelijk hebben gemaakt: René Leemans, Rob Tollenaar, Christi van Asperen, Peter Neijenhuis, Sanne Veltkamp en Maud Geenen. Daarnaast wil ik alle onderzoeksverpleegkundigen en medewerkers van het secretariaat bedanken voor hun gastvrijheid, hulp en gezelligheid.

In dit proefschrift heb ik meerdere, voor mij nieuwe statistische analyses gebruikt. Ik wil Birgit Lissenberg-Witte en Judith Rijnhart bedanken voor hun prettige begeleiding, hulp en advies hierbij.

In het bijzonder wil ik Nelly van Uden-Kraan bedanken. Nelly, zonder jou had ik hier niet gestaan. En dat komt niet alleen doordat je me weer opbelde toen er een nieuwe vacature vrijkwam. Bedankt voor jouw positiviteit, steun en warmte in de jaren daarna. Er zijn meerdere mensen die me tijdens mijn studies religiewetenschappen en psychologie gevormd hebben, misschien zonder dat ze het weten. Met naam wil ik graag Ulrike Popp-Baier en Sander Koole noemen. Ulrike, mijn proefschrift sluit rechtstreeks aan bij alles wat ik geleerd en ontdekt heb tijdens de research master religious studies. Ik vind het een eer om nog steeds gastcolleges te geven en daarna gezellig een hapje te eten. Sander Koole, het vak experimentele existentiële psychologie heeft mij erg gefascineerd. Nog regelmatig pak ik het "Handbook Experimental Existential Psychology" er weer bij.

Al mijn collega's van de onderzoeksgroep Samen Leven met Kanker wil ik bedanken en vooral iedereen die deel uitmaakt, of heeft uitgemaakt, van het Oncokompas team: Irma Verdonck-de Leeuw, Nelly van Uden-Kraan, Heleen Melissant, Anja van der Hout, Anouk Schuit, Matthijs de Wit, Koen Neijenhuijs, Margot Veegers, Nienke Hooghiemstra en Valesca van Zwieten. De afgelopen jaren hebben we heel wat meegemaakt, variërend van het uitbreiden van Oncokompas en het ontwikkelen van animatiefilmpjes tot het geven van presentaties en het bezoeken van de CCA retreat en NVPO congressen. Vooral Anouk en Nienke wil ik bedanken voor de intensieve en prettige samenwerking en alle boeiende gesprekken. Sandra Biemans staat altijd met een warm woord voor iedereen in de onderzoeksgroep klaar. Bedankt daarvoor!

Daarnaast mag ik bijdragen aan verschillende andere projecten, waaronder LearnPAL, een e-learning over palliatieve zorg, en de Adjust-studie naar aanpassingsstoornissen bij mensen met kanker. Ook mag ik een steentje bijdragen aan het onderwijs van de afdeling Klinische Psychologie door het begeleiden van bachelor- en mastertheses en het coördineren van het vak Psyche en Soma. Alle studenten en collega's betrokken bij deze projecten wil ik bedanken voor de fijne samenwerking.

In acht jaar aan de VU heb ik twaalf kamergenoten gehad en veel hilarische of ontroerende momenten gedeeld. Femke, in de pre-coronatijd deelden wij een kamer op de vijfde verdieping met uitzicht over de botanische tuin. We hebben wereldwijd verschillende congressen samen bezocht, waaronder de IPOS congressen in Dublin en Hong Kong. In de pub in Dublin, op de roltrappen in het centrum van Hong Kong en hoog in de lucht in het vliegtuig zijn we bevriend geraakt. Wat een eer dat jij me wilt bijstaan als paranimf.

Veel vriendinnen hebben ervoor gezorgd dat ik niet alleen maar gewerkt heb de afgelopen jaren. Lieneke, sinds we elkaar een jaar of vijftien geleden ontmoet hebben in de bibliotheek van de VU hebben we altijd veel te bespreken gehad. Ik kijk altijd uit naar onze (gehaaste) kopjes cappuccino op de VU en etentjes in Amsterdam. Eva, na onze opleiding religie en levensbeschouwing hebben wij contact gehouden en zijn we zelfs huisgenoten geweest. Leuk om telkens iets nieuws te ontdekken als we een dagje samen weggaan. Jessica, Jantien, Jolien, Anke, Marijke, Annemarie, Mirjan, Célia en andere hardlopers, bootcampers en wandelaars, door jullie ben ik de stress de baas gebleven. Jessica, heerlijk om op vrijdagavond de wandelschoenen weer aan te trekken en samen op pad te gaan.

Als kleuters en op de middelbare school waren we al vriendinnen: Femke, Marleen, Annemarie, Mirjan, Nicole, Anne-Marie en Désiré. Via het proefmonstersparen, onze eerste echte vakantie op de camping in Epe en vele avonden in De Leeren Lampe zijn we dan toch volwassen geworden. Annemarie, vroeger hadden we altijd de slappe lach, nu eindeloze gesprekken over wat we belangrijk vinden, hoe we willen leven en de keuzes die we maken. Mirjan, sinds ik door jouw carnavalsplannen Hans heb ontmoet, zien we elkaar vaak: verjaardagen, dagjes uit met de kinderen, 's ochtends vroeg in de trein of 's avonds een drankje bij Neuf.

Lieve Marijke, Jessica, Anke, Milou, Ellen, Jolien en Marjolein, meteen als we weer bij elkaar zijn, voor een weekendje weg, een verjaardag of zomaar, is er weer die gezellige, ontspannen sfeer. Onze vriendschap kent voor mij alleen maar hoogtepunten. Voor

mijn gevoel kunnen wij niet alleen de leuke dingen met elkaar delen, maar ook de moeilijkere dingen die op ons pad komen. Ik kijk uit naar het moment waarop het weer veilig genoeg is, tijdens of na de corona-pandemie, om ons weekendje weg in te halen!

Tot slot kom ik aan bij mijn familie. En wat voor familie! Ik had me geen fijnere familie en schoonfamilie kunnen wensen. Dat komt niet in de laatste plaats door jullie, Cor en Ineke. Wat fijn dat ik nog zo lang deel heb kunnen uitmaken van jullie gezin en wat verdrietig dat die tijd opeens, zo plotseling afgelopen is. Marc, Célia, Jessie en Feline, door de warmte en gezelligheid die jullie met je meebrengen, en door jullie gevoel voor humor, kijk ik altijd uit naar familie-dingen. Heerlijk ook om Jessie, Feline, Julian en Luca samen te zien spelen.

Mijn vader August en moeder Marian, jullie hebben ons altijd gestimuleerd om onze eigen weg te zoeken. En jullie staan altijd vol liefde voor ons klaar. Op allerlei manieren hebben jullie de voorwaarden geschapen voor het schrijven van dit proefschrift. Ook mijn oma Jenny wil ik bedanken. Je bent altijd vol interesse en vragen over hoe het met ons, en aan de universiteit, gaat. Lieve Ellen, waar ook ter wereld jij je bevindt – en nu als paranimf naast me – altijd lijken we op dezelfde manier over dingen na te denken. Er is niemand die mij zo goed begrijpt als jij. Joost, je kwam als ‘mijn verjaardagscadeautje’ ter wereld, maar inmiddels heb ik je af moeten staan aan Marike. Iets waar ik trouwens heel blij mee ben. Joost en Marike, het is altijd genieten als jullie bij ons blijven logeren of als wij afreizen naar Eindhoven. Ik kijk ontzettend uit naar het Holtmaatje dat op komst is!

Lieve Hans, Julian en Luca, wat ben ik blij dat ik, net terug uit Helsinki, carnaval ben gaan vieren. Even moest ik wennen toen jij je pruik afzette, maar inmiddels zijn we al vele reizen, drie woonplaatsen en twee kinderen verder. We hebben (bijna) altijd net zoveel plezier, liefde en gezelligheid als in het begin. Niet alleen bij de grote dingen, maar ook als we met Julian en Luca een nieuwe fietsroute ontdekken, of als we elkaar 's avonds weer zien op de bank. Mijn allerliefste Julian en Luca, de afgelopen jaren heb ik geprobeerd iets te begrijpen van zingeving, maar jullie zorgen voor dat gevoel. Nooit had ik kunnen denken dat jullie elk moment de moeite waard maken. En dat ik zo zou genieten van elke grote en kleine stap, van elke ondeugende lach en onmogelijk te beantwoorden vraag.

ABOUT THE AUTHOR

Karen van Dijk-Holtmaat was born on January 7, 1985 in Raalte. She completed secondary education (gymnasium) at Carmel College Salland in 2003. In 2012, she obtained a research master's degree in religious studies at the University of Amsterdam (cum laude) and a master's degree in clinical psychology at the Vrije Universiteit Amsterdam (cum laude). She interrupted her studies for one year to travel in India (2004) and studied six months abroad in Helsinki, Finland (2008).

Since 2012, she works as a researcher at the Department of Clinical, Neuro- and Developmental Psychology at the Vrije Universiteit Amsterdam in the research group 'Living Together with Cancer', chaired by prof. dr. I.M. Verdonck-de Leeuw. This research group is embedded in research institute Amsterdam Public Health (APH) and Cancer Center Amsterdam. For her PhD research, she joined a collaboration with Ingeborg Douwes Center for Psycho-Oncology Care (OLVG Hospital) in which the efficacy of meaning-centered group psychotherapy for cancer survivors was investigated. Karen is involved in several other research and valorisation projects, mainly related to the online self-management tool Oncokompas. Karen coordinated several bachelor thesis projects and supervises students with their master thesis. She is BKO-certified, coordinates the course Psyche and Soma in the master clinical psychology and she regularly gives guest lectures. Recently she became a member of the editorial board of the magazine 'Psychosociale Oncologie' of the Dutch Association for Psychosocial Oncology (NVPO).

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1. **Holtmaat, K.**, van der Spek, N., Rijnhart, J.J.M., Lissenberg-Witte, B.I., Breitbart, W., Cuijpers, P., & Verdonck-de Leeuw, I.M. Does enhanced meaning after meaning-centered group psychotherapy mediate a reduction in depressive symptoms in cancer survivors? *Submitted*.
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