Power of the past: Life review therapy in palliative cancer care

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Power of the past

Life review therapy in palliative cancer care

Gitta Kleijn

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VRIJE UNIVERSITEIT

POWER OF THE PAST: LIFE REVIEW THERAPY IN PALLIATIVE CANCER CARE

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. J.J.G. Geurts,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Gedrags- en Bewegingswetenschappen
op donderdag 13 oktober 2022 om 13.45 uur
in een bijeenkomst van de universiteit,
De Boelelaan 1105

door

Gitta Kleijn

geboren te Amsterdam

Maak prachtige herinneringen,
je hebt ze nodig, vroeg of laat.
Ze zullen je dragen,
wanneer het even minder gaat.

Papa

CONTENTS

CHAPTER 1

General introduction

INTRODUCTION

We all have a life story. Every life story is built on a unique and endless collection of experiences and life events. The majority of these, we have no memory or recollection of, but others will result in memories of little things or single events, like day-to-day activities or a first kiss, or more substantial life events or discrete experiences that disrupt an individual's usual activities, causing substantial change and readjustment, such as marriage, childbirth, or a serious illness like cancer [1].

For most people (patients and their loved ones), a cancer diagnosis is considered a life-threatening event, and a confrontation with their own mortality [2,3]. They become aware of unfulfilled accomplishments and goals and realize that they might not live long enough to participate in important, meaningful life events in the future, such as the birth of grandchildren [4]. These circumstances often trigger a natural response to loss and change, in which they think about the meaning of life and review their lives [5,6]. Feelings of ego-integrity or despair may occur, which may be positively or negatively affect quality of life. Life review therapy has been developed to improve ego-integrity and reduce despair, and maintain good quality of life, but information on the effectiveness of this intervention in cancer populations is scarce. Therefore, the main aim of this dissertation is to investigate the effect of life review therapy among cancer patients and their loved ones.

In this chapter, an overview will be provided of the epidemiology and treatment of cancer and palliative care, and the challenges this disease and its treatment puts on patients and their informal caregivers. Also, life review therapy will be introduced including its components: autobiographical memory, reminiscence, and life review. After that, the intervention "Dear Memories" (a life review therapy combined with autobiographical memory specificity training; LRT-MST) [7] will be described, which is at the heart of this dissertation. Finally, the main aim and outline of the dissertation will be provided.

Epidemiology and treatment of cancer
With an estimated 18 million new cancer cases [8] and 9.6 million deaths in 2018 due to cancer (one in every six deaths), cancer is the second leading cause of death globally. In the Netherlands, one in three people gets cancer during their life span. In 2020, 115.000 new cancer cases were reported in the Netherlands and approximately 604.000 lived with and beyond cancer. During the past years, overall survival rate increased due to

earlier detection, more effective treatments (e.g. advances in surgery, radiotherapy, chemotherapy, and targeted therapy, and hormone therapy), and lower prevalence of some cancer with high mortality rate [9], but still around half of all cancer patients will not recover (cijfersoverkanker.nl). In the Netherlands, there are yearly around 45.000 deaths due to cancer (approximately 30% of all deaths), which makes cancer the leading cause of death in the Netherlands (cijfersoverkanker.nl; Volksgezondheidenzorg.info).

The impact of cancer and palliative care
The impact of a diagnosis of cancer on someone's life is enormous, especially when the cancer is expected to be incurable. Whereas the physical impact of cancer and its treatment are well-known, studies suggest that in advanced cancer patients the impact on psychological, spiritual, and existential issues may even be of greater concern [10,11]. Previous research showed that depressive states and mood-related disorders are common among incurably ill patients [3,12] and that the level of psychological distress and the need for palliative care increases when the disease progresses [13].

Informal caregivers as the partner or other loved ones are essential for incurably ill cancer patients [14,15]. They are often involved in medical decisions [14] and are confronted with many different tasks, like assisting the patient with symptom management, medication, personal and instrumental care, financial and emotional support [16,17]. Although most informal caregivers cope rather well, for some these circumstances and responsibilities negatively affect their physical and mental well-being [18,19].

According to the World Health Organisation [15] palliative care is recognized under the human right to health. Palliative care aims to provide support to and improve the quality of life of patients and their families who are facing problems associated with life-threatening illness [14]. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual (www.who.int/news-room/fact-sheets/detail/palliative-care). It is estimated that only 14% of advanced cancer patients who need palliative care receive it (www.who.int/health-topics/palliative-care), while in more than 90% of the patients, relief from physical, psychosocial, and spiritual problems can be achieved through palliative care (who.int) [20]. Lack of good quality palliative care can lead to a decreased quality of life, suicidal ideation, anxiety, depression, and desire for a hastened death [21]. This may result in more suffering for patients and their informal caregivers [14,15].

There are various types of psychological interventions for people with incurable cancer, such as dignity therapy [14], existential interventions [22], and life review therapy (LRT) [21,23,24]. In this dissertation we will focus on life review therapy (LRT) combined with (autobiographical) memory specificity training (LRT-MST).

LIFE REVIEW THERAPY

LRT was first developed by psychiatrist Dr. Robert Butler who theorized that having older people think back on their life could be therapeutic [25]. LRT is based on knowledge about the working of the autobiographical memory and about reminiscence and life review processes. Reminiscence and life review are processes that people may experience by themselves, but can also be actively stimulated in therapy. In this paragraph we will provide more information on the autobiographical memory, reminiscence, and life review as such, and how they can be used in life review therapy.

Autobiographical memory

The autobiographical memory is the part of the brain were someone's memories of personally experienced past events are recollected and knowledge about the world is stored [26-28]. The autobiographical memory has a hierarchical organisation regarding level of specificity [3,27]. The most specific autobiographical memories are personally significant memories of events (episodic memories) that took place on a specific day and place (e.g., "the day my child was born"). At the general level, there are two kinds of memories: extended memories and categorical memories. Extended memories are associated with general memories to events who last more than a day (e.g., "the time I spent in treatment for a medical problem"), and categorical memories are memories describing general, repeated events who can be grouped together in a category (e.g., "Saturday-night dinners with friends") [3,29].

Research showed that people with depressive symptoms or clinical depression are more likely to retrieve general memories than non-depressed individuals [28,30,31]. This is called reduced autobiographical memory specificity. Nieto et al. [3] reported that patients with cancer also have a significant lower autobiographical memory specificity compared to people without cancer. Many patients who underwent chemotherapy and/ or hormone therapy encounter cognitive disturbances, mainly regarding the domains: memory, processing speed and functioning. Several underlying factors or processes

(e.g. age, comorbidity, or emotional functioning) may influence these treatment-induced cognitive deficits, which makes it difficult to explain [3].

Reminiscence

Looking back or retrieving memories is called reminiscence. Bluck and Levine [32] defined reminiscence as "the volitional or nonvolitional act or process of recollecting memories of one's self in the past. It may involve the recall of particular or generic episodes that may or may not have been previously forgotten, and that are accompanied by the sense that the remembered episodes are veridical accounts of the original experiences. This recollection from autobiographical memory may be private or shared with others".

This form of reminiscence is mainly unstructured autobiographical storytelling and has different functions [26,33]. First of all, it has social functions. Sharing personal memories stimulates bonding between people and can be used to teach and inform others about past experiences [26]. Secondly, reminiscence also serves instrumental functions. Looking at challenges and corresponding problem-solving strategies in the past could help cope with problems in the presence. It can also be a coping strategy; retrieving positive memories may help regulate current negative feelings or can enhance positive feelings [33]. When it is used to avoid feelings or emotions of problems this strategy becomes maladaptive [5]. Reminiscence can also help with coming to terms with the loss of someone by maintaining symbolic bonds due to retrieving memories [26]. The third function that is distinguished is that retrieving memories also has an integrative function. Especially in times of change, such as being diagnosed with incurable cancer, reflecting on the past may help to continue or adjust one's identity. It can be used to strengthen one's positive identity by focusing on successes and strengths of the past. However, some people define their identity by a negative past event or episode, also called obsessive reminiscence or bitterness revival. Via evaluating one's course of life and providing new meaning and value to negative memories reduction of bitterness revival can be achieved [5,34]. It may also lead to improved psychological resources (social support, mastery, coping, meaning in life, and self-esteem), and mental health and well-being (less depressive and anxiety feelings, and more happiness and life satisfaction [26].

Reminiscence mainly seem to support the social function with retrieving and sharing autobiographical memories and is therefore often used in nursing home amongst others [35]. The integrative function comes closest to life review as described by Butler [5,26].

Life review

Life review is a more structured process than "simple reminiscence". Butler [25] described life review as a "naturally occurring process of recalling the past, that is hypothesized to resolve conflicts from the past and make up the balance of once life" [6,36]. It focuses on the (re-)evaluation of life events and on the integration (and acceptance) of positive and negative life events in a coherent life story [33]. It also allows people to come to terms with their own death [36,37].

Life review therapy

LRT uses life review processes in a therapeutic form. LRT targets people who have (an increased risk for) mental health problems, such as depression [5,38]. It has been shown to be an effective intervention in elderly, and more recently it also has been used in advanced cancer patients [21]. LRT seems to effect various aspects that are relevant in end-of-life practice [33]. Amongst others, LRT may reduce bitterness revival and boredom and promote a positive view on one's past [33]. If this results in accepting "one's one and only life cycle as something that had to be" it is called ego-integrity [39,40], if someone experiences regret about life this may result in despair [41]. Also, earlier studies showed that LRT may help patients to address their existential suffering, enhance their quality of life, life satisfaction and self-esteem, and promote good death [21,33]. Chochinov et al. [11] stated that the potential benefit of LRT for terminally ill patients is not just the relief of stress, but also the prevention of psychological distress, improvement of well-being, and establishment of a sense of personal meaning and life purpose. As such, LRT may help to improve the quality of end-of-life care and support patients and their families in the best possible way.

A meta-analysis by Pinquart and Forstmeier [33] supported the assumption that patients with chronic somatic illness benefit more from reminiscence (including LRT) interventions than healthy individuals. This is at least with regard to depressive symptoms, which might be caused by elevated levels of depression at pretest and/or a need to find ego-integrity because of their limited life-expectancy.

Dear memories

In the Netherlands, the protocol "Dear Memories" [7] was developed, a combination of LRT and memory specificity training (LRT-MST). The protocol is based on the intervention developed by Serrano et al. [42] for older adults with depressive symptomatology. It aims to improve the life review process and to train the autobiographical memory

by increasing positive memory retrieval [43]. The intervention consists of four weekly sessions of approximately 1 hour and each session focusses on a particular lifetime period: childhood, adolescence, adulthood, and whole life span. Each period contains 14 questions, which are developed to retrieve positive specific memories. The sessions are led by a trained psychologist. The sessions take place at the respondent's residence or at the hospital. Every session is recorded on mp3 and copies are offered as a remembrance for the patients and/or their informal caregivers.

Although there is some evidence on the efficacy of LRT [21,23,24,44], high quality research is needed to enhance our knowledge on the benefits of LRT in palliative care.

AIM AND OUTLINE OF THIS DISSERTATION

The main aim of this dissertation is to obtain insight in the efficacy of the structured Life Review Therapy combined with memory specificity training (LRT-MST), named ''Dear Memories'' among incurably ill cancer patients. Based on previous research [21,23,24,44] it is hypothesized that patients with incurably ill cancer who receive LRT-MST will experience improved ego-integrity and less despair. It is also hypothesized that LRT-MST will be effective in improving the specificity of the autobiographical memory, and quality of life, and in reducing depressive symptoms among advanced cancer patients, and possibly among their informal caregivers.

The general outline of this dissertation is as follows:

Chapter 2 presents the study protocol of the randomized controlled trial (RCT) to assess the efficacy of LRT-MST in incurably ill cancer patients.

Chapter 3 describes a study on the psychometric characteristics of the primary outcome measure in in the RCT: the North-western Ego-integrity Scale (NEIS).

Chapter 4 presents the results of the RCT testing the efficacy of LRT-MST among incurably ill cancer patients.

Chapter 5 gives more in-depth knowledge on motivation to start with LRT-MST, experiences with LRT-MST, and perceived outcomes of LRT-MST in incurably ill cancer patients.

Chapter 6 describes the study investigating whether LRT-MST delivered to incurably ill cancer patients, may also benefit their informal caregivers.

Chapter 7 provides a general discussion putting the findings of the studies conducted in this dissertation in broader perspective. Also, strengths, limitations, implications for clinical practice and recommendations for future research are provided.

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CHAPTER 2

The efficacy of Life Review Therapy in advanced cancer patients: protocol of a randomized controlled trial

> " *Kunt u zich een zeer gelukkige dag herinneringen die u als kind samen met uw ouders beleefde?* "

ABSTRACT

Background: Advanced cancer patients and their spouses often experience a reduced quality of life and feelings of psychological and spiritual distress. The aim of this study is to investigate the effectiveness of the Life Review Therapy (LRT) "Dear Memories" among advanced cancer patients and their spouses.

Methods/design: This study is designed as a randomized clinical trial with 2 treatment arms. A sample of 150 cancer patients without curative treatment options, with a prognosis of > 3 months, and with depressive symptoms (HADS-D and/or HADS-A >7, HADS-total >14) will be included. Exclusion criteria are cognitive impairment, inability to communicate verbally, insufficient mastery of the Dutch language, and psychotic symptoms or behaviour (delusions or hallucinations). Patients will be randomly assigned to either the intervention group (LRT) or control group (care as usual). The LRT, is a brief psychological intervention (4 sessions in the home situation of the patient), in which patients are trained to retrieve positive specific memories from the past and thereby generating a coherent and meaningful autobiography. Primary outcome is depressive symptoms (HADS). Secondary outcomes are the presence or absence of clinical depression (MINI), specificity of Autobiographical Memory (AMT), quality of life (EORTC QLQ-PAL15), and ego-integrity and despair (NEIS). Spouses are measured on level of depressive symptoms (HADS), personal growth (PTGI), and care giving burden (CRA). Spouses will not receive LRT themselves, but because it is expected that patients will talk about their memories during the intervention period with their spouses. It is hypothesized that LRT may have a positive effect on them as well. Outcome measures for spouses are symptoms of anxiety and depression (HADS), personal growth (PTGI), and caregivers' burden (CRA). Outcomes are evaluated before and after intervention and at 1 month after intervention.

Discussion: There is an urgent need for evidence-based psychosocial interventions targeting advanced cancer patients. The goal of LRT is to train patients to retrieve positive specific memories from the past enabling re-evaluation of life events and reconstruction of the story of life, including the diagnosis of incurable cancer. This study is investigating the effectiveness of LRT among advanced cancer patients and their spouses. If proven effective, the intervention will be implemented in regular psycho-oncological care.

Trial registration: Netherlands Trial Registration NTR2256

BACKGROUND

Being diagnosed with advanced cancer has a great impact on quality of life, especially when there is little hope for cure, and many advanced cancer patient experience psychological distress. In a recent study on patients with incurable cancer, prevalence was high regarding anxiety (34%) and depressed mood (56%) [1]. Earlier studies demonstrated that psychological interventions have a positive effect on depression and anxiety in (advanced) cancer patients [2,3]. Some studies suggest that psychological, spiritual, and existential issues may be of even greater concern to advanced cancer patients than pain and other physical symptoms [4,5]. Informal caregivers of cancer patients also are vulnerable to develop psychological distress. A recent review revealed that 20-30% of the carers develop a depressive, anxiety or adjustment disorder [6]. Their psychological problems often increases in frequency as the illness of the patient progresses, particularly when patients are suffering from an advanced or terminal disease [6]. Life review interventions have proven to be beneficial to address psychological distress [7-11]. Life review is defined as 'the progressive return to consciousness of prior experience, which can be re-evaluated with the intention of resolving and integrating past conflicts, thereby giving new significance to one's life' [9]. Furthermore, Butler support that life review leads to greater achievement of ego integrity and suggested that reviewing one's life and coming to terms with their memories would make older person more accepting and be less anxious about his or her eventual death [9]. Besides older persons, advanced cancer patients are also confronted with their eventual death. Therefore they might benefit from life review as well. Ando et al. [7,8] found significant effects of their short term life review intervention on improving mood, spiritual, psychosocial and physical well-being and overall quality of life of advanced cancer patients. Potential predictors of treatment success were positive view of life, pleasure in daily activities and good human relationships and a balanced evaluation of life [7,8]. However, a disadvantage of these studies was that they were not designed as randomized controlled trials. Ando et al. [11] also carried out a randomized controlled trial examining the efficacy of short-term life review interviews in terminally ill cancer patients [11]. They found positive effects on meaning of life, hope, life completion, preparation for death, anxiety and depression. A disadvantage of this study was that most patients in the study were in a palliative care ward or hospice home care clinic, and generalization of the findings to other settings cannot be assumed. A second disadvantage is that this study was carried out in Japan and therefore not applicable to western settings [11].

A recently developed intervention called ''Dear Memories'' targets both the life review process and the autobiographical memory. This Life Review Therapy (LRT) combined with Memory Specificity Training (MST) (LRT-MST) is a brief, structured psychological intervention focusing on positive memories from the past [10,12]. Autobiographical memory, one's individuals past, can best be defined as a type of episodic memory for both retrospective (memories) and prospective information (expectations) related to the self [13]. Overgeneral memory (the difficulty in retrieving or recollecting specific autobiographical memories), is identified as a risk factor for depression [14,15]. In previous studies with depressed older adults (not being cancer patients) LRT proved to be effective in decreasing depressive symptoms and feelings of hopelessness and improving life satisfaction [10].

In the present study we will investigate the efficacy of LRT-MST, named ''Dear Memories'', among advanced cancer patients and their spouses. It is hypothesized that this LRT will be effective in improving the specificity of the autobiographical memory, ego-integrity, and quality of life, and in reducing depressive symptoms among advanced cancer patients. Spouses will not receive LRT-MST themselves, but because we expect that cancer patients will talk about their memories with their spouses during the intervention period, we hypothesize that the intervention may also have a positive effect on the spouses regarding symptoms of anxiety and depression, posttraumatic growth, and caregiver burden.

METHODS/DESIGN

Design
This study is a prospective randomised controlled trial with two parallel groups, the intervention group (receiving LRT) or the control group (care-as-usual; CAU). In order to assess the effectiveness of LRT, assessment takes place before and after intervention and at 1 month follow up. Patients in the control group are offered to receive LRT after the follow up assessment.

Recruitment
A total of 150 advanced cancer patients who are treated at VU University Medical Center (Departments of Otolaryngology/Head and Neck Surgery and Pulmonary Diseases) or the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (Department of Otolaryngology - Head and Neck Surgery) will be recruited.

The patients who fulfil the in- and exclusion criteria will receive information brochures from their physician and after one week they will be phoned by a researcher. During this phone call patients will be further informed that the study is investigating the effects of memory recall on (depressive) mood and that the interviews are designed to evoke positive memories. If they agree to participate and after informed consent, a pre-test assessment session is scheduled at the patient's home (see outcome parameters for questionnaires administered). Patients will be randomly assigned to either the intervention condition receiving LRT or control group (care as usual - CAU).

Spouses of the patients will be asked to participate via the patient. At the pre-test assessment of the patient they will receive information. After written informed consent they are asked to complete questionnaires at the same assessment times as the patient.

Study sample
Inclusion criteria are: aged 18 and over, cancer without curative treatment options, prognosis of ≥ 3 months, and with depressive symptoms (HADS-D and/or HADS-A >7, HADS-total >14). Exclusion criteria are: psychotic behaviour, cognitive impairment, severe impairment in oral communication, insufficient mastery of the Dutch language to complete questionnaires and to answer the questions of the life review interviews, no informed consent. Exclusion criteria for the spouses are: insufficient mastery of the Dutch language to complete questionnaires, no informed consent.

Randomization
After completion of baseline questionnaires patients are randomly assigned to either the intervention condition or the care as usual condition. Randomization will be performed by an independent researcher using a computer-generated randomization procedure. The independent researcher is not in contact with the respondents and keeps the randomization list in secure custody. Block randomization of 20 is used, to make sure that the interviewers can process a gradually inflow of respondents. The psychologists involved in the life review intervention will be informed by researcher GK of the assignment a few days after the pre-test assessment. One week later they will start with the intervention. Due to the nature of the intervention neither patients, the interviewers nor the researcher can be blinded to the research condition. However, randomization and statistical analyses will be performed blindly.

Intervention

In this study, the Life Review Therapy called "Dear Memories" is an autobiographical memory retrieval practice, focussing on bringing up positive specific events [10,12]. LRT consists of four weekly sessions with every session focusing on a particular period in life: childhood, adolescence, adulthood and whole life span, respectively. For each period, 14 questions are prepared that are designed to prompt specific positive memories. For example: "Do you remember, as a child, receiving a present which was very special to you?" or "Do you remember, as an adult, reaching a particular goal that made you very proud?" The interviewer tries to get a specific view of the situation by asking for more information. Participants are explicitly encouraged, by means of feedback on how well they are doing, to retrieve positive specific memories to the positively stated questions.

Here is an example from our protocol of a positive specific and an ''overgeneral'' answer to the same question. Interviewer: ''During your childhood, did you have a favourite toy?'' Reaction from a patient: (positive specific answer): ''Oh yes! I had a beautiful brown teddy bear. I got it for my birthday from my mom and dad. It was dark brown, real soft, had great dark eyes and I took it everywhere I could''. An example of an ''overgeneral'', non-specific or categorical answer on the same question by another patient: ''No, I can't remember having a favourite toy. I did not play, I did not have that much to play with either''. After this reaction interviewer tries to get patient more specific, by means of asking some questions. Interviewer: ''Please try to think as best as you can, try to go back to the age of let's say 5 years old. Can you remember what kind of games you did? ''. If the patient than answers again he/she can't recollect a memory, the next topic is addressed. It is possible that patients respond by expressing an ''overgeneral'' memory: ''I can remember I played soccer with the children in the neighbourhood. Is this an answer to your question?''.

The interviews will take approximately one hour each and will be led by an experienced psychologist who is trained in the LRT-protocol "Dear Memories". The interviewer is not allowed to be very directive and should not pose more than one or two questions to get a more specific memory. They receive a structured standardized training in using the protocol. The interviews will take place at the respondent's residence or in the hospital. The interviews will be recorded on mp3 and copies are offered as a remembrance for the respondents and/or their family members.

Care as usual

During visits to the hospital, physicians and nurses provide emotional support and give advice how to cope with deterioration of quality of life on an ad hoc basis. If urgent problems emerge, the patient is referred to other services, like a social worker, a psychologist or their general practitioner. After the follow-up assessment, the patients in the control group are offered LRT as well.

Outcome assessment

Primary outcome is the level of depressive symptoms (HADS). Secondary outcome measures in patients are the presence or absence of clinical depression (MINI), specificity of Autobiographical Memory (AMT), quality of life (EORTC QLQ-PAL15), and ego-integrity and despair (NEIS). Spouses are measured on level of depressive symptoms (HADS), personal growth (PTGI), and care giving burden (CRA).

Depressive symptoms

Psychological distress is measured by the Hospital Anxiety and Depression Scale [24]. The HADS consist of 14 items with 2 subscales: depression (HADS-D) and Anxiety (HADS-A). The two subscales are combined in one overall score on psychological distress (HADS-T). Scores on each item range from 0-3, with a total score ranging from 0-42. In psycho-oncology the total HADS-score is proven to be an accurate instrument to identify cancer patients with psychological distress and increased risk for depression or anxiety and other psychological sequelae [25,26].

The validated Mini-International Neuropsychiatric Interview (MINI) [27] will be used to assess the presence of Major Depressive Disorder (MDD) current and lifetime, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [28].

Autobiographical memory specificity

By using the Autobiographical Memory Test (AMT) [16], the ability to retrieve a specific memory is measured in response to cue words. The AMT consists of 10 cue words, like "restaurant", "drawing" or "success", presented orally, one at the time. Respondents are asked to retrieve a specific autobiographical memory in response to the cue word. Specific events are defined as events that occurred at a particular place and time and lasted less than a day. Answers are coded as specific, repeated (occurring more than 1 day) or extended (lasting longer than 1 day). Previous research showed that the presence of psychopathology, especially depression or a depressed mood is associated with poor

memory specificity and the tendency to recall only overgeneral memories [13]. Codes given to the memories were rated by the interviewers and controlled by the coordinating researcher. Because the total number of stimulus words is 10 and each memory is rated as general or specific, the maximum score for either category is 10. When for example the patient gives to 4 cue words a categorical or 'overgeneral' response and to 6 a specific memory is recalled, than patients total score on specific memories recalled is 6.

Quality of life
The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire EORTC QLQ-PAL15 will be used, a shortened version of the EORTC QLQ-C30. The EORTC QLQ-PAL15 was developed as a 15-item 'core questionnaire' in the assessment of quality of life of cancer patients in palliative care [17-21].

Ego-integrity and despair
The North-Western Ego Integrity Scale (NEIS) [22] is a 15-item questionnaire reflecting Erikson's conception of the eighth and final developmental crisis in the human lifespan, that is the conflict between ego-integrity and despair [23]. Respondents are asked to indicate their agreement concerning their general attitude to statements such as: "I have reached a point where I can accept the events in my life as having been necessary", "I have done exactly what I wanted to with my life", and "I wish I had more time to take a different path in life".

Use of care
The Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) [29] will be used to assess the use of care. The TiC-P is developed to generate quantitative data about the medical costs within the healthcare system and the economic consequences of production losses outside the healthcare system due to psychiatric disorders. It is designed in such a way that it is suitable for broad application, i.e. various psychiatric disorders. The questionnaire is modular in structure, enabling items to be left out that do not apply to a specific population. For this study the TIC-P was adjusted to the target group of advanced cancer patients in order to assess use of palliative care.

Caregivers' burden
The Caregivers Reaction Assessment Scale is an instrument designed to assess subjective caregiver burden [30]. The CRA consist of 24 items, which can be divided in five dimensions, including both positive ('care-derived self-esteem') and the negative

burdens of care giving ('lack of family support', 'financial problems', disrupted schedule' and 'loss of physical strength') [31,32].

Posttraumatic growth
The posttraumatic growth inventory (PTGI) [33] is a questionnaire based on the five identified domains of posttraumatic growth: relating to others, new perspectives, personal strength, spiritual change and appreciation of life. It consists of 21 items answered on a 6-point scale ($0 = I$ did not experience this change through $5 = I$ experienced this change to a very great degree). Although examinations of construct validity for the PTGI have yielded conflicting results, many people report positive changes in the aftermath of highly stressful and traumatic life events [34]. Less research is done on posttraumatic growth in spouses of cancer patients. Zwahlen et al. [35] examined the effects of gender and role on benefit finding in couples using the PTGI, finding a correlation between total scores of patients and their spouses.

Sample size calculation
The HADS is the primary outcome measure. Based on a medium standardized effect size (Cohen's d) of 0.60, alpha of 0.05 and a statistical power (1-beta) of 0.90, we need 60 participants in each study arm. With a drop-out rate of 25% we will need 150 patients at baseline.

Statistical analysis
Data will be analysed using the SPSS statistical software package. Descriptive statistics will be generated for the range of outcome variables, in particular to gauge whether randomization resulted in a balanced distribution of patient characteristics across the experimental conditions. The primary outcomes will be evaluated on an intention-to-treat basis.

The primary clinical outcome, treatment response in DSM-IV depression/anxiety, will be evaluated with intention-to-treat logistic regression analysis to produce the odds ratio (OR).

Repeated measures ANOVA will be used to determine the efficacy of intervention for continuous outcomes such as changes in HADS depression/anxiety symptom severity. Longitudinal changes over time in these variables will also be evaluation over all time points simultaneously using generalized estimating equations (GEEs). We will use

multivariate variance analysis for repeated measurements to test whether the outcome measures increase/chance significantly more in the experimental group than in the control group. All the analyses are to be conducted on the intention-to-treat principle. If missing values emerge at t1 and t2 on the outcome measures as a result of drop-out, they will be imputed according to the last-observation-carried-forward principle or in a more advanced fashion (regression imputation or multiple imputation, both as implemented in Stata) using available baseline data from the responders as well as the non-responders. This means that not every non responder received the same post-test score, but post-test score will be dependent on the particular characteristics as defined by baseline (e.g. gender, age).

Ethical considerations

The study protocol has been approved by the medical ethical committee of the VU University Medical Center, Amsterdam, the Netherlands.

DISCUSSION

This study investigates the efficacy of Life Review Therapy (LRT) in advanced cancer patients. Also, the effect on their spouses will be investigated.

Studies suggest that physicians and advanced cancer patients are ambivalent about talking about death and often avoid the conversations [36,37]. LRT might help advanced cancer patients in mentally understanding their prognosis and their end of life. By acknowledging that death is near, patients, caregivers, and physicians can focus on clarifying patients' priorities and relieving pain and improving symptom management [37]. Butler [9] was the first to introduce life review as a therapy. He considered life review as the expression of a universal mental process reflecting the need to come to terms with one's life when the end is approaching. Advanced cancer patients might experience the same feelings and need to review their past when the end of their life is approaching suddenly or unexpected. A meta-analyse have proven the effectiveness of life review therapy on both depression and psychological well-being in later life [38].

The protocol ''Dear Memories'' that will be investigated in the present study includes a training in retrieving specific positive autobiographical memories. These memories seem to enhance feelings of mastery, of being in control of one's own life. Feelings which are severely affected by suffering from incurable cancer. Receiving LRT can fulfil various

functions for the individual; it implies constructing his or her life story and an evaluation of one's past in order to accept negative events and re-evaluate important life events, resolve past conflicts, re-think and modify the original purposes or goals into attainable ones and increase the feeling of positive mood, and may thereby improve quality of life. This may contribute to reconstruct his or her life being congruent with the diagnosis of cancer and may result in a greater achievement of ego-integrity and be more accepting and less anxious about his or her eventual death.

The LRT protocol in this study is based on research about autobiographical memory, part of the memory where personal memories are stored. Studies on autobiographical memory retrieval show that if depressed people are presented with a cue word, they retrieve less specific and more general memories than a control group or than nondepressed persons [39-41]. This so called overgeneral memory is one of the most reliable features of memory in depression [40]. Although overgeneral memory was originally described as a stable characteristic it may in fact be open to change [42]. Serrano et al. [12] using ''Dear Memories'' in a Spanish population of older adults found a significant increase in number of specific memories reported by the patients at post-test. Previous studies investigating the effectiveness of this intervention in depressed older adults, showed a decrease in depressive symptoms, feelings of hopelessness and improvement of mastery and life satisfaction [12,14].

In this study, we face an important challenge. The target population is a very fragile one and in performing this study we face the risk of a high drop-out rate due to fast physical deterioration or death. A major challenge in this study will therefore be to include patients in an early stage of the palliative phase of cancer. In case the LRT appears to be beneficial for advanced cancer patients, this intervention will be introduced in regular psychosocial palliative care.

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CHAPTER 3

Psychometric characteristics of a patient reported outcome measure on ego-integrity and despair among cancer patients

" *Herinnert u zich een speciaal moment dat u bijvoorbeeld uw eerste kus kreeg of dat u verliefd was op iemand?* "

ABSTRACT

Purpose: To evaluate psychometric characteristics of a questionnaire (the Northwestern Ego-integrity Scale (NEIS)) on ego-integrity (the experience of wholeness and meaning in life, even in spite of negative experiences) and despair (the experience of regret about the life one has led, and feelings of sadness, failure and hopelessness) among cancer patients.

Methods: Cancer patients (n=164) completed patient reported outcome measures on ego-integrity and despair (NEIS), psychological distress, anxiety and depression (Hospital Anxiety and Depression Scale (HADS)), and quality of life (EORTC QLQ-C30 (cancer survivors, n=57) or EORTC QLQ-C15-PAL (advanced cancer patients, n=107)). Confirmatory Factor Analysis was used to assess construct validity. Cronbach's alpha was used to assess internal consistency. Convergent validity was tested based on a priori defined hypotheses: a higher level of ego-integrity was expected to be related to a higher level of quality of life, and lower levels of distress, depression and anxiety; a higher level of despair was expected to be related to a lower level of quality of life, and higher levels of distress, depression and anxiety.

Results: The majority of all items (94.5%) of the NEIS were completed by patients and single item missing rate was below 2%. The two subscales, labelled as Ego-integrity (5 items) and Despair (4 items) had acceptable internal consistency (Cronbach's alpha .72 and .61, respectively). The Ego-integrity subscale was not significantly associated with quality of life, distress, anxiety, or depression. The Despair subscale correlated significantly ($p<.001$) with quality of life ($r=-.29$), distress ($r=.44$), anxiety ($r=.47$) and depression ($r=.32$).

Conclusion: The NEIS has good psychometric characteristics to assess ego-integrity and despair among cancer patients.

INTRODUCTION

According to Erikson's theory, ego-integrity and despair are key topics in the eighth developmental stage, when people enter the final stage of life and reflect on the meaning of life and how they lived it. A person experiences ego-integrity, if he or she accepts his or her life cycle as something that had to be, feels connected to others, and experiences a sense of wholeness, meaning and coherence as he or she faces (the approach of) death. Achieving ego-integrity is supposed to be associated with achieving wisdom [1–4] and less death anxiety [5]. In contrast, a person experiences despair, if he or she experiences regret about the life he or she has led, and has feelings of sadness, failure and hopelessness. It is suggested that despair is related to psychological distress, depressive symptoms, loneliness and isolation [3].

Not only older people in the final stage of life are confronted with death, ego-integrity and despair, but people with a life-threatening disease as cancer as well [3]. Much is known about the impact of cancer and its effect on quality of life [6–8]. We also know that prevalence of distress and depression among cancer patients is high [9]. However, information on ego-integrity and despair is scarce and a valid questionnaire to assess ego-integrity and despair among cancer patients is lacking. Such a questionnaire is important, because it is hypothesized that patients who do not achieve ego-integrity and have a high level of despair can experience more psychological problems and death anxiety, have fewer personal and interpersonal resources for facing cancer, and are more vulnerable to developing depressive symptoms [3,5].

The Northwestern Ego-integrity Scale (NEIS) - a questionnaire targeting ego-integrity and despair -was developed earlier based on research in the general population [10]. Recently, Westerhof et al. [11] investigated the NEIS among the general population aged 50-95 and reported that the NEIS has a two factor structure comprising Ego-integrity and Despair.

The aim of the present study was to investigate the psychometric characteristics of the NEIS among cancer patients. The research questions were: 1) Is the NEIS feasible among cancer patients?, 2) Is the same factor structure found compared to the general population [11]?, 3) Is the scale reliable in a cancer population, and 4) Has the scale validity in a cancer population?. Convergent validity of the questionnaire NEIS was tested based on a priori defined hypotheses: a higher level of ego-integrity was expected to

be related to a higher level of quality of life, and lower levels of psychological distress, depression and anxiety; a higher level of despair was expected to be related to a lower level of quality of life, and higher levels of psychological distress, depression and anxiety [3]. The results of this study are expected to contribute to the development of a patient reported outcome measure to evaluate ego-integrity and despair among cancer patients.

METHODS

Subjects and procedure

From 2009 to 2014, cancer patients were recruited for two intervention studies, on the effectiveness of life review therapy targeting advanced cancer patients (n=107), and on the effectiveness of autobiographic writing targeting cancer survivors (n=57). The studies were approved by the Medical Ethical Committee of the VU University Medical Center Amsterdam. In the present study, we used baseline data (before start of the intervention) of the patient reported outcomes measures: the Northwestern Ego-integrity Scale (NEIS), the Hospital Anxiety and Depression Scale (HADS) and the quality of life questionnaires EORTC QLQ-C30 (EORTC QLQ-C30 (cancer survivors) or EORTC QLQ-C15-PAL (advanced cancer patients)). In both studies patients under 18 years of age or with psychotic behaviour, severe cognitive dysfunction or insufficient mastery of the Dutch language were excluded.

Study measures

Patients completed a study specific questionnaire on sociodemographic characteristics (age, gender, marital status (married, widowed, divorced), children (number), and educational level (none, primary education, secondary general or vocational education, higher general or vocational education or academic education)), and clinical characteristics (treatment intent (curative or advanced cancer) and type of cancer (according to the ICD-10)).

The Northwestern Ego-integrity Scale (NEIS) [10,12] is a 15-item questionnaire to assess despair and ego-integrity, with higher mean scores indicating more despair and ego-integrity [13]. The NEIS reflects Erikson's conception of the eighth and final developmental phase in a person's life, regarding ego-integrity and despair [1]. Respondents are asked to indicate their agreement to statements such as, 'I have reached a point where I can accept the events in my life as having been necessary' or 'I wish I had more time to take a different path in life' on a scale from 1 (strongly disagree) to 6 (strongly agree). A recent

study among the general population aged 50-95, showed that the NEIS has 2 subscales, Ego-integrity (5 items) and Despair (4 items) [11].

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire [14]. The HADS consists of two subscales, depression (HADS-D; 7 items) and anxiety (HADS-A; 7 items). The two subscales are combined in one overall score on psychological distress (HADS-T; 14 items). Scores on each item range from 0-3, with a score on the subscales ranging from 0-21 and a total score ranging from 0-42.

The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC QLQ-C30) is a 30-item questionnaire assessing quality of life among cancer patients [15]. It consists of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global quality of life scale. The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire PAL15 (EORTC QLQ-C15-PAL) is a shortened version of the EORTC QLQ-C30. It is developed as a 15-item questionnaire assessing quality of life of cancer patients in palliative care [16]. In the present study, the single item for global quality of life (identical in the QLQ-C30 and QLQ-C15-PAL) was used (How would you rate your overall quality of life during the past week?), which is scored on a 7-point scale ranging from 1, 'very poor', to 7, 'excellent'. According to the EORTC guidelines, this scale was transformed to a 100-points scale with a higher score indicating a better quality of life.

Statistical analyses

Descriptive statistics were used to investigate the number of missing items. Confirmatory Factor Analysis was used to analyse whether the factor structure found in Westerhof et al. [11] could be replicated. Criteria for an acceptable fit were: 1) Root Mean Square Error of Approximation (RMSEA) <.06 and Comparative Fit Index (CFI) and Tucker-Lewis Index-Non-Normed Fit Index ≥.9. Measurement invariance of the factor structure was investigated between advanced cancer patients and patients treated with curative intent. Internal consistency of the subscales was assessed by calculating Cronbach's alpha coefficient. Sum scores of the NEIS subscales were computed by summing all standardized item scores and rescaling the total score to a percentage score. Spearman's rank correlation coefficients were computed to examine the relationship between the NEIS subscales and quality of life, psychological distress, anxiety and depression. The statistical comparisons were two-sided and a p-value <.05 was considered statistically

significant. SPSS (version 20, IBM Crop., Armonk, NY USA), Mplus version 6.11 [17] and R version 3.1.1. (www.r-project.org) with the package lavaan [18] were used for the analyses.

RESULTS

Subjects
A total of 164 cancer patients (57 patients treated with curative intent and 107 advanced cancer patients) participated. Mean age of the patients was 60.6 years (range 29 - 86; SD = 9.6), and 38.4% were male. Patients' characteristics are shown in Table 1.

Missing items
Overall, the majority of all items (94.5%) of the NEIS were completed by patients. Regarding the single items, missing item responses ranged from .6% to 1.2%.

Confirmatory Factor Analysis
Westerhof et al. [11] suggested a 9-item factor structure with two subscales for the NEIS (Table 2). Assuming uncorrelated factors the fit was nearly acceptable ($\chi^2(27) = 62.0$, p=.0001; RMSEA = .089; CFI = .919; TLI = .892) and improved little when assuming correlated factors ($\chi^2 (26) = 56.4$, p=.0005; RMSEA = .084; CFI = .930; TLI = .902). Only configural invariance ($\chi^2(52) = 74.1$, p=.023; RMSEA = .073; CFI = .905) and no metric invariance ($\Delta\chi^2(7) = 27.1$, p=.0003; ΔCFI = .086) could be proven between advanced cancer patients and patients treated with curative intent.

Internal consistency
Cronbach's alpha coefficient .72 for the Ego-integrity subscale and .61 for the Despair subscale.

Subscale scores
To compute the scores of both subscales, all individual item scores were first transformed to Z-scores. Z-scores of items 6, 7, 10, 13 and 15 were summed for the subscale 'Ego-integrity', Z-scores of items 2, 5, 8, and 14 were summed for the subscale 'Despair'. The obtained subscale 'Ego-integrity' ranged from -10.2 to 7.3 and the 'Despair' subscale ranged from 5.6 to 6.6. Final scores were obtained by rescaling the summed Z-scores as follows: Total score = ((sum Z-score – minimum sum Z-score) divided by (maximum sum Z-score – minimum sum Z-score)) times 100. The mean total score for the subscale 'Ego-integrity' was 58.1 (SD=19.6) and for the subscale 'Despair' 45.1 (SD=21.7).

Table 1. *Demographic characteristics of participants*

Scale	Total group (n=164) Distribution	%	Advanced cancer patients (n=107) Distribution	%	Cancer survivors (n=57) Distribution	%
Gender						
Male	63	38.4	57	55.3	6	10.5
Female	101	61.6	50	46.7	51	89.5
Age						
Mean (SD)	60.6 (9.7)		62.75 (9.3)		56.68 (9.2)	
Range	29-86		31-86		29-73	
Marital status						
Married	99	60.4	75	70.1	24	42.1
Divorced	29	17.7	13	12.2	16	28.1
Widowed	12	7.3	7	6.5	5	8.8
Never married	24	14.6	12	11.2	12	21.0
Children						
Yes	134	81.7	91	85.0	43	75.4
No	30	18.3	16	15.0	14	24.6
Level of education						
Academic education	27	16.5	15	14.0	12	21.1
Higher general or vocational education	54	32.9	27	25.2	27	47.4
Secondary general or vocational education	52	31.7	35	32.7	17	29.8
Primary education	28	17.1	28	26.2	0	0
None	2	1.2	2	1.9	0	0
Unknown	1	0.6	0	0	1	1.8
Religion						
Yes	76	46.3	35	32.7	41	71.9
No	87	53	72	67.3	15	26.3
Unknown	1	0.6	0	0	1	1.8
Tumor type						
Lung cancer	66	40.2	66	61.1	0	0
Head and neck cancer	2	1.2	2	1.9	0	0
Hematological cancer	33	20.1	23	21.5	10	17.5
Breast cancer	32	19.5	5	4.7	27	47.4
Other	21	12.8	11	10.3	10	17.5
Unknown	10	6.1	0	0	10	17.5

3

Table 2. *Confirmatory Factor Analysis of the Northwestern Ego-integrity Scale, correlated factors were assumed*

	Item	EIS	DS	*M*	*SD*
6.	I have reached a point where I can accept the events in my life as having been necessary.	.75		3.4	1.7
7.	As I grow older, I understand people more.	.30		4.7	1.2
10.	I see a meaningful thread running through the many events in my life.	.66		3.5	1.5
13.	Even my sufferings have had meaning.	.69		3.7	1.6
15.	As I get older, my life story makes more sense to me.	.61		4.0	1.3
2.	It pains me to think about dreams and goals I have had that I did not fulfill.		.47	3.6	1.7
5.	I wish I had loved more in my life.		.72	3.3	1.7
8.	I am bothered by mistakes I have made in the past.		.47	3.0	1.5
14.	I wish I had more time to take a different path in life.		.64	3.3	1.7

EIS=Ego-integrity subscale, DS=Despair subscale, *M*=Mean, *SD*=standard deviation.

Convergent validity

The Ego-integrity subscale did not correlate significantly with quality of life, psychological distress, anxiety or depression. The Despair subscale correlated significantly (p<.001) and negatively with global quality of life (r=-.29), and positively with psychological distress (HADS-T score; r=.44), anxiety (HADS-A; r=.47) and depression (HADS-D; r=.32) (see Table 3).

Table 3. *Convergent validity*

	Ego-integrity subscale		Despair subscale	
	Spearman	P-value	Spearman	P-value
QoL	.11	.18	-.29	<.001
HADS T	-.084	.29	.44	<.001
HADS A	-.005	.95	.47	<.001
HADS D	-.14	.072	.32	<.001

DISCUSSION

In the present study, we investigated psychometric characteristics of the NEIS, a patient reported outcome measure on ego-integrity and despair among cancer patients. The feasibility was good: the majority of all patients (94.5%) completed all items, missing item rate was below 2%. The factor structure of the NEIS consisting of two subscales 'Ego-integrity' (5 items) and 'Despair' (4 items) was confirmed in the present study among patients treated with curative intent as well as advanced cancer patients. We found acceptable internal consistency for Ego-integrity (α = .72), which is in accordance with earlier research in the general population [11–13,19], and somewhat lower internal consistency for Despair (α = .61).

In the present study, the scores on the Despair subscale correlated significantly and negatively with global quality of life, and positively with psychological distress, anxiety and depression, which confirms our hypothesis and earlier research [3]. However, in contrast to our hypotheses, the scores on the Ego-integrity subscale did not correlate significantly with quality of life, psychological distress, anxiety or depression. Janis [10] stated that 'ego-integrity is a complex psychological state that involves a belief that life has been meaningful, a sense of contentment or satisfaction, and a feeling that one's desires have been adequately met'. It may be that the construct of ego-integrity is more related to existential issues and not to quality of life (which also entails physical aspects of life, especially among cancer patients) or psychological distress or psychiatric disorders like depression and anxiety. The findings of Westerhof et al. [11] seem to support this. Their results showed that ego-integrity was related to well-being. They also found that more depressive symptoms are significantly related to more despair, but not to ego-integrity. Future research is needed to explore these associations, for example via qualitative research methods.

There are some limitations to our study. Our sample comprised patients participating in randomized controlled trials and our sample size was relatively small which may have affected correlations among items. Future research to test the hypotheses in a more representative sample would therefore be interesting. Also, in the present study both cancer survivors and patients with advanced cancer participated. Although the factor structure was comparable with two scales (Ego-integrity and Despair), the factor loadings on these scales differed between the two groups. It may well be that these groups differ in

how they experience ego-integrity and despair. Further research is necessary to examine this.

In this study we investigated the feasibility, internal consistency, and validity. Furthermore, we used summed Z-scores instead of standardized scoring coefficients, because in general summed Z-scores are more accessible in clinical practice. However, further research is needed to determine cut-off scores, cross-cultural validity, and responsiveness of the NEIS. Cut-off scores, and responsiveness are also important in clinical practice. Furthermore, investigating cross-cultural validity is necessary so that the NEIS can be used in other cultural groups outside of the Netherlands. In future research the NEIS can be used to investigate ego-integrity and despair among cancer patients. More insight is needed in the prevalence of ego-integrity and despair, and the course from diagnosis and treatment to long-term survivorship or end-of-life. Also, knowledge on factors that may influence ego-integrity and despair among cancer patients can be enriched, such as sociodemographic (age, gender, socio-economic status), clinical (cancer type and stage, treatment modality, treatment intent), and psychological factors (such as perceived threat of cancer, optimism, anxiety and depression).

In clinical practice, addressing ego-integrity and despair among cancer patients does not seem to be standard practice yet, but could be an important aspect of psychological functioning. Therefore, more attention to ego-integrity and despair is important to be able to support the patients better. It is also important to develop and investigate more interventions that aim to improve ego-integrity and prevent despair. The NEIS can be used as a tool to investigate the effectiveness of these interventions targeting cancer patients.

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CHAPTER 4

The efficacy of Life Review Therapy combined with Memory Specificity Training (LRT-MST) targeting cancer patients in palliative care: A randomized controlled trial

" *Is er een moment geweest dat u moest opkomen voor uzelf of een dierbare en dat ook lukte?* "

ABSTRACT

Background: The aim of this study was to evaluate the efficacy of an intervention combining Life Review Therapy (LRT) and Memory Specificity Training (MST) (LRT-MST) to improve ego-integrity and despair among cancer patients in palliative care.

Methods: In this multicentre randomized controlled trial, cancer patients in palliative care were randomized to the intervention group (LRT-MST; n=55) or waiting-list control group (n=52). LRT-MST is a 4-session home-based psychological intervention that aims to retrieve specific positive memories, to re-evaluate life events and to reconstruct the story of a patient's life, including the diagnosis of incurable cancer. Outcome measures were ego-integrity and despair (NEIS), psychological distress, anxiety and depression (HADS), quality of life (EORTC QLQ-C15-PAL), and specificity of the autobiographical memory (AMT). NEIS, HADS and EORTC QLQ-C15-PAL were assessed at baseline (T0), 1 month later (post-treatment; T1), and at 1 month follow-up (T2). AMT was assessed at T0 and T1. Linear mixed models (intention to treat) were used to assess group differences in changes over time. Independent samples t-tests were used to assess group differences at T0, T1, and T2, and effect sizes (ES) were calculated at T1 and T2.

Results: The course of ego-integrity (not despair) improved significantly over time (p=.007) in the intervention group compared to the waiting-list control group, with moderate, but insignificant, effect sizes at T1 (ES=.42) and T2 (ES=.48). Compliance rate was 69% and total dropout rate was 28%, both primarily related to disease progression and death.

Conclusions: LRT-MST seems effective among cancer patients in palliative care to improve the course of ego-integrity.

INTRODUCTION

Being diagnosed with advanced cancer has a great impact on quality of life and studies suggest that psychological, spiritual, and existential issues may be of greater concern to advanced cancer patients than pain and other physical symptoms [1,2]. In 2009, Holland et al. [3] reviewed interventions that may help cancer patients, such as meaning-centered therapy and dignity therapy. Since then, several randomized controlled trials showed evidence of the effectiveness of meaning-centered therapy [4,5] and dignity therapy [6–9] targeting advanced cancer patients. Holland et al. [3] also presented a theoretical framework for the development of new interventions targeting elderly cancer patients utilizing psychological and educational approaches in conjunction with recall of memories from the past (life review).

Life review is defined as 'the progressive return to consciousness of prior experience, which can be re-evaluated with the intention of resolving and integrating past conflicts, thereby providing new significance to one's life' [10]. Reviewing one's life and coming to terms with their memories may make older persons more accepting and be less anxious about their approaching death [10]. Given that life review is "helping individuals integrate memories into a meaningful whole, and providing a harmonious view of past, present and future" [11], it may lead to greater achievement of ego-integrity. Ego-integrity is described as accepting your life cycle as something that had to be, feeling connected to others, and experiencing a sense of wholeness, meaning and coherence as a person facing (the approach of) death. It is also supposed to be associated with achieving wisdom [3,12–15] and less death anxiety [16]. Achieving ego-integrity is part of Erikson's eight and final life stage [14]. The absence of achieving ego-integrity is called despair. Despair is described as experiencing regret about one's life, and associated feelings of sadness, failure and hopelessness. It is also suggested to be related to psychological distress, depressive symptoms, loneliness and isolation [3].

A life review intervention aims to integrate positive and negative life events in a coherent life story. It is a structured variant of reminiscence (recalling memories from the past) and typically addresses distinct lifetime periods such as childhood, adolescence, adulthood, and a life summary including the present time. Life review therapy (LRT) refers to the use of life review in patients with mental health problems [17]. Although life review was developed for elderly [10], not only elderly in the final stage of life are confronted with death, reminiscence, ego-integrity and despair, but people with cancer as well [3].

Pickrel [18] described that a life review process for terminally ill (of any age) can help a person to complete the last chapter of his or her life, to maintain some control, to make things right or finish up unfinished business and to enhance a good feeling at the end. This may result in that one is better able to deal with the loss of life. Among cancer patients, observational studies indicate that LRT decreases depressive feelings and improves spiritual and psychosocial well-being [19,20]. Two randomized controlled trials showed that LRT is indeed effective among terminally ill cancer patients in Japan [21] and China [22]. Although both studies investigated LRT among terminally ill cancer patients, they had different outcome measures, a different number of sessions of LRT and different residences. Both studies showed significant effects on domains related to ego-integrity and despair (life completion [21]; existential distress and value of life [22]), but this was only based on a subscale or domain of a questionnaire. An important aspect in LRT is the autobiographic memory, consisting of memories from an individual's life and knowledge about the world [23,24]. Previous research showed that depression and depressed mood are associated with difficulty in recollecting specific and positive autobiographical memories, which is called reduced memory specificity [24–26]. Reduced memory specificity also predicts increased emotional (depressive) reactivity to stressful events in a non-clinical population and the course of recovery of depressed patients. Memory specificity training has been shown to improve the recall of specific memories in depressed patients [27,28].

Based on these previous studies in palliative cancer patients, of which some experiencing a great sense of end-of-life despair [29] and who are at risk for developing depression [30], we investigated an intervention that combines LRT with memory specificity training (MST) (LRT-MST). This intervention is named 'Dear Memories' and focusses on retrieving specific, and positive memories of different lifetime periods and aims to improve autobiographical memory specificity via the structured way of life review therapy.

The aim of the present study was to assess the efficacy of LRT-MST to improve ego-integrity and reduce despair among cancer patients in the palliative phase. Secondary aim was to explore the effect of LRT-MST on psychological distress, anxiety and depression, quality of life, and on the specificity of the autobiographical memory.

MATERIALS AND METHODS

Study design and population

This study was a multicentre randomized controlled trial with two parallel groups; an intervention group (receiving LRT-MST) and a waiting-list control group (receiving care-as-usual; CAU). The trial was approved by the Medical Ethics Committee of VU University Medical Center and registered in the Netherlands Trial Register (NTR 2256).

Eligible participants were adult (>18 years old) cancer patients, with all types of cancer and all cancer treatment modalities, receiving palliative care and an expected prognosis of more than 3 months. At the start of this study significant depressive symptoms (HADS (HADS A/D > 7/ HADS-T >14) was an inclusion criteria, but shortly after trial commencement this was not part of the inclusion criteria (and primary outcome) anymore. Exclusion criteria were psychotic behaviour, severe cognitive dysfunction, severe impairment in verbal communication or insufficient mastery of the Dutch language.

Patients who were treated at VU University Medical Center (Departments of Head and Neck Surgery, Pulmonary Diseases, Hematology, Radiotherapy, and Medical Oncology) or the Netherlands Cancer Institute/ Antoni van Leeuwenhoek (Department of Head and Neck Surgery) (after trial commencement the number of departments participating expanded), fulfilled the in- and exclusion criteria, and provided written informed consent, were scheduled for a pre-test assessment session at the patient's residence, after which they were randomly assigned to either the LRT-MST or CAU group. Clinical characteristics were retrieved from the medical files. The Mini-International Neuropsychiatric Interview (MINI) [31] was used to assess the presence of Major Depressive Disorder (MDD) current and lifetime, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV [32]. The full trial protocol can be requested via the corresponding author.

Intervention

LRT-MST called 'Dear Memories' [33] aims to improve the life review process and to train the autobiographical memory, with a focus to retrieve positive specific events from the past. This protocol is based on the a life review protocol designed by Serrano et al. [25] for older adults with depressive symptomatology. LRT-MST consists of four weekly sessions on a particular lifetime period: childhood, adolescence, adulthood, and whole life span. For each period, 14 questions are designed to prompt specific positive memories. Participants are explicitly encouraged to retrieve positive specific memories to the

positively stated questions. Each interview, conducted in Dutch, took approximately one hour and was led by a psychologist who was trained in the LRT-MST-protocol "Dear Memories". The intervention took place at the respondent's residence or at the hospital. The interviews were recorded on mp3 and copies were offered as a remembrance for the patients and/or their informal caregivers.

Care as usual

During visits to the hospital, physicians and nurses provided emotional support and advice how to cope with deterioration of quality of life on an ad hoc basis. If urgent problems emerged, the patient was referred to other services, like a social worker, a psychologist or their general practitioner. In the present study, after the follow-up assessment, the patients in the waiting-list control group were offered LRT-MST as well.

Outcome measures

Outcome measurements were collected at baseline (T0), after the intervention or after four weeks (post-treatment; T1), and after one-month post-treatment (Follow-up; T2).

The primary outcome measures were ego-integrity and despair (NEIS). Secondary outcome measures were psychological distress (HADS), quality of life (EORTC QLQ-PAL15), and the specificity of Autobiographical Memory (AMT).

The Dutch version of the Northwestern Ego-integrity Scale (NEIS) [34–37] was used. This is an 15-item questionnaire reflecting Erikson's conception of the eight developmental phase in a person's life [13]. It assesses despair (4 items) and ego-integrity (5 items), with higher mean subscale scores indicating more despair and ego-integrity. Participants are asked to indicate their agreement to statements such as, 'I have reached a point where I can accept the events in my life as having been necessary' or 'I wish I had more time to take a different path in life' on a scale from 1 (strongly disagree) to 6 (strongly agree). Cronbach's alpha was .71 for Ego-integrity and .57 for Despair in the current study.

The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire PAL 15 (EORTC QLQ-C15-PAL) is a shortened version of the EORTC QLQ-C30 targeting cancer patients in palliative care and available in Dutch [38]. In this study we used the single item global quality of life scale (HRQOL) (How would you rate your overall quality of life during the past week?), which is scored on a 7-point scale ranging

from 1, 'very poor', to 7, 'excellent'. According to the EORTC guidelines, this scale was transformed to a 100-points scale with a higher score indicating a better quality of life.

A validated Dutch version of the Hospital Anxiety and Depression Scale (HADS) was used to assess psychological distress and consists of 14 items with 2 subscales: depression (HADS-D) and anxiety (HADS-A), and a total score (HADS-T). Scores on each item range from 0-3, with a total score ranging from 0-42 [39]. Cronbach's alpha was high for both subscales and the total score, .79 (HADS-D), .83 (HADS-A) and .87 (HADS-T), in this study.

The Autobiographical Memory Test (AMT) [40] was used to test the ability to retrieve a specific memory, measured in response to cue words. The AMT consists of 10 Dutch cue words, like "restaurant", "drawing" or "success", presented orally, one at the time. Participants are asked to retrieve a specific autobiographical memory in response to the cue word. Specific events are defined as events that occurred at a particular place and time and lasted less than one day. Answers are coded as specific, repeated (occurring more than 1 day) or extended (lasting longer than 1 day). Codes given to the memories were rated by the interviewers and checked by the coordinating researcher. Because the total number of stimulus words is 10 and each memory is rated as specific (2 points), general (1 point) or no memory (0 points), the maximum score is 20. Cronbach's alpha, in this study, was .72.

Sample size calculation

Based on a two-sided effect size (Cohen's d) of .60 at one month post treatment (T2), an alpha of .05 and a statistical power (1-beta) of .80, we needed 45 patients in each study arm. With an expected drop-out rate of 20% we aimed to include 108 patients at baseline.

Randomization

This study was a parallel-group RCT, with block randomization of 20, to make sure that the psychologists could process a gradually inflow of patients. Randomization was conducted centrally by an independent researcher (not involved in the trial) using a computer-generated randomization procedure. Patients and psychologists were aware of treatment allocation.

Statistical analysis

Independent samples t-test and chi-square test were used to gauge whether randomization resulted in a balanced distribution of patient characteristics and outcome

measures at baseline across the groups. Intention-to-treat analyses were performed. To test differences in changes from baseline to follow-up between experimental conditions, linear mixed models were used with fixed effects for group, assessment (i.e. time), and their two-way interaction, and a random intercept for subjects. If changes from baseline to follow-up between groups were significant, an independent samples t-test was performed to post-hoc assess differences between the experimental conditions immediately after the intervention or control period (T1) and follow-up assessment (T2). In that case, also effect sizes (ES) were calculated by dividing the difference between the means of the intervention and the waiting-list control group by the SD of the control group. Low, moderate and high ES were defined as, ES=.10-.30, ES=.30-.50 and ES>0.50, respectively [41]. For all statistical analyses, a p-value<.05 was considered statistically significant. Analyses were performed with SPSS 20.0 (IBM Corp., Armonk, NY USA).

RESULTS

Participants

During the inclusion period of 42 months (June 2010 until December 2013) a total of 538 patients were recruited. Of these patients 107 agreed to participate (20%): 55 were randomized in the intervention group, and 52 in the waiting-list control group. In total, 30 patients (28%) did not complete the study, 17 in the intervention group and 13 in the control group. Of the 55 patients in the intervention group, 39 completed the intervention (38 at home and 1 at the hospital; compliance rate 69%). Reasons for not completing the intervention were mainly disease progression and death; furthermore one patient preferred other help, one patient suffered from severe stress and didn't want to continue, and one patient refrained from participation without an explanation. Figure 1 shows the consort flow diagram.

An overview of study population is provided in Table 1. At baseline there were no significant differences between the groups with respect to sociodemographic or clinical characteristics, or baseline outcome measures, except for the EORTC QLQ-C15-PAL Quality of Life Scale (*p*=.034). Also, the groups did not differ significantly regarding the presence of a major depressive disorder (9.3% in the intervention group versus 11.5% in the waiting-list control group; *p*=.70).
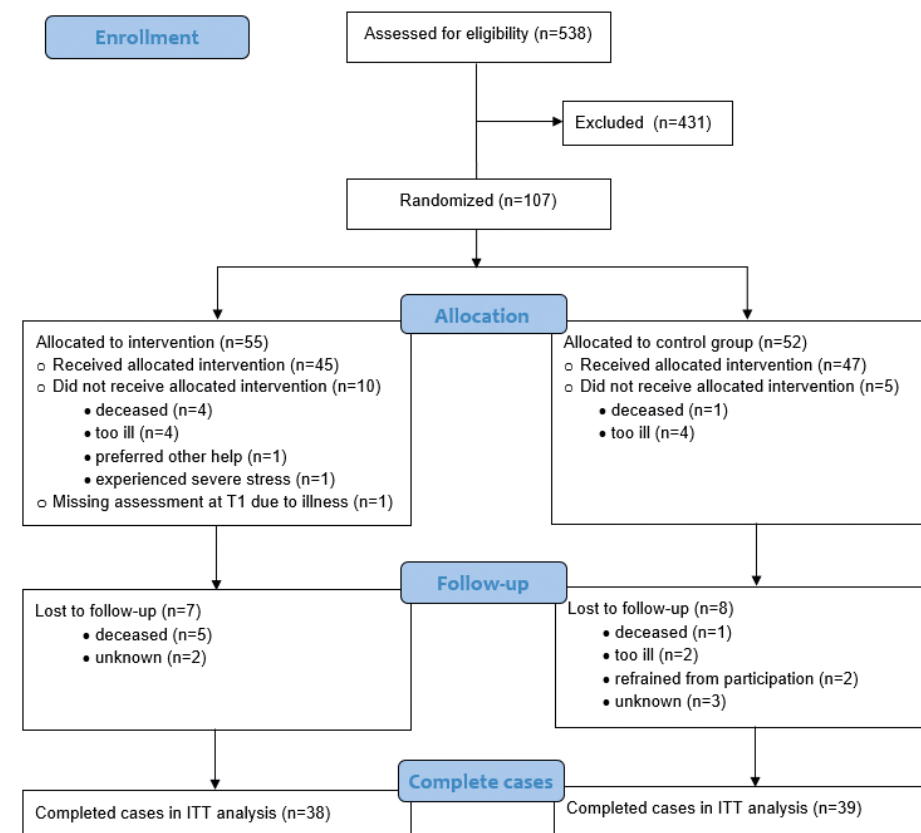

Figure 1. *Consort flow diagram of study population. ITT, intention to treat.*

Table 1. *Overview of patient characteristics*

Scale	Total group (n=107) Distribution	%	LRT (n=55) Distribution	%	CAU (n=52) Distribution	%	P*
Gender							0.91
Male	57	53.3	29	52.7	28	53.8	
Female	50	46.7	26	47.3	24	46.2	
Age							0.10
Mean (SD)	62.7 (9.3)		64.2 (8.5)		61.2 (9.9)		
Range	31-86		46-83		31-86		
Marital status							0.30
Married/living together	75	70.1	41	74.5	34	65.4	
Divorced	32	29.9	14	25.5	18	34.6	
Children							0.13
Yes	91	85.0	44	80.0	47	90.4	
No	16	15.0	11	20.0	5	9.6	
Level of education							0.95
Academic education	15	14.0	9	16.4	6	11.5	
Higher general or vocational education	27	25.2	14	25.5	13	25.0	
Secondary general or vocational education	35	32.7	18	32.7	17	32.7	
Primary education	28	26.2	13	23.6	15	28.8	
None	2	1.9	1	1.8	1	1.9	
Religion							1.00
Yes	35	32.7	18	32.7	17	32.7	
No	72	67.3	37	67.3	35	67.3	
Tumor type							0.61
Lung cancer	66	61.7	31	56.4	35	67.3	
Head and neck cancer	2	1.9	1	1.8	1	1.9	
Hematological cancer	23	21.5	12	21.8	11	21.2	
Breast cancer	5	4.7	3	5.5	2	3.8	
Other	11	10.3	8	14.5	3	5.8	

Note. LRT = Intervention group, CAU = Waiting-list control group - Care-as-usual, SD = Standard deviation, *chi-square test (age = independent samples t-test)

Effectiveness of the intervention

Descriptive statistics of the outcome measures are provided in Table 2. The course of the ego-integrity subscale of the NEIS (Figure 2) improved significantly over time (*p*=.007) in the intervention group compared to the waiting-list control group. Ego-integrity of patients in the intervention group improved after the intervention and scores remained better at follow-up compared to baseline, while ego-integrity of patients in the waiting-list control group decreased at post-test and follow-up. No significant differences between the two groups were found regarding the course of despair (NEIS despair subscale: *p*=.89), distress (HADS-T: *p*=.30), anxiety (HADS-A: *p*=.44) depression (HADS-D: *p*=.54), quality of life (EORTC QLQ-PAL15, *p*=.058) or autobiographical memory (AMT, *p*=.070). For ego-integrity, there were moderate, borderline significant, effect sizes post-intervention (mean difference=8.1, 95% CI: -0.71 – 16.9, ES=.42, t=1.8, *df*=88, *p*=.071) and at follow-up (mean difference=9.8, 95% CI: -0.13 – 19.6, ES=.48, t=2.0, *df*=74, *p*=.053). In the control group, CAU comprised psychological care in 15% of the patients at T1 and 13% at T2. After the one-month follow-up assessment (T2), nine patients in the control group agreed to start the intervention (17.3%). Reasons for not starting LR-MST were among others that patients were too ill or already died.

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Table 2. Outcomes of ego-integrity, despair, psychological distress, quality of life and AMT (over time).

Scale	Assessment	Pre-test n	Pre-test M	Pre-test SD	Post-test n	Post-test M	Post-test SD	Post-test ES	Post-test p	Follow-up n	Follow-up M	Follow-up SD	Follow-up ES	Follow-up p	Interaction LLM F	Interaction LLM p
NEIS																
Ego-integrity	LRT	55	55.0	20.9	43	62.1	22.7	.42	.071	38	57.3	22.9	.48	.053	5.1	.007*
	CAU	52	54.5	21.0	47	54.1	19.3			38	47.6	20.3				
Despair	LRT	55	42.4	22.9	43	37.9	22.5			38	38.1	23.8			.12	.89
	CAU	51	42.4	21.2	47	39.3	20.8			36	41.8	21.6				
HADS																
Anxiety	LRT	55	5.7	4.4	44	4.6	3.8			38	5.2	4.7			.83	.44
	CAU	52	5.4	3.7	47	5.3	3.9			38	5.5	4.3				
Depression	LRT	55	6.1	4.1	44	4.9	3.7			38	5.8	4.8			.62	.54
	CAU	52	5.9	4.1	47	5.9	4.2			39	6.4	4.8				
Distress (Total)	LRT	55	11.8	7.7	44	9.5	6.9			38	11.0	8.8			1.2	.30
	CAU	52	11.3	6.9	47	11.1	6.9			38	11.6	7.7				
EORTC-PAL15																
Global Qol	LRT	55	59.4	22.9	44	68.6	18.8			37	64.9	21.4			2.9	.058
	CAU	52	68.6	21.3	47	67.0	19.2			37	65.3	21.7				
AMT	LRT	55	15.0	3.7	44	15.4	3.0			-	-	-			3.4	.070
	CAU	52	14.2	3.7	47	12.9	3.9			-	-	-				

Note. CAU = Waiting-list control group - Care-as-usual; LLM = Lineair mixed models; M = Mean; SD = Standard deviation; F = assessment x group; p = p-value, *= p<.05; a = Independent samples t-test; ITT analyses were performed
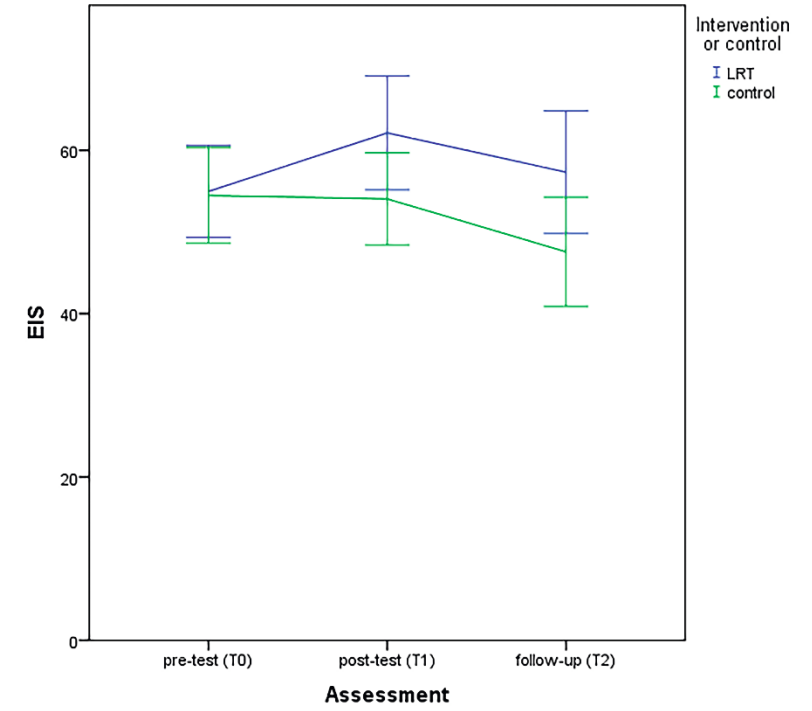
Figure 2. *Course of NEIS: Ego-integrity Scale.*

DISCUSSION

The present study showed that LRT-MST has a positive effect on the course of ego-integrity among cancer patients in palliative care. LRT-MST had no effect on despair, psychological distress, or quality of life. There may be an effect on the specificity of the autobiographical memory.

This study confirms findings of earlier studies on the efficacy on life review interventions in patients with incurable cancer. A randomized controlled trial on the effect of life review therapy (four weekly sessions) among advanced cancer patients in a hospice in China showed positive effects on quality of life (single item) and on five of the eight scales of the Quality of life Concerns in the End of Life Questionnaire. These five scales addressed support, negative emotions, sense of alienation, existential distress, and value of life. The three non-significant scales addressed physical discomfort, food-related concerns, and healthcare concerns [22]. A trial on the effect of life review (three weekly sessions) among terminally ill cancer patients in hospitals in Japan showed a positive effect on

spiritual well-being (FACIT-sp12), on psychological distress (HADS), and on aspects as hope and life completion but not on aspects as pain and symptoms (GDI) [21]. The results of these three trials indicate that life review interventions improve ego-integrity, value of life, and spiritual well-being. Whether life review interventions also improve quality of life and psychological distress remains inconclusive. Main problems comparing these three studies (although all three targeting advanced cancer patients) are the different outcome measures, but also the number of sessions of life review therapy (three or four weekly sessions) and the different residences (private home, hospice, hospital), which may have a moderating effect [17], and also the different cultures (Netherlands, China, Japan).

Future studies may provide insight into possible moderators of the intervention effect on ego-integrity such as gender, age, educational level, and clinical factors as time to death, or burden of treatment related symptoms before the intervention, as well as level of ego-integrity, quality of life or psychological distress [17].

In the present study life review therapy was combined with an autobiographical memory training. LRT-MST had a borderline effect on the autobiographical memory, which suggests that the effect of LRT-MST on ego-integrity might be mediated by improvement of the specific autobiographical memory. Future (qualitative) studies are needed to obtain better insight into the effect of LRT-MST on ego-integrity and possible mediators.

There are some limitations of this study that must be acknowledged. The follow-up assessment was only 1 month after treatment, and therefore we cannot generalize the results regarding a long-term effect. Also, there was a higher dropout percentage (28%) than expected (20%). It appeared to be very difficult to recruit cancer patients in palliative care timely. This is a problem also experienced in other studies, especially with advanced cancer patients [42,43]. In clinical practice it is often unclear when it is the right time to transfer a patient from treatment with intent to cure to palliative care due to for example uncertainty of patient's disease progression, lack of accepting the failure of treatment by healthcare professionals, patients and/or patients' family, or poor understanding of palliative care [44]. For patients, this timely offering of palliative care is important, because research showed that near end-of-life issues with meaning and purpose of life are more important than physical symptoms or physical well-being [45]. Therefore, further research and discussion in clinical practice about this topic is necessary.

Despite these limitations, it can be concluded that the LRT-MST seems effective to improve ego-integrity among cancer patients in palliative care. Because there are currently no interventions addressing this specific and important theme, this intervention appears to be a valuable addition to psycho-oncological health care. Further research is recommended to investigate possible moderators and mediators of the intervention, the efficacy of this intervention in specific groups (for example hospice patients) and to obtain insight in the uptake and reach of the intervention in routine practice.

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CHAPTER 5

Patients' experiences of life review therapy combined with memory specificity training (LRT-MST) targeting cancer patients in palliative care

> " *Stel u mag een moment uit uw leven nog een keer meemaken. Welk moment uit uw leven zou u dan kiezen?* "

ABSTRACT

Purpose: Life Review Therapy combined with Memory Specificity Training (LRT-MST) is effective in cancer patients in palliative care, but the effect size is moderate. The aim of this qualitative study was to obtain more in-depth knowledge on motivation to start with LRT-MST, experiences with LRT-MST, and perceived outcomes of LRT-MST.

Methods: Semi-structured interviews were conducted with 20 cancer patients in palliative care who participated in a randomized controlled trial investigating the effect of LRT-MST. All interviews were digitally recorded and transcribed verbatim. Data were analyzed by means of thematic analysis independently by two coders and coded into key issues and themes.

Results: Patients started LRT-MST for intrinsic (e.g. potential benefit for personal well-being) and extrinsic reasons (e.g. potential benefit for future patients). Patients indicated mainly positive experiences with the intervention. They appreciated sharing their memories and regaining memories with a specific focus on retrieving positive memories. Some disliked the fact that negative memories could not be addressed. Most patients perceived positive outcomes of the intervention belonging to the overarching themes "ego-integrity" and "psychological well-being" in the here and now, as well as in the nearby future (including end-of-life).

Conclusions: LRT-MST is of added value as a psychological intervention in palliative care. This study provided in depth insight into reasons to start the intervention, and the experiences and outcomes, which are important to further tailor LRT-MST and for development or improvement of other psychological interventions targeting cancer patients in palliative care.

INTRODUCTION

When people are diagnosed with cancer this can halt their life. All attention goes to the disease and being ill. Concepts such as past, present and future suddenly get a whole different meaning. Many incurably ill cancer patients have trouble coping with the disease and suffer from psychological distress, depressive symptoms or even depression [1]. Previous research showed that depressed mood and depression are associated with difficulties in recollecting specific and positive autobiographical memories [2–4], while these memories can give strength in difficult times.

In a recent randomized controlled trial (RCT) we examined the efficacy of an intervention, 'Dear Memories' [5], that focuses on retrieving positive memories among palliative cancer patients [6]. The intervention combines life review therapy (LRT) with memory specificity training (MST). Butler [7] defined life review as "the progressive return to consciousness of prior experiences, which can be re-evaluated with the intention of resolving and integrating past conflicts, thereby providing new significance to one's life". A life review intervention aims to integrate positive and negative life events in a coherent life story and into a meaningful whole. This may lead to a greater experience of ego-integrity, which is described as accepting your life cycle as something that had to be, feeling connected to others, and experiencing a sense of wholeness, meaning and coherence when facing death [6,8]. LRT is a structured variant of reminiscence (recalling memories from the past) and refers to the use of life review in psychotherapy. An important aspect in LRT is the autobiographical memory, consisting of memories from an individual's life and knowledge about the world [2,9]. The MST included in LRT-MST aims to improve the recall of specific and positive memories instead of more generic memories [10,11].

Results of the RCT investigating LRT-MST in cancer patients in palliative care, showed that the course of ego-integrity improved significantly over time in the intervention group compared to a control group who received care as usual [6]. However, the effect size in this study was moderate, indicating that not all patients benefitted from the intervention. Therefore, more in-depth information on the experiences of the participants is called for.

The aim of this study was to qualitatively investigate motivation to start LRT-MST, experiences with, and, perceived outcomes of participation in LRT-MST. Results are relevant to further improve LRT-MST and interventions targeting cancer patients in palliative care in general.

5

METHODS

Context and study participant selection

The present study was conducted in the context of a RCT on LRT-MST [6]. LRT-MST is an autobiographical memory retrieval practice, focussing on bringing up positive specific events. It consists of four individual sessions focusing on a particular life period: childhood, adolescence, adulthood and the whole life span [3,5]. For each period, 14 questions are prepared to prompt specific positive memories (e.g. "Do you remember, as a child, receiving a present which was very special to you?"). For each question, the interviewer tries to get a specific view of the situation by asking for more (detailed) information, thereby training patients in regaining more specific and positive memories. Each session takes approximately one hour and is led by a trained psychologist. The sessions were recorded on mp3 and copies were offered as a remembrance for the respondents and/or their family members.

In the RCT, patients in palliative care received LRT-MST mainly at their home. Inclusion criteria for participating in the RCT were age above 18 years a diagnosis of cancer without curative treatment options and a prognosis of more than 3 months. Participants were excluded if they had psychotic behaviour, a severe cognitive dysfunction, a severe impairment in oral communication, insufficient mastery of the Dutch language to complete questionnaires and to answer the questions of the life review interviews. In total, 107 cancer patients in palliative care were randomly assigned to the intervention (n = 54) or a waiting-list control group (n = 53), of whom 38 patients in the intervention group and 4 patients in the waiting-list control group completed LRT-MST (n = 42). Of these 42 patients who completed LRT-MST, 18 had already died and three patients were too ill at the moment of purposive recruitment in the present study. Patients were approached by telephone with information about the current follow-up study and all 21 eligible patients agreed to participate. Unfortunately, one of the interviews recorded was deleted accidently, leaving a study sample of 20 patients. Although we made use of total population sampling, data saturation was reached since no new information related to our research questions was gained during the last interviews. The study was approved by the Medical Ethical Committee of VU University Medical Center in Amsterdam and registered in the Netherlands Trial Register (NTR2256). All patients provided written informed consent. Patients' characteristics are shown in Table 1.

Table 1. *Characteristics of participants*

	n	%
Gender		
Male	10	50
Female	10	50
Age		
Mean (SD)	65.6 (8.7)	
Range	48-85	
Marital status		
Married	13	65
Not married	7	35
Children		
Yes	18	90
No	2	10
Level of education		
Academic education	3	15
Higher education	6	30
Secondary education	7	35
Primary education	3	15
None	1	5
Tumor type		
Lung cancer	10	50
Haematological cancer	5	25
Other	5	25

Instrument and procedure

The semi-structured interview scheme consisted of three themes (motivation, experiences and perceived outcomes) with associated questions (Table 2). Topics and questions were derived from clinical experience and from previous studies [5,12]. The single interviews with the patients were conducted in a home setting, by a trained female researcher (MP) with a psychological background. Interviews were digitally recorded, transcribed verbatim and lasted approximately 60-75 minutes. Field notes were made when relevant (e.g. Patient is difficult to understand, because of speech problems).

Table 2. *Interview topics*

Themes	Key questions
Motives to start	Why did you decide to participate?
	What were your expectations?
Experiences	How did you experience participation?
	How did you experience it to actively focus on your own life story?
Perceived outcomes	Did participation help you? In which way?
	Did participation lead to changes in the way that you look back on your own life?

Data analysis

Transcripts were independently coded by means of thematic analysis by two coders (GK, MP) using Atlas.ti 7. Both coders read all transcripts. Motivation to start LRT-MST and citations about experiences with and perceived outcomes of partaking were selected and coded into key-issues and themes. After every three transcripts coded, findings were discussed and differences resolved until consensus was reached. The coders together created a coding framework. In case of disagreement, a third coder (CvU) was consulted. The literature was revisited to seek for conceptual tools that could be used to categorize the key-issues and themes. A single coder (GK) examined the raw data again to ensure that all data were present in the coding. For this paper, quotes were translated from Dutch into English and anonymized. We followed consolidated criteria for reporting qualitative research (COREQ) guidelines in reporting this study [13].

RESULTS

Motivation to start LRT-MST

Patients noted both intrinsic and extrinsic motives to start LRT-MST (Table 3). An intrinsic reason mentioned was the potential benefit for personal well-being. Some considered the intervention as an alternative for emotional support as provided by for example a psychologist or support group. A few indicated to especially appreciate the positive focus of LRT-MST.

Table 3. *Motivation and considerations towards starting LRT-MST*

Key issues	Themes
Intrinsic motives	
Potential benefit for personal well-being	Hope for guidance in end-of-life care
Participation because of positive focus of intervention	
Interest in reviewing life story	Wish to leave a legacy
Extrinsic motives	
Participation because of treatment in academic hospital	
Potential benefit for future patients	
Considerations to not participate	
Doubts because of fear that hard times would come up	
Inner circle having doubts about participation	
Sceptical towards psychologist/alpha sciences	

"It intrigued me, that it was the opposite of the psychologist who assumes the negative."

Another intrinsic motive to start was being interested in reviewing one's life story. Some remarked that they already knew of "life review" and wanted to try this themselves. An attractive element considered by some concerned leaving a legacy (in the form of audio recordings). One participant specified that he hoped to receive some form of guidance in end-of-life. Others indicated to start because of extrinsic reasons; doing something in return for being treated in a university hospital or because of a potential benefit for future patients.

Some mentioned that they did not have clear reasons or even had some considerations, like the risk that 'difficult times from the past' would arise.

Experiences with participation in LRT-MST

The majority indicated that they enjoyed reviewing their lives (Table 4).

Table 4. *Experiences with participation in LRT-MST*

Key issues	Themes
Sharing memories	Experiences of talking about self
Regaining memories	Regaining more memories than expected
	Ability to remember details
	Regaining underexposed memories
	Active elaboration on specific life phase (between interviews)
	Relived memories
	Regaining unresolved memories
Focusing on the positive side of your life	Enhanced awareness of (lack of) positive moments in life story
	(Unavoidable) recall of negative memories
Feeling acknowledged by…	A specific intervention for advanced cancer patients
	The psychologist
	Opportunity to participate in home setting
	Obtaining a CD with their life story
Being distracted from medical situation	

Sharing memories

Most patients mentioned to appreciate the opportunity to talk about themselves and their memories. Several described that sharing memories is not an everyday occurrence. They indicated to lack family members to talk with about the past and that sharing memories is not something you normally do.

"I enjoyed doing it, telling your life story to someone else, a perfect stranger, for a change. […] You do not sit down with your own wife thinking 'now I am going to tell all of this'."

Others mentioned it to be an advantage to talk with a stranger about topics they perceived as too sensitive to discuss with their own family. Several mentioned that they did not want to bother their own inner circle.

One patient mentioned that he was not totally open.

"From day one I said: 'I will never tell the truth.' […] I mean, there are certain things you don't tell. […] I didn't make up anything, but I skipped certain things."

Regaining memories

Most patients noted that they regained more memories than expected and that their ability to remember details increased because of the focus on specific life phases and questions posed.

"All sorts of things came to the surface that I really had forgotten. […] His [the interviewer] questioning did this."

Patients indicated that before partaking they did not think about the past or they thought they had forgotten certain life events.

Some noted that in between the sessions they were thinking about the specific life phase that was discussed in the previous session or delved into the life phase that was planned. They mentioned that they sometimes relived the session and could even remember more.

"What else do I remember from those days? Well, I think that in hindsight I could have told another twenty stories at least, so it does bring back things too."

A few patients noticed that they also regained some unresolved or unhandled memories.

"I had not expected that it would bring back unresolved things too. […] Yes, maybe a little, but not as violently. That was the drawback for me: the good things surfaced, but the sad things too."

Focusing on the positive side of your life

Most patients appreciated to retrieve positive memories only. Several experienced an enhanced awareness of positive moments, while some noticed only few positive moments.

Patients mentioned that despite the positive focus, negative memories were recalled anyhow. Some felt the urge to also discuss these.

"When you tell your life's story, you also want […] to get the bad things off your chest, […] your experiences. So that was a bit of a drawback, really."

Another patient explained that he was disappointed to not be able to share negative events at first, but that he learnt how to master this.

Feeling acknowledged

Some patients mentioned that they felt acknowledged by an option focusing on patients in palliative care, because of a lack of options for them. The majority felt appreciated by the psychologist who interviewed them.

Most felt that their circumstances were acknowledged by offering the opportunity to participate at home. They lacked the energy to participate elsewhere, already had much travel expenses for hospital visits or experienced it as more comfortable.

Finally, several considered it of value to receive the audio recordings.

"It would of course be really nice for me to listen to this once again, because it has brought me so much positive energy. And I think: it is beautiful, isn't it, to conclude your life by going through your own history one more time. That is such a gift."

Provides distraction from the medical situation
Patients also mentioned that the intervention distracted from their medical situation.

"Uhm, well, it's more like this, it's already a very lonely situation anyway, because in fact everything goes on, except your life, and you just can't go anywhere [for help]. And I liked this [intervention] very much, because I don't have to talk about the disease, and I do think it was uplifting and positive. It just gives you energy and that is exactly what you need."

Outcomes of participating in LRT-MST

Most patients perceived several positive outcomes, belonging to two overarching themes "Ego-integrity" and "Psychological well-being" (Table 5). A few mentioned that they did not experience any outcomes of partaking. They already felt "positive" or found it difficult to distinguish between outcomes of having an incurable disease versus outcomes of partaking. One patient indicated that partaking had brought him nothing.

Ego-integrity

Re-evaluation of life
The majority mentioned that thinking and talking about live events, incited them to re-evaluate their lives, by which they obtained increased insight in their own life story.

"I never looked back, I had no rear-view mirror in my mind, and so now I have one. In that sense it has been useful to me, then you are looking at it all from another perspective."

Achieved ego-integrity
Several noted to recognize themes, a structure, patterns or a "golden tread" in their lives:

"It aren't pieces, it is a connected chain; it all goes together. The past is part of the present and will also have to do with your future. The piece of future you still have."

Table 5. *Perceived outcomes of participation in LRT-MST*

Key issues	Themes
Overarching theme "Ego-integrity"	
(Re-)evaluation of life	Obtained insight in life story
Achieved ego-integrity	Recognition of a 'golden thread' in life
	Recognition of positive experiences in negative life periods
	Processing and acceptance of negative life events
	Make more sense of life story
	Recognition of personal growth
	Acceleration of maturation process
	Increased acceptance of others (milder)
	Acceptance of disease
	Seeing life as a whole
	Confidence in end-of-life
	Solved past conflicts (reconciliation)
Overarching theme "Psychological well-being"	
Finding meaning in the now	Awareness of living in the now
	Leaving the past behind
	Awareness that life is worth living
	Feeling prepared for the future
	Able to focus of the positive aspects of life
	Gratefulness
Mastery	Empowerment
Improved coping	Resilience
Self-acceptance and self-appreciation	
(Changed) mood	Ability to recall memories to improve mood
Increased social life	Social interaction
	Restarting activities

Some indicated that they were able to recognize positive experiences in negative life periods. Or described that thinking and talking about the past helped them to process and accept their life including negative events. Some also mentioned that they could make more sense of their life story and recognized their own personal growth.

"I have experienced far more strength in it, and continuity too; that in essence it were basically the same problems, which I apparently had to face in this life. And yes, it comes with ups and downs, but that is okay. For you do undergo a development in it and you do grow in it. […] I have now had a far better look at this growth, and this growth must also help you to take that final short stretch. That is the insight it has clearly given me."

Some patients indicated they became more accepting and understanding towards others. Others mentioned they started the conversation about or even resolved disagreements or conflicts from the past.

Some patients indicated that as a result of partaking they experienced "feelings of increased acceptance of the disease". They explained that they were more "at peace" with the situation.

> "At first, I was really only thinking about, ehm, with every plant I planted in the garden, I thought: I will not even see that one grow, I don't even know if it will make through winter. Well, in everything: last Christmas, last birthdays, all last things. (…) I have now let it go. We will wait and see."

One patient specifically mentioned that he was fixated on the disease since diagnosis. Due to LRT-MST he started seeing life as a whole again.

> "The moment that you hear that you are ill, you focus on your illness. You do not attach, involve other things in that. 'Dear Memories' did that. You start looking at the bigger picture. Before then, I was only focused on how can I stay here for as long as possible, in the world below the moon?"

One participant said to have gained more confidence to face their end-of-life.

> "Then the last stage arrives in which new things will also happen again in your life, but in which you will have also have developed unbelievably great strength and skills to face it. So, it has shifted from a kind of fear to a kind of curiosity and a kind of, all in all, self-confidence."

Psychological well-being

Finding meaning in the now
Patients mentioned to leave the past behind or to be more aware of living in the now. They noted that their lives are still worthwhile and explained that they felt boosted and encouraged not to give up.

Some said that they were able to focus on the positive aspects more and felt glad to be alive.

> "I am still here, and that is utterly wonderful. And Dear Memories, yes, that only proves that there are still a lot of wonderful things. So if you can think and talk of nice things in the past, those are now still happening too."

Others described to feel better prepared for the future.

> "To focus on the present and also – and then – when it comes to that 'Dear Memories' I have the idea that […] you can go into the future more complete, better, more positive, so to speak."

Several patients expressed an increased sense of gratefulness. They noted to be more aware of the good that life has offered, like a good upbringing, lovely people, opportunities to experience and learn.

Mastery
Some patients noted that partaking in the intervention led to a feeling of improved empowerment and that they were more resilient.

> "It really gave me the feeling of 'okay, put it on my plate, I can handle it.' Because of course you have already lived through a number of these situations. They may have looked differently, but in essence it were the same problems."

Improved coping
Several patients mentioned that partaking helped them to improve their coping skills and as result they "can put daily events into perspective", "have learnt what matters in life" and "ruminate less".

> "Also a bit like, God, things run as they run. […] Well, that I do not get so excited about things anymore. Politics too, for instance, we can make a fuss about it or we don't."

Self-acceptance and self-appreciation
Patients described that due to partaking in the intervention they redeemed more self-acceptance.

> "Yes, let me say, in everything that life offers you, you suddenly see yourself standing there with your own experiences. And that gives you such an unbelievable amount

of strength, insight and certainty, but also a kind of joy and pleasure, this continually,
like 'I am who I am and I am becoming more me by the day'. And I am allowed to."

Others described that the intervention had an influence on their self-appreciation that
they became more aware of achievements and felt proud.

"There are also moments when you suddenly think like 'well, I haven't done too bad'
or 'oh, not too bad that it happened this way'. And yes, that always strengthens you
in your self-appreciation for, hey, I am also a type that needs pats on the back and
this method makes you pat yourself on the back."

On the contrary, one patient mentioned that he felt that his self-appreciation slightly
decreased, because of being confronted with his negative sides and failures.

(Changed) mood
Some patients mentioned that partaking in the intervention enhanced their mood and
that they learned to recall positive memories to improve their mood.

"By bringing back those memories of the past, or situations that were positive or that
made you happy in the past, that you can recall them and think: 'wow, that was fun!'
and that can put you in a more positive mood for a while."

In contrary, one patients described that partaking had a negative influence on her mood.

"That, really, the thoughts about life [...] Like: I do not want to hide from it, but I do
not want to dive into it either. That combination a bit, it is just enough as it is. Well, I
have to say I think the sadness, that this surprised me. [...] Yes, it became a bit harder."

Increased social life
Several patients mentioned that their social interaction increased.

"Because I have now started to think about things in a friendlier way, you do become
somewhat more outgoing, somewhat more social, at least, that is how I translate it.
And I enjoy having people around me again."

Others indicated that increased social interaction resulted from sharing and retrieving
memories with others. One patient noted that because of retrieving memories he was
encouraged to undertake activities in the present.

"That you suddenly think like, yes, we did things in the past, we went out for dinner
more often, and we should actually do that again more often."

DISCUSSION

In this study, we qualitatively explored motivation to start, experiences with and the
perceived outcomes of participation in LRT-MST among cancer patients in the palliative
phase. Patients started LRT-MST for both intrinsic reasons and for extrinsic reasons.
Some indicated to be motivated to start because of the positive focus. This preference fits
in with a new movement within psychology; positive psychology. While, psychotherapy
traditionally addresses psychological disorders, positive psychology aims to focus on
the positive features that make life worth living such as hope, optimism, happiness and
well-being [14,15].

Patients indicated mainly positive experiences with LRT-MST. They enjoyed sharing
memories and most noted that they regained more memories than expected and that
their ability to remember details and underexposed memories increased. A negative
experience with LRT-MST mentioned by some concerned the upbringing of and limited
time for sharing negative emotions and events.

The contrast between the results of the RCT on LRT-MST (showing no clear effect (p=.070)
on improving autobiographical memory as measured by the Autobiographical Memory
Test (AMT) before and after the intervention [6], and the experiences and outcomes as
reported by the patients (improved and more detailed memories) call for further research
into the assessment and working mechanisms of MST. Also, for clinical practice purposes,
we suggest to inform future participants of LRT-MST that "negative emotions" can also
come up and may need to be addressed.

Various perceived outcomes reported by patients could be conceptualized as part of
achieving "ego-integrity", accepting your life cycle as something that had to be, feeling
connected to others, and experiencing a sense of wholeness, meaning and coherence
when facing death. Patients noted that they obtained more insight in their life stories due

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to re-evaluation of their lives and recognized things they were not aware off before ("a golden thread") and more acceptance of negative life events. These findings support the beneficial effect on ego-integrity, the primary outcome of the RCT on LRT-MST [6]. Other perceived outcomes belonged to the overarching theme of improved "Psychological well-being". Patients expected to re-use successful coping strategies from the past, since partaking in LRT-MST provided them with the insight into efficacy of these strategies in earlier life events. In LRT-MST, this outcome is aimed for by striving to recall memories involving a successful adaptation [3,5,15,16].

Despite the emphasis on perceived outcomes on positive mental health and flourishing, some patients perceived negative outcomes such as a negative influence on mood. This mixture of positive and negative reported outcomes may explain why the results in the RCT did not show effect on psychological distress, anxiety and depression and health related quality of life. Also, some patients noted that they already felt positive at the start of the intervention, which implies that the intervention is not beneficial for all patients in palliative care. Future research should disentangle which patients most likely will benefit from LRT-MST.

A face-to-face intervention in a home setting as LRT-MST proved to have value in this group of palliative cancer patients, but is relatively costly compared to interventions provided in a care setting. A cost-effectiveness study is warranted. Also, alternative formats can be investigated, like an online-guided self-help version of LRT-MST or conduction the interviews via telephone or videoconference [17].

A limitation of this study is that the time after participation in LRT-MST differed among patients. Patients, who had participated more recently, are expected to have recalled more detailed experiences of partaking. Also, only half of the patients who enrolled in LRT-MST participated in the current study. The main reasons for not participating were that patients were too sick or already deceased at time of the present study, which may have induced bias: it may be that patients who were the sickest at time of LRT-MST experienced the intervention differently from those who survived longer.

LRT-MST is of added value as a psychological intervention in palliative care. This study provided in depth insight into reasons to start the intervention, and the experiences and outcomes, which are important to further tailor LRT-MST and for development or improvement of other psychological interventions targeting cancer patients in palliative care.

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CHAPTER 6

A randomized controlled trial on the efficacy of Life review therapy targeting incurably ill cancer patients: do their informal caregivers benefit?

" Wat ziet u nu als belangrijkste keerpunt in uw leven? "

ABSTRACT

Objective: Investigate whether Life Review Therapy and Memory Specificity Training (LRT-MST) targeting incurably ill cancer patients, may also have a beneficial effect on caregiving burden, symptoms of anxiety and depression, and posttraumatic growth of the informal caregiver.

Methods: Data was collected in the context of a randomized controlled trial (RCT) on the effect of LRT-MST among incurably cancer patients. Informal caregivers of participating patients were asked to complete outcome measures at baseline, post-intervention and 1 month follow-up: caregiver burden (Caregivers Reaction Assessment Scale; CRA), symptoms of anxiety and depression (Hospital Anxiety and Depression Scale), and posttraumatic growth (PostTraumatic Growth Inventory). Linear mixed models (intention to treat) were used to assess group differences in changes over time. Effect size and independent samples t-tests were used to assess group differences at T1, and T2.

Results: In total, 64 caregivers participated. At baseline, 56% of the caregivers experienced anxiety and 30% depression. No significant effect was found on these symptoms nor on post-traumatic growth or most aspects of caregiver burden (CRA). There was a significant effect of LRT-MST on the course of self-esteem (subscale CRA) (*p*=.013). Effect size was moderate post-intervention (ES=-.38, *p*=.23) and at 3 months follow-up (ES=.53, *p*=.083).

Conclusions: Many caregivers of incurably ill cancer patients experience symptoms of anxiety and depression. LRT-MST does not seem beneficial in reducing symptoms of depression and anxiety, negative aspects of caregiver burden or facilitating post-traumatic growth. LRT-MST may have a protective effect on self-esteem of informal caregivers (positive aspect of caregiver burden).

BACKGROUND

Informal caregivers of incurably ill cancer patients face a broad variety of tasks; assisting the patient with disease and treatment monitoring, symptom management, medication, personal and instrumental care, financial and emotional support [1-3]. Often caregivers take all these responsibilities with little or no preparation or training and with limited resources [2] and they feel committed to provide limitless care [2,4]. Pitceathly & Maguire [5] showed in a systematic review that most informal caregivers cope well, but also that a part of them becomes highly distressed or develop mental health problems. Their review showed that based on self-report questionnaires 20 – 30% of caregivers are at risk for psychiatric morbidity. In caregivers of patients with advanced cancer receiving palliative care this rate is up to 30 – 50%. In studies using diagnostic interviews lower levels of morbidity were found, ranging from 10% among carers of newly diagnosed patients to 33% among carers of terminally ill patients [5]. Rha et al. [2] reported that family caregivers experience a considerable amount of distress in their efforts to provide care for cancer patients. This happens especially if the demand of care exceeds the resources the caregiver has available, which causes caregivers to feel overwhelmed and experience high levels of stress. This stress negatively affects a caregivers' psychological well-being, but can also negatively affect their physical well-being [6]. The negative effects of caregiving on psychological well-being include increased emotional distress, anxiety, and/or depression (with rates up to 40% in case of palliative care), feelings of helplessness, loss of control, signs of posttraumatic stress disorder, uncertainty and hopelessness [6,7]. Despite these challenges informal caregivers of cancer patients are often facing, being a caregiver can also result in the experience of positive psychological changes, like personal growth and psychological strength [8].

In a randomized controlled trial (RCT) [9], we examined the efficacy of a life-review intervention named Dear Memories [10,11], which combines life review therapy with memory specificity training (LRT-MST), among incurably ill cancer patients. We found a positive effect on ego-integrity. Ego-integrity is described as accepting your life cycle as something that had to be, feeling connected to others, and experiencing a sense of wholeness, meaning, and coherence when facing death) [9]. Additionally, reasons to start, experiences and perceived outcomes were studied via a qualitative approach among patients who underwent LRT-MST [12]. Patients reported positive outcomes on ego-integrity and psychological well-being in the here and now, as well as in the nearby future (including end-of-life). Also, patients noted that they appreciated sharing and

regaining memories and some noted positive outcomes on their social life; e.g. increased social interaction, enjoying having people around again.

Two meta-analyses [13,14] evaluating emotional distress in cancer patients and their informal caregivers reported that distress was correlated and that couples often react as an "emotional system" [6]. Therefore, in the present study we investigated whether LRT-MST offered to incurably ill cancer patients (but not to the informal caregivers themselves), may also have an effect on their informal caregivers. The results are relevant, because previous research showed that caregivers are less likely to disclose their own concerns and worries as their primarily focus is on the patients' need and often they do not to seek help [5].

METHODS

Study design and population
This study was conducted (June 2010 until December 2013) in the context of a randomized controlled trial (RCT) evaluating the efficacy of LRT-MST targeting cancer patients in palliative care [9]. All informal caregivers of the 107 (55 randomized in the intervention group; 52 in the waiting-list control group) included incurably ill cancer patients (all types of cancer and all palliative care modalities) were asked to participate as well (the intervention was not targeting the informal caregivers themselves, but the patients only). All included caregivers (and patients) provided informed consent. Hereafter, caregivers were asked to complete questionnaires (at home) at the same assessment times as the patients: before the start of the intervention (baseline; T0), after the intervention or after four weeks waiting time in the control group (post-treatment; T1), and at one-month post-treatment (follow-up; T2). Caregivers who participated in the current study followed treatment allocation of the patients in the RCT [9]. The RCT was approved by the Medical Ethics Committee of VU University Medical Center and registered in the Netherlands Trial Register (NTR 2256). Data is available upon request.

Intervention
LRT-MST called 'Dear Memories' [10] aims to improve the life review process and to train the autobiographical memory, with a focus to retrieve positive specific events from the past. This protocol [10] is based on the life review protocol designed by Serrano et al. [11] for older adults with depressive symptomatology. LRT-MST consists of four weekly sessions covering a particular lifetime period: childhood, adolescence, adulthood, and

whole life span. For each period, 14 questions are designed to prompt specific positive memories. Participants are explicitly encouraged to retrieve positive specific memories to the positively stated questions. Each interview, conducted in Dutch, takes approximately 1 hour and is led by a psychologist who was trained in the LRT-MST-protocol "Dear Memories". The intervention takes place at the patient's residence or at the hospital. The interviews are recorded on mp3 and copies are offered as a remembrance for the patients and/or their informal caregivers [9].

Care as usual
In care as usual (CAU) physicians and nurses provide emotional support and advice how to cope with being an informal caregiver of an incurably ill cancer patient on an ad hoc basis during hospital visits. Caregivers can also be referred to other services, like a social worker, a psychologist, or the general practitioner.

Outcome measures
Caregivers completed questionnaires on caregiver burden (Caregivers Reaction Assessment Scale; CRA), psychological distress, anxiety, and depressive symptoms (Hospital Anxiety and Depression Scale; HADS), and posttraumatic growth (posttraumatic growth inventory; PTGI). Caregivers also filled out a study specific questionnaire on age, gender, relationship status, children, and education level.

The CRA-D (Dutch version) [15,16] is a 24-item instrument designed to assess subjective caregiver burden and comprises 5 subscales, including both positive ('self-esteem') and negative burden ('disrupted schedule', 'financial problems', 'lack of family support', and 'loss of physical strength'). Answers were rated on a 5-point Likert scale, ranging 1 to 5 [15,16]. In the present study Cronbach's alpha was .75 for care-derived self-esteem subscale, .79 for 'disrupted schedule' subscale, .77 for 'financial problems' subscale, .76 for 'lack of family support' subscale, and .74 for 'health problems' subscale.

The validated Dutch version of the HADS [17] is a 14-item self-assessment scale for measuring psychological distress (HADS-T) and consists of two subscales: anxiety (HADS-A) and depression (HADS-D). Answers are given on a 4-point Likert scale ranging from 0 to 4. The total HADS score ranges from 0 to 42 and the subscales range from 0 to 21. A subscale score from >7 indicates an increased risk for an anxiety or depressive disorder and a total score >14 indicates psychological distress [17,18]. Cronbach's alpha in the present study was .90, .80, and .87 for HADS-T, HADS-A, and HADS-D respectively.

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Tedeschi & Calhoun [19] developed the PTGI and defined posttraumatic growth as psychological growth beyond previous levels of functioning, as a result of the struggle with a traumatic event. The PTGI is a 21-item questionnaire measuring posttraumatic growth including five subscales: relating to others, new possibilities, personal strength, spiritual change, and appreciation of life. Answers are given on a 6-point Likert scale with 0 = 'I did not experience this change as a result of my crisis' till 5 = 'I experienced this change to a very great degree as a result of my crisis'. Subscales scores are calculated via the summation of the given responses to items belonging to the subscale [19]. The total score is derived by the summation of all 21 items and ranges from 0 till 105 and a higher score indicates a higher level of posttraumatic growth [18,20,21]. Cronbach's alpha in the current study for the subscales relating to others, new possibilities, personal strength, spiritual change, and appreciation of life was .83, .72, .85, .64, and .73 respectively.

Statistical methods

Descriptive statistics (mean and standard deviation or frequency and percentage) were used to describe the study population characteristics and scores on caregiver burden, psychological distress, and posttraumatic growth. Independent samples t-test and chi-square test were used to gauge whether randomization resulted in a balanced distribution of caregiver characteristics and outcome measures at baseline across the groups. Intention-to-treat analyses were performed. Changes over time (from baseline to follow-up) between experimental conditions were investigated using linear mixed models with fixed effects for group, assessment, and their two-way interaction, and a random intercept for subjects. If changes from baseline to follow-up between groups were significant, an independent samples t-test was performed to post-hoc assess differences between the experimental conditions immediately after the intervention or control period (T1) and follow-up assessment (T2). Effect sizes (ES) were calculated by dividing the difference between the means of the intervention and the waiting-list control group at post and follow-up measurements by the standard deviation (SD) of the control group. Low, moderate and high ES were defined as, ES=.10-.30, ES=.30-.50 and ES>0.50, respectively [22]. For all statistical analyses, a p-value <.05 was considered statistically significant. Analyses were performed with SPSS 24 (IBM Corp., Armonk, NY USA).

RESULTS

Study population

In total, 64 caregivers out of 75 participated (85%): 35 caregivers of patients in the LRT-MST condition and 29 caregivers of patients who were randomized in the control group. In total 19 caregivers (30%) did not complete all the questionnaires; 12 in the LRT group and 7 in the control group. Figure 1 shows the flow diagram. An overview of the study population is provided in Table 1. At baseline there were no significant differences between the conditions with respect to sociodemographic characteristics and baseline outcomes. Mean age was 62 years, all except one (who was a brother living with the patient) were partners of the patient, most were female (61%), had children (88%), were caregiver of a patient who was treated for lung cancer (63%) or hematological cancer (27%). Many caregivers had an increased risk for an anxiety disorder (56%) or a depressive disorder (30%).

Effect of the intervention on caregivers

Descriptive statistics of the outcome measures at T0, T1, and T2 of the caregivers in the intervention group versus those in the control group are provided in Table 2. A significant change (*p*=.013) was found over time on the course of the scores on the subscale 'self-esteem' of the CRA: self-esteem of caregivers of patients in the intervention group remained stable over time, while self-esteem in caregivers of patients in the control group decreased. Post hoc analyses showed a moderate ES post-intervention (mean difference=-.18, 95% CI: -0.48 – 0.12, ES=-.38, t=-1.21, *df*=45, *p*=.23), and at 3 months follow-up (mean difference=.30, 95% CI: -0.041 – 0.64, ES=.53, t=1.78, *df*=43, *p*=.083). The results of these post hoc analyses were not statistically significant. No effect was found on the scores of the other subscales of the CRA, HADS or PTGI.

Table 1. *Overview of patient characteristics*

	Total group (n=64)		LRT (n=35)		CAU (n=29)		
	n	%	n	%	n	%	*P**
Age							0.093
Mean (SD)	61.6	(9.9)	63.6	(9.2)	59.4	(10.4)	
Range	36 - 85		50 - 81		36 - 85		
Gender							0.73
Male	25	39.1%	13	37.1%	12	41.4%	
Female	39	60.9%	22	62.9%	17	58.6%	
Marital status							0.53
Married	59	92.2%	33	94.3%	26	89.7%	
*Not married^*	5	7.9%	2	5.7%	3	10.3%	
Children							1.00
No	8	12.5%	4	11.4%	4	13.8%	
Yes	56	87.5%	31	88.6%	25	86.2%	
Level of education							0.48
Primary education	17	27.0%	11	32.4%	6	20.7%	
Secondary education	19	30.2%	8	23.5%	11	37.9%	
Higher education	10	15.9%	6	17.6%	4	13.8%	
Academic education	9	14.3%	6	17.6%	3	10.3%	
Other	8	12.7%	3	8.8%	5	17.2%	
Religion							0.46
No	41	64.1%	21	60.0%	20	69.0%	
Yes	23	35.9%	14	40.0%	9	31.0%	
Tumor type							0.74
Lung cancer	40	62.5%	21	60.0%	19	65.5%	
Haematological cancer	17	26.6%	9	25.7%	8	27.6%	
Breast cancer	1	1.6%	1	2.9%	0	0.0%	
Other	6	9.4%	4	11.4%	2	6.9%	
Risk on psychiatric morbidity							
Anxiety (HADS-A>7)	36	56.3%	20	58.8%	16	55.2%	0.77
Depression (HADS-D>7)	19	29.7%	13	38.2%	6	21.4%	0.14

Note. LRT = Intervention group, CAU = Waiting-list control group - Care-as-usual, SD = Standard deviation, *chi-square test (age = independent samples t-test), ^= one couple were brothers living together.
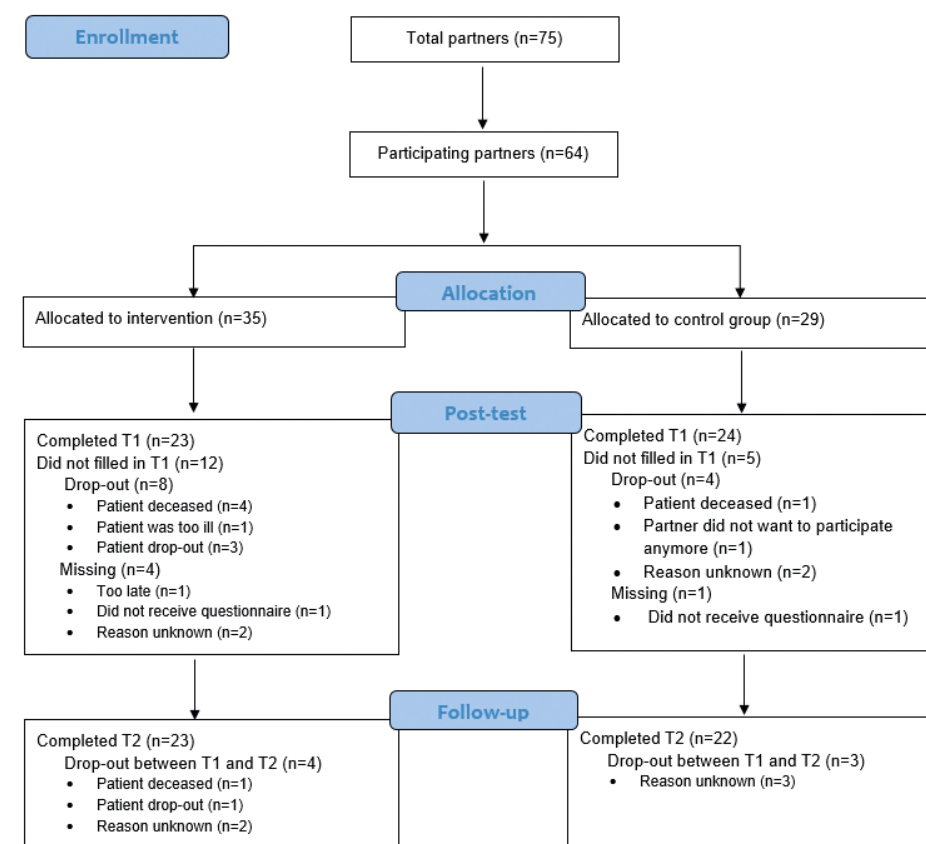

Figure 1. *Flow diagram of study population.*

Table 2. *Overview of the effect of the intervention on the patient reported outcomes over time*

		Pre-test			Post-test			Follow-up			Interaction LLM			
		M	SD	n	M	SD	n	M	SD	n	F	df1	df2	p
CRA														
Disrupted schedule	LRT	3.3	0.8	35	3.2	0.8	23	3.3	0.9	23	0.07	2	92	0.93
	CAU	3.0	1.0	28	2.9	0.9	24	3.0	0.9	22				
Financial problems	LRT	2.5	0.8	34	2.5	0.9	23	2.5	0.8	23	0.33	2	91	0.72
	CAU	2.5	0.9	27	2.8	0.9	23	2.6	1.1	22				
Lack of family support	LRT	2.3	0.6	35	2.3	0.7	23	2.5	0.9	23	0.31	2	91	0.74
	CAU	2.2	0.6	28	2.3	0.8	24	2.3	0.7	22				
Health problems	LRT	2.6	0.7	35	2.6	0.7	23	2.5	0.8	23	0.23	2	93	0.80
	CAU	2.5	0.9	28	2.4	0.7	24	2.5	0.7	22				
Self-esteem	LRT	4.2	0.6	35	4.0	0.5	23	4.1	0.6	23	4.57	2	94	0.013*
	CAU	4.1	0.4	28	4.2	0.5	24	3.8	0.6	22				
HADS														
Total	LRT	14.7	7.7	33	12.3	6.5	23	14.2	7.5	23	1.27	2	90	0.29
	CAU	12.8	5.8	28	14.2	5.8	24	14.8	8.8	22				
Anxiety	LRT	8.3	3.3	34	6.9	3.2	23	7.9	3.5	23	1.27	2	93	0.29
	CAU	7.6	3.4	29	8.0	3.2	24	8.3	4.6	22				
Depression	LRT	6.4	4.6	34	5.5	3.8	23	6.3	4.9	23	0.92	2	90	0.40
	CAU	5.2	3.0	28	6.1	3.4	24	6.5	4.7	22				

Table 2. *Continued.*

		Pre-test			Post-test			Follow-up			Interaction LLM			
		M	SD	n	M	SD	n	M	SD	n	F	df1	df2	p
PTGI														
Total	LRT	40.3	19.6	32	39.3	19.7	21	41.4	19.5	21	0.62	2	82	0.54
	CAU	36.7	21.1	26	37.5	20.6	22	38.4	19.3	20				
Relating to others	LRT	17.1	7.1	35	15.9	7.0	22	16.9	6.7	22	0.31	2	86	0.73
	CAU	14.2	8.2	26	15.3	7.7	23	15.2	8.5	20				
New possibilities	LRT	8.4	5.0	33	8.3	4.8	21	9.5	4.9	22	0.85	2	93	0.43
	CAU	7.3	5.8	28	8.0	5.3	24	7.3	4.7	21				
Personal strength	LRT	7.1	5.9	34	6.5	5.1	23	8.0	4.8	23	1.38	2	88	0.26
	CAU	7.1	5.4	28	7.8	5.7	24	7.6	5.3	21				
Spiritual change	LRT	1.2	2.2	35	1.0	2.2	23	1.1	2.2	23	0.29	2	92	0.75
	CAU	1.1	2.0	28	0.7	1.6	24	1.0	1.6	21				
Appreciation of life	LRT	6.5	4.2	34	6.9	4.0	23	7.1	4.3	23	0.77	2	89	0.47
	CAU	6.2	3.6	28	6.3	3.7	23	6.8	3.7	22				

Note. CRA = Caregiver Reaction Assessment; HADS = Hospital Anxiety and Depression Scale; PTGI = Posttraumatic Growth Inventory; LRT = Intervention group; CAU = Waiting-list control group - Care-as-usual; M = Mean; SD = Standard deviation; F = assessment x group; p = p-value; * = $p<.05$.

DISCUSSION

This study showed that LRT-MST targeting incurable ill cancer patients had no significant effect on their caregivers regarding symptoms of depression or anxiety, post-traumatic growth, or most of the subscales of caregiver burden. There was a significant difference on the course of self-esteem (subscale of the CRA) over time. We also found that 56% of the caregivers reported symptoms of anxiety and 30% symptoms of depression at baseline. These percentages are in line with data from a meta-analysis of Pitceathly and Maguire [5]. LRT-MST did not have a significant effect on symptoms of anxiety of depression among caregivers, nor among the patients themselves [9]. In our studies, we did not preselect participants with anxiety of depression, but included all patients and all caregivers. A meta-analysis using individual patient data showed that psychosocial interventions in general seem to be more effective when they target cancer patients with symptoms of anxiety or depression [23], which could explain our findings.

It is striking that LRT-MST also does not seem to be effective on other negative psychological constructs as negative caregiver burden (financial problems, lack of family support, and loss of physical strength) (present study) and despair (among patients [9]), but does seem to have a beneficial effect on positive mental health as self-esteem (among caregivers, present study) and ego-integrity (among patients [9]).

Assuming that patients talked about their memories during and after the intervention period with their informal caregivers and the positive (experienced) effect on ego-integrity of the patient, might explain the effect of LRT-MST on self-esteem of caregivers. While self-esteem in caregivers of patients in the control group decreased, self-esteem of caregivers of patients in the intervention group remained stable over time, which suggests that LRT-MST may have a protective effect. However, positive mental health is complex and involves various theoretical constructs [24]. Previous research showed that data from questionnaires on psychological well-being and personal meaning overlap to a large extent. Posttraumatic growth seemed to be a separate construct, which might explain why no effect was found on posttraumatic growth in the present study. However, the question remains whether this separate construct is an artefact of the different type of item response of the PTGI (which asks about how feelings differ from before cancer instead of how feelings are at the moment). Another question that remains unanswered is whether the intervention itself may trigger participants to respond differently on questionnaires targeting positive mental health compared to questionnaires targeting

psychological problems. LRT-MST clearly focusses on retrieving positive memories while actively avoiding negative memories. This may have been of influence on the questionnaire based data. More qualitative research is needed to understand these complex interrelations and operationalizations of positive and negative psychological constructs and the effect that LRT-MST may or may not have among advanced cancer patients and their informal caregivers.

Study limitations
This study had some limitations that should be considered. Firstly, the number of partners included in the study was limited which may have hampered the statistical power of the study and could explain not finding further significant effects. Also, for most partners item 16 (part of the subscale 'disrupted schedule') of the CRA was missing in the questionnaire by mistake. Therefore, we were unable to make assumptions about this subscale or total caregiver burden. Another limitation is the follow-up assessment being only 1 month after treatment, and longer-term effects remain unknown.

Clinical implications
LRT-MST targeting incurably ill cancer patients, may help their informal caregivers to maintain their sense of self-esteem. However, caregivers who suffer from psychological distress (which is common in this population) may be better off with a psychological intervention targeting themselves.

Conclusions
Many informal caregivers of incurably ill cancer patients experience symptoms of anxiety and depression. LRT-MST targeting incurably ill cancer patients does not seem beneficial for caregivers in reducing symptoms of depression and anxiety, negative aspects of caregiver burden, or facilitating post-traumatic growth. LRT-MST may have a protective effect on self-esteem of informal caregivers (positive aspect of caregiver burden).

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6

CHAPTER 7

General discussion

" *Wat hoopt u nog mee te maken in de komende tijd?* "

GENERAL DISCUSSION

The main aim of this dissertation was to obtain insight in the efficacy of the structured Life Review Therapy combined with memory specificity training (LRT-MST), named ''Dear Memories'' among incurable ill cancer patients. The hypotheses were that patients would experience improved ego-integrity and less despair, and that LRT-MST would be effective to improve the specificity of the autobiographical memory and quality of life, and to reduce symptoms of distress, anxiety and depression. Also, it was expected that the intervention, though delivered to patients, might have an indirect positive effect on their informal caregivers. In this final chapter, the overall findings are summarized and discussed, study limitations are described, and implications for clinical practice and future research are addressed.

Efficacy of LRT-MST

The randomized controlled trial (RCT) showed that LRT-MST had a positive effect on the course of ego-integrity in the intervention group compared to the control group (Chapter 4). This confirms our hypothesis and findings of other studies [1-5]. The findings of the subsequent qualitative study (Chapter 5), that aimed to obtain more in-depth insight in LRT-MST, supported the finding that LRT-MST has a beneficial effect on ego-integrity. Patients reported various effects that were related to "achieving ego-integrity". Due to (re-)evaluation of their lives, they obtained more awareness of positive aspects of their lives and they experienced more acceptance of negative life events. This was not only in the here and now, but in the nearby future (including end-of-life) as well. This beneficial effect of LRT-MST is in line with theories on the therapeutic effect of life review. Trueman and Parker [6] described that the procedure of recalling, evaluating, and integrating life experiences aims to achieve ego-integrity in the final stage of life. Huang et al. [7] noted that life review therapy "assists people to cope with feelings of loss, guilt, conflict, and defeat, and supports to identify and examine past experiences and achievements, enabling them to find meaning, resolve conflicts, make amends with friends and family, and finish incomplete work".

The RCT did not show a significant beneficial effect of LRT-MST on despair, symptoms of distress, anxiety or depression, or on health-related quality of life. This is in contrast to our hypotheses. There are some explanations for these results. Firstly, a recent meta-analysis of Kalter et al. [8] showed that psychosocial interventions targeting cancer patients are more effective when patients have symptoms of anxiety or depression.

The initial intention of our RCT on LRT-MST was to include incurable ill cancer patients with symptoms of depression. However, in the first phase of the project, fewer of the recruited patients had symptoms of depression than expected, and it was estimated that it would take at least 5 years to include the required number of participants, which was not feasible within the time frame of the project. Therefore, the inclusion criterion "symptoms of depression" was abandoned. The final study population had a relatively low level of symptoms of depression at baseline and there might have been a floor effect, explaining why the RCT showed no effect on symptoms of depression. This floor effect is also described in other studies [4,9,10]. Also, Holland et al. [11] suggested that despair is related to psychological distress and depressive symptoms, which might explain why no effects were found on any of these outcomes as well. Also, theories on life review therapy and the autobiographical memory are partly based on the hypothesis that depressive symptoms are related to a lack of specificity of the autobiographical memory and that training this specificity would reduce depressive symptoms. In this thesis, the effect of LRT-MST on the autobiographical memory was ambiguous. The quantitative results of the RCT (Chapter 4) did not show a significant effect on autobiographical memory, while in the qualitative study (Chapter 5) some patients reported that they "regained more memories than expected and that their ability to remember details and underexposed memories increased". Incurable ill cancer patients may have cognitive impairments due to brain metastases, adverse effects of treatment (chemotherapy or radiation), mood and sleeping disorders, medication effects or other various co-morbidities [12-14]. It is well possible that a part of the included patients had cognitive impairments limiting the potential for ameliorating specificity of autobiographical memory, which may have hampered (an effect of) LRT-MST training. Another possible explanation for these results might be that LRT-MST focusses on positive autobiographical memories and negative memories are actively avoided, while not every patient appreciates this approach (Chapter 5).

Among informal caregivers, LRT-MST did have a significant effect on self-esteem (a positive aspect of caregiving). Self-esteem of caregivers of patients in the control group (care as usual) decreased, while self-esteem of caregivers of patients in the intervention group remained stable over time. It could be that patients discussed their experiences with their informal caregivers. This might have resulted in reminiscing together (retrieving shared positive experiences or important moments of the relationship), more or improved communication, or having quality time as a couple. It could also be that

informal caregivers of the patients in the intervention group were inspired to review their own life with a positive effect on self-esteem.

No significant effects were found on negative aspects of caregiving nor on post-traumatic growth or on symptoms of depression and anxiety. An explanation for these findings might be that during this study the informal caregivers were still providing care for their loved ones, which in some caregivers could cause distress [15] or negatively affect psychological or physical well-being [16]. Also, post-traumatic growth differs from mental well-being, because the outcome measure (the Post Traumatic Growth Inventory) has a different type of item response. Participants are not asked to rate how they feel at the moment, but how their feelings differed from before the trauma [17]. Among caregivers in this study, this might explain why no effect was found on post-traumatic growth, because they were still facing the end of life of their loved ones.

For both patients and caregivers, it may also be that the time frame between baseline and follow-up measurements (eight weeks) was too short to measure any effect on symptoms of mental illness.

In conclusion, the LRT-MST intervention *Dear Memories* focussing on retrieving positive memories, had both in patients and indirectly on caregivers, a significant effect on mental well-being (ego-integrity, self-esteem) but not on symptoms of mental illness (despair, distress, symptoms of anxiety and depression, caregiver burden).

Mental health in palliative care: mental well-being and mental illness
Recently, Bohlmeijer and Westerhof [18] introduced a model for sustainable mental health, integrating positive psychological interventions into mental health care. This model reflects the growing awareness that mental health is not only the absence of mental illness, but also the presence of mental well-being as a related but separate dimension [19-23]. Whereas mental well-being not only reduces the risk of future incidence of mental illness [24-27], it is also valued as an important aspect by people receiving psychological treatment [28]. Our findings seem to support this distinction in the model and therefore we adapted this model targeting incurable ill cancer patients (Figure 1). Regarding the outcomes in our adapted model in the context of incurable cancer, various concepts of mental illness occur, such as (symptoms of) depression, anxiety, fear of suffering, fear of death, and despair [11,29]. Previous research also showed that theoretical concepts and definitions of mental well-being in cancer are complex

and vary throughout studies, as well patient reported outcome measures used in these studies. These concepts include dignity, meaning, post-traumatic growth, resilience, (spiritual) well-being, and ego-integrity [17,30].

Another component in this model refers to psychosocial adaption and how people cope with different challenges or moments in life. This ability to adapt can be undermined by dysfunctional cognitions, regulation of negative emotions and behaviour. For incurable ill cancer patients, cognitive impairment, denial, emotional avoidance of dealing with end-of-life issues and repetitive negative thinking may be particularly relevant barriers. In addition, the ability to adapt can also be promoted by enhancing regulation of positive emotions and strengthening positive resources such as use of strengths, self-compassion, meaning and optimism. It can be argued that LRT-MST builds positive resources such as positive emotions amongst others via retrieving positive memories, re-evaluation of life, benefit finding and a sense of coherence. In our qualitative study (Chapter 5) we found that several patients described improvement of their coping skills after partaking to LRT-MST.

An important component of the model are contextual factors such as ecological, social, historical and cultural factors. These factors could either positively or negatively influence a patient's barriers and resources, ability to adapt and mental health. In incurable ill cancer patients the role of informal and professional caregivers is vital. As described in Chapter 6, informal caregivers have various tasks which are important when providing care for incurable ill cancer patients. However, levels of distress of informal caregivers were high. Two previous meta-analyses [31,32] described that couples can be considered as an emotional system. It confirms a relationship between the patient's and the caregiver's psychological distress, and that if one is distressed that the other is more likely to become distressed as well. This emphasizes the influence of contextual factors and the relevance of addressing these (in professional healthcare). This also confirms the importance of offering interventions to informal caregivers themselves or to couples together.

A final component is the spectrum of psychological treatments and interventions. In the Netherlands, professional palliative care is well-organized via hospitals and primary care, but it is warranted to increase more awareness on psycho-oncological care to facilitate access to this type of palliative care [33]. In psycho-oncology, there are several evidence-based treatments and interventions. Some primarily focus on reducing

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barriers such as cognitive behavioural therapy; other interventions primarily focus on enhancing positive resources such as dignity therapy, meaning-centered therapy or hope-fostering interventions. Other interventions target both barriers and resources such as mindfulness-based interventions and life review therapy [8,29,34-37].

In this thesis, the focus was on LRT-MST and the results show that LRT-MST can be added to this spectrum of psychological interventions, especially to amplify positive resources and to improve mental well-being.
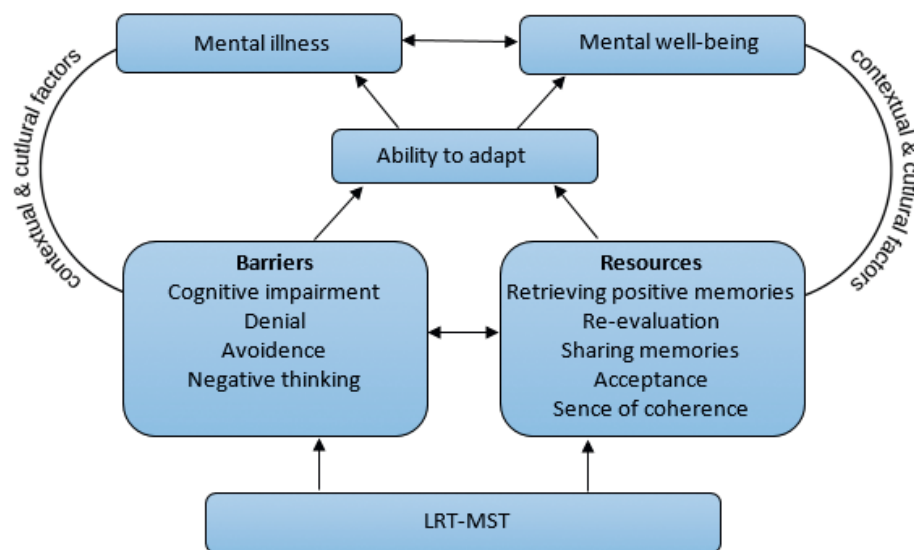

Figure 1. *LRT-MST and the conceptual model from Bohlmeijer & Westerhof [18].*

Limitations

At the start of this project, the aim was to include incurable ill head and neck cancer and lung cancer patients with clinically relevant symptoms of distress, anxiety or depression (Chapter 2). Inclusion appeared to be very difficult and therefore, soon after the start of recruiting, the strategy was changed and patients with other types of cancer and without symptoms of distress, anxiety or depression were included as well. This change in (patient)focus, to improve statistical rigor, and in line with previous studies that reported that life review therapy aims to achieve ego-integrity in the final stage of life [6], the NEIS (targeting ego-integrity and despair) was selected as primary outcome measure. Dropout rate was higher than expected, due to physical or mental deterioration or passing away of the patients. This is a problem also experienced in other studies targeting (advanced)

cancer patients [38,39]. Because of these limitations, generalizability of the findings in the advanced cancer population is hampered.

Furthermore, statistical significance does not directly mean clinical significance. To measure the efficacy of LRT-MST on ego-integrity and despair in the RCT (Chapter 4), a psychometric study was carried out on the Northwestern Ego-Integrity Scale (NEIS) (Chapter 3). This study showed that the NEIS has good psychometric characteristics to assess ego-integrity and despair among cancer patients. However, no cut-off scores or minimally important differences were defined regarding the primary outcome measure what makes it difficult to draw conclusions on clinical significance.

In the RCT (Chapter 4), the follow-up assessment was one month after the intervention. This time frame was chosen so that participation in the project would not put too much burden on the patients. However, insight into efficacy of LRT-MST in the longer term remains unknown.

Finally, the hypothesis that the intervention might have an indirect effect on informal caregivers was based on the assumption that patients would talk about their memories and experiences with their informal caregivers. However, this assumption was not investigated directly, as well as the (quality of the) relationship itself.

Clinical implications

This thesis provides several implications for clinical (psycho-oncological) practice. Addressing ego-integrity and despair among cancer patients does not seem to be routinely integrated in palliative care yet, while this is also important to maintain or improve mental well-being, when facing end-of-life.

LRT-MST had primarily a beneficial effect on mental well-being (ego-integrity), and patients reported also positive effects of the intervention on meaning, mastery, coping, self-acceptance, self-appreciation, mood and social life. Furthermore, several patients mentioned to highly appreciate the audio-recordings of the sessions as a legacy. Some family members contacted the researcher as well, also after losing their family member, to emphasize the value of these recordings which made it possible for them to hear their (deceased) loved one, cry, laugh and talk about their life stories. This "recording a legacy" might be a good addition to standard end-of-life (psychological) care.

However, no beneficial effect of LRT-MST was found on symptoms of mental illness. Some patients mentioned that LRT-MST sometimes induced "negative emotions" that needed to be addressed. Based on the outcomes of this study LRT-MST can be used in clinical practice among incurably ill cancer patients in general to address ego-integrity or psychological well-being. However, among patients with symptoms of mental illnesses, these symptoms must be closely monitored. In case symptoms become more severe, these patients might need a symptom targeted psychological intervention such as cognitive behavioural therapy.

In general, it was difficult to include participants and drop-out rate was high. Our intervention was offered as part of palliative care, and an important reason of these difficulties was that patients were often already too ill to participate. In oncological care it is often complicated to decide when a patient needs to be transferred from treatment with intent to cure to palliative care, for example because patient's disease progression is uncertain or a lack of awareness of the importance in palliative care [40]. However, research showed that among patients who are in palliative care, meaning and purpose of life are more important than physical symptoms or physical well-being [41]. This means that it is really important for healthcare professionals to be aware of timely referral to (psychological) palliative care. More integration of psycho-oncological care into standard (palliative) cancer care could be helpful to achieve this.

Last but not least, this research showed that part of the informal caregivers experienced psychological distress, including symptoms of anxiety and depression and that there was almost no indirect beneficial effect of LRT-MST on these (symptoms of) mental illness among informal caregivers. Because of their important role in providing informal care and research showed that they are not likely to seek help [15], it is important to pay attention to this group and offer them (psychological) support if needed. This could have an important impact on how patients and their caregiver deal with the disease and end-of life issues.

Recommendations for future research

This thesis provided evidence on the efficacy of LRT-MST among incurable ill cancer patients and their informal caregivers. The results also raised several new questions that need future research.

Regarding the psychological intervention, more insight into LRT-MST is needed to further tailor LRT-MST to the needs of this specific group of patients and to further substantiate (cost-)efficacy. Future research on possible moderators and mediators is needed to get more insight in which patients are likely to benefit from LRT-MST and which (autobiographical) mechanisms are involved in the efficacy of the intervention. In this future research, it is also important to take possible cognitive impairments into account.

Also, despite the difficulties in this group, more longitudinal studies are recommended, preferably in patients with high levels of depressive symptoms on baseline as well. In this study LRT-MST was performed at home. Although it has proven to have value for palliative cancer patients, it is relatively costly and time consuming. Further studies are needed to investigate alternative formats, such as providing the intervention via the telephone of online.

Future studies might also investigate how informal caregivers could benefit from LRT-MST delivered to them directly [42]. In case it is delivered as couple therapy, it is important to investigate the quality of the relationship and the communication between partners, for example via the Couple Communication Scale (CCS) [43].

The model on sustainable mental health in palliative care (Figure 1), needs further evidence and refinement. Regarding the outcomes, more research is needed on the complexity of the concepts of the outcomes on mental well-being and on mental illness, as well as associations and interactions between these groups of outcomes. Further research is also needed to get more insight into the prevalence of ego-integrity and despair of patients and their informal caregivers in palliative care in larger study populations. Also, the NEIS as measurement instrument needs further investigation, for instance to establish cut-off scores to make it useful in clinical practice as well.

Conclusion

This thesis provided evidence that life review therapy combined with memory specificity training (LRT-MST) is effective in improving or maintaining some aspects of mental well-being in incurable ill cancer patients (ego-integrity) and their informal caregivers (self-esteem), but not in reducing symptoms of mental illness. A new model for sustainable mental health proposes that it is vital to offer both complaint-oriented and strength- or growth-oriented interventions. Our quantitative and qualitative results provide evidence for LRT-MST as a strength-based intervention. Furthermore, in-depth insight

into experiences with and perceived outcomes of participating with LRT-MST has been provided and can be used in future research to investigate different aspects of and further tailor LRT-MST targeting incurable ill cancer patients. This intervention seems to be an addition in clinical practice and hopefully, LRT-MST will be used to (re-)evaluate many life stories of patients.

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APPENDICES

SUMMARY

Chapter 1 contains the general introduction of this thesis. In this Chapter, an overview is provided of the epidemiology and treatment of cancer and palliative care, and the challenges this disease and its treatment puts on patients and their informal caregivers. Also, life review therapy is introduced including its components: autobiographical memory, reminiscence, and life review. After that, the intervention "Dear Memories" (a life review therapy combined with autobiographical memory specificity training; LRT-MST) is described, which is at the heart of this dissertation. Also, the main aim and the hypotheses of this dissertation are presented. The main aim of this dissertation is to obtain insight in the efficacy of LRT-MST among incurable ill cancer patients. Based on previous research it is hypothesized that patients with incurable ill cancer who receive LRT-MST will experience more ego-integrity and less despair. It is also hypothesized that LRT-MST will be effective in improving the specificity of the autobiographical memory, and quality of life, and in reducing depressive symptoms among incurable ill cancer patients, and possibly among their partners. Finally, an outline of the dissertation is provided.

Chapter 2 describes the study protocol of a randomized controlled trial which aims to investigate the efficacy of LRT-MST among advanced cancer patients and their spouses. It was planned to include 150 cancer patients without curative treatment options and with a prognosis of > 3 months, with depressive symptoms (HADS-D and/or HADS-A >7, HADS-total >14) and randomly assign them to either the intervention group (LRT-MST) or control group (care-as-usual). LRT-MST is a brief psychological intervention (4 sessions in the home situation of the patient), in which patients are trained to retrieve positive specific memories from the past and thereby generating a coherent and meaningful autobiography. Primary outcome is depressive symptoms (HADS). Secondary outcomes are the presence or absence of clinical depression (MINI), specificity of Autobiographical Memory (AMT), quality of life (EORTC QLQ-PAL15), and ego-integrity and despair (Northwestern Ego-integrity Scale; NEIS). Spouses will not receive LRT themselves, but because it was expected that patients will talk about their memories during the intervention period with their spouses, it was hypothesized that LRT-MST may have a positive effect on them as well. Outcome measures among spouses were level of depressive symptoms (HADS), personal growth (PTGI), and caregiver burden (CRA).

In patients, the NEIS, HADS and EORTC QLQ-C15-PAL were assessed at baseline (T0), 1 month later (post-treatment; T1), and at 1 month follow-up (T2). AMT was assessed at T0 and T1. In caregivers, the HADS, PTGI, and CRA were assessed at T0, T1, and T2.

Chapter 3 presents a validation study evaluating the psychometric characteristics of the Northwestern Ego-integrity Scale (NEIS), a questionnaire on ego-integrity (the experience of wholeness and meaning in life, even in spite of negative experiences) and despair (the experience of regret about the life one has led, and feelings of sadness, failure and hopelessness), among cancer patients. A total of 164 cancer patients completed patient reported outcome measures on ego-integrity and despair (NEIS), psychological distress, anxiety and depression (Hospital Anxiety and Depression Scale; HADS), and quality of life (EORTC QLQ-C30 (cancer survivors, n=57) or EORTC QLQ-PAL15 (cancer patients without curative treatment options, n=107)). Principal Component Analysis was used to assess construct validity. Cronbach's alpha was used to assess internal consistency. Convergent validity was tested based on a priori defined hypotheses: a higher level of ego-integrity was expected to be related to a higher level of quality of life, and lower levels of distress, depression and anxiety; a higher level of despair was expected to be related to a lower level of quality of life, and higher levels of distress, depression and anxiety. The majority of all items (94.5%) of the NEIS were completed by patients and single item missing rate was below 2%. There were two subscales, labeled as Ego-integrity (5 items) and Despair (10 items) that had acceptable internal consistency (Cronbach's alpha .72 and .77, respectively). The Ego-integrity subscale was not significantly associated with quality of life, distress, anxiety, or depression. The Despair subscale correlated significantly (p<.001) with quality of life (r=-.36), distress (r=.59), anxiety (r=.63) and depression (r=.41). It was concluded that the NEIS has good psychometric characteristics to assess ego-integrity and despair among cancer patients.

Chapter 4 describes the multicentre randomized controlled trial (RCT) investigating the efficacy of LRT-MST. The protocol of this study as described in detail in Chapter 2 was slightly changed: the inclusion criteria of symptoms of depression was dropped and all incurable ill cancer patients could participate. Based on a two-sided effect size (Cohen's d) of .60 at one month post treatment (T2), an alpha of .05 and a statistical power (1-beta) of .80, we needed 45 patients in each study arm. With an expected drop-out rate of 20% we aimed to include 108 patients at baseline. A total of 107 patients were randomized to the intervention group (LRT-MST; n=55) or waiting-list control group (n=52). Linear mixed models (intention to treat) showed that the course of ego-integrity (not despair)

improved significantly over time (*p*=.007) in the intervention group compared to the waiting-list control group, with moderate, but statistically not significant, effect sizes at T1 (ES=.42) and T2 (ES=.48). Compliance rate was 69% and total dropout rate was 28%, both primarily related to disease progression and death. This study showed that LRT-MST seems effective to improve ego-integrity among cancer patients in palliative care.

Chapter 5 includes the outcomes of a qualitative study which provided in-depth insight into reasons to start with LRT-MST, experiences with LRT-MST, and perceived outcomes of LRT-MST in incurable ill cancer patients. Semi-structured interviews were conducted with 20 cancer patients in palliative care who participated in the RCT described in chapter 4. Patients started LRT-MST for intrinsic (e.g., potential benefit for personal well-being) and extrinsic reasons (e.g., potential benefit for future patients). Patients indicated mainly positive experiences with the intervention. They appreciated sharing their memories and regaining memories with a specific focus on retrieving positive memories. Some disliked the fact that negative memories could not be addressed. Most patients perceived positive outcomes of the intervention belonging to the overarching themes "ego-integrity" and "psychological well-being" in the here and now, as well as in the nearby future (including end-of-life). The results of this study are important to further tailor LRT-MST and for development or improvement of other psychological interventions targeting cancer patients in palliative care.

Chapter 6 investigated whether Life Review Therapy and Memory Specificity Training (LRT-MST) targeting incurable ill cancer patients, may also have a beneficial effect on careger burden, symptoms of anxiety and depression, and posttraumatic growth of the informal caregivers. Data was collected in the context of the RCT described in chapter 4. Informal caregivers of patients were asked to complete questionnaires at the same assessment measures as the patients. In total, 64 caregivers participated. Many caregivers experienced symptoms of anxiety (56%) and depression (30%). LRT-MST did not improve symptoms of depression and anxiety, negative aspects of caregiver burden or post-traumatic growth. LRT-MST may have a protective effect on self-esteem of informal caregivers (positive aspect of caregiver burden).

Chapter 7 provides a general discussion of this dissertation and the findings of the studies conducted in this dissertation are discussed in a broader perspective. This thesis provides evidence that life review therapy combined with memory specificity training (LRT-MST) is effective in improving or maintaining some aspects of mental well-being in incurable ill cancer patients (ego-integrity) and their informal caregivers (self-esteem), but not in reducing symptoms of mental illness (despair, symptoms of distress, anxiety or depression, or on health-related quality of life). The results are put in perspective using a new model for sustainable mental health proposing that it is vital to offer both complaint-oriented and strength- or growth-oriented interventions. Our quantitative and qualitative results provide evidence for LRT-MST as a strength-based intervention. Furthermore, in-depth insight into experiences with and perceived outcomes of participating with LRT-MST has been provided and can be used in future research to investigate different aspects of and further tailor LRT-MST targeting incurable ill cancer patients. This intervention seems to be an addition in clinical practice and hopefully, LRT-MST will be used to (re-)evaluate many life stories of patients.

SAMENVATTING

Hoofdstuk 1 geeft een algemene inleiding van dit proefschrift weer. In dit hoofdstuk wordt een overzicht gegeven van de epidemiologie en behandelingen van kanker en palliatieve zorg en van de uitdagingen die de ziekte en de behandelingen met zich meebrengen bij de patiënten en hun naasten. Ook wordt er uitleg gegeven over life review therapie, inclusief de componenten hiervan: autobiografisch geheugen, reminiscentie en life review. Tevens wordt de interventie "de Levensverhaalmethode - Dierbare herinneringen" (een life review therapie gecombineerd met autobiografische geheugentraining; LRT-MST) beschreven, wat de kern is van dit proefschrift. Verder worden de doelstelling en hypotheses van dit proefschrift beschreven. De doelstelling van dit proefschrift is om inzicht te krijgen in de effectiviteit van LRT-MST bij patiënten met kanker in de palliatieve fase (patiënten). Op basis van eerder onderzoek is de hypothese dat patiënten die LRT-MST ontvangen meer ego-integriteit en minder despair zullen ervaren. Ook is de verwachting dat LRT-MST zal leiden tot het verbeteren van de specificiteit van het autobiografisch geheugen en de kwaliteit van leven en het verminderen van depressieve klachten onder patiënten.

Hoofdstuk 2 bevat het onderzoeksprotocol van het onderzoek (randomized controlled trial; RCT), welke als doel heeft om de effectiviteit van LRT-MST te onderzoeken onder patiënten met kanker in de palliatieve fase en hun naasten. Het doel was om 150 patiënten met longkanker of hoofd-halskanker zonder curatieve behandelopties, met een prognose van meer dan drie maanden en met depressieve symptomen (HADS-D en/of HADS-A >7, HADS-total >14) te includeren, die at random toegewezen werden aan de interventiegroep (LRT-MST) of de controle groep (care-as-usual, standaard zorg). LRT-MST is een psychologische interventie (bestaande uit vier sessies bij de patiënt thuis), waarbij patiënten worden getraind om positieve specifieke herinneringen op te halen en op die manier een coherente en betekenisvolle autobiografie te genereren. De primaire uitkomstmaat is depressieve klachten (HADS). De secundaire uitkomstmaten zijn de aanwezigheid of afwezigheid van klinische depressie (MINI), de specificiteit van het autobiografisch geheugen (AMT), kwaliteit van leven (EORTC QLQ-PAL15) en ego-integriteit en despair (Northwestern Ego-integrity Scale; NEIS). Naasten zullen LRT-MST niet zelf ontvangen, maar er wordt verwacht dat patiënten over hun herinneringen zullen praten met hun naasten gedurende de interventie, waarbij de hypothese is dat LRT-MST ook een positief effect op hen zal hebben. Uitkomstmaten bij naasten waren de mate van depressieve klachten (HADS), posttraumatische groei (PTGI) en caregiver burden (ervaren zorglast door naasten) (CRA). Bij patiënten werden de NEIS, HADS en EORTC

QLQ-PAL15 onderzocht op de nulmeting (T0), één maand later (post-interventie; T1) en na één maand een follow-up (T2). AMT werd onderzocht op T0 en T1. Bij de naasten werden de HADS, PTGI en CRA onderzocht op T0, T1 en T2.

Hoofdstuk 3 beschrijft een validatie studie naar de psychometrische kenmerken van de Northwestern Ego-integrity Scale (NEIS). De NEIS is een vragenlijst gericht op ego-integriteit (het ervaren van coherentie en zinvolle betekenis van het leven, zelfs ondanks negatieve ervaringen) en despair (het ervaren van spijt over het leven dat is geleefd met gevoelens van verdriet, falen en hopeloosheid), onder patiënten met kanker. Een totaal van 164 patiënten met kanker hebben deelgenomen en vragenlijsten ingevuld gericht op ego-integriteit en despair (NEIS), psychologische distress, angst en depressie (Hospital Anxiety and Depression Scale; HADS), kwaliteit van leven (EORTC QLQ-C30 (overlevers van kanker, n=57) of EORTC QLQ-PAL15) (patiënten met kanker in de palliatieve fase, n=107). Principale-componenten analyse was gebruikt om de construct validiteit te onderzoeken en Cronbach's alpha om de interne consistentie te onderzoeken. De convergente validiteit was getest op basis van een a priori gevormde hypothese; er wordt verwacht dat een hoger niveau van ego-integriteit gerelateerd is aan een hogere kwaliteit van leven en lagere niveaus van distress, depressie en angst; er wordt verwacht dat een hoger niveau van despair gerelateerd is aan een lagere kwaliteit van leven en een hoger niveau van distress, depressie en angst. De meerderheid van alle items (94,5%) van de NEIS waren ingevuld door de patiënten en het percentage ontbrekende items was onder de 2%. Er zijn twee subschalen, Ego-integriteit (5 items) en Despair (10 items), met een acceptabele interne consistentie (Cronbach's Alpha .72 en .77, respectievelijk). De Ego-integriteit subschaal was niet significant geassocieerd met kwaliteit van leven, distress, angst of depressie. De Despair subschaal correleerde significant ($p<.001$) met kwaliteit van leven ($r=-.36$), distress ($r=.59$), angst ($r=.63$) en depressie ($r=.41$). Geconcludeerd wordt dat de NEIS goede psychometrische kenmerken heeft om ego-integriteit en despair in patiënten met kanker te onderzoeken.

Hoofdstuk 4 beschrijft een multicenter gerandomiseerd, gecontroleerd onderzoek (RCT) waarin de effectiviteit van LRT-MST bij patiënten met kanker in de palliatieve fase wordt onderzocht. Het protocol van dit onderzoek, zoals gedetailleerd beschreven in hoofdstuk 2, is enigszins aangepast: het inclusie criterium van symptomen van depressie is vervallen en alle patiënten met kanker in de palliatieve fase konden meedoen. Gebaseerd op een tweezijdige effectgrootte (Cohen's d) van .60 één maand post-treatment (T2), een alpha van .05 en een statische power (1-beta) of .80, waren er 45 patiënten in elke studie arm

nodig. Met een verwachte drop-out van 20% was het doel om 108 patiënten te includeren op baseline. In totaal werden 107 patiënten random verdeeld in de interventiegroep (LRT-MST; n=55) of in de wachtlijst controle groep (care-as-usual; n=52). Linear mixed model analyses (intention to treat) lieten zien dat het verloop van ego-integriteit (niet despair) significant verbeterde over tijd (*p*=.007) in de interventiegroep ten opzicht van de controle groep, met middelmatige, maar statistisch gezien geen significante, effectgroottes op T1 (ES=.42) en T2 (ES=.48). De compliance was 69% en de drop out was 28%, beiden vooral verklaard door ziekteprogressie en overlijden van de patiënten. Dit onderzoek laat zien dat LRT-MST effectief lijkt in het verbeteren van ego-integriteit bij palliatieve kankerpatiënten.

Hoofdstuk 5 laat de uitkomsten zien van een kwalitatief onderzoek welke inzicht geeft in de redenen om te starten met, de ervaringen met en de ervaren uitkomsten van patiënten met LRT-MST. Semigestructureerde interviews werden uitgevoerd bij 20 patiënten die deelgenomen hadden in de RCT zoals beschreven in hoofdstuk 4. Patiënten gaven aan met LRT-MST te starten om intrinsieke (bijvoorbeeld: mogelijke verbetering van het persoonlijk welzijn) en extrinsieke (bijvoorbeeld: mogelijk voordeel voor toekomstige patiënten) redenen. Patiënten gaven aan met name positieve ervaringen te hebben met de interventie. Zij waardeerden het delen en ophalen van hun herinneringen, waarbij de focus lag op het ophalen van positieve herinneringen. Sommigen gaven wel aan het vervelend te vinden dat negatieve herinneringen niet besproken werden. De meeste patiënten ervaarden positieve resultaten die passende waren bij de overkoepelende thema's "ego-integriteit" en "psychologisch welzijn" in het hier en nu, en in de toekomst (inclusief de laatste levensfase). De resultaten van deze studie zijn belangrijk om LRT-MST verder aan te passen en voor de ontwikkeling en verbetering van andere psychologische interventies gericht op patiënten met kanker in de palliatieve fase.

Hoofdstuk 6 heeft onderzocht of LRT-MST gegeven aan patiënten ook een effect heeft op de ervaren zorglast door naasten (caregiver burden), symptomen van angst en depressie en posttraumatische groei bij de naasten. De data was verzameld in de context van de RCT zoals beschreven in hoofdstuk 4. Naasten werden gevraagd vragenlijsten in te vullen op hetzelfde moment als de patiënten. In totaal hebben 64 naasten meegedaan. Veel van de naasten ervaren symptomen van angst (56%) en depressie (30%). LRT-MST bij patiënten heeft geen significant effect op symptomen van angst en depressie, de negatieve aspecten van caregiver burden of op posttraumatische groei. LRT-MST bij de patiënt heeft wel een effect op het zelfvertrouwen (positief aspect van caregiver burden) bij naasten.

Hoofdstuk 7 geeft een algemene discussie weer van dit proefschrift en de bevindingen van de gedane onderzoeken zijn in een breder perspectief geplaatst. Dit proefschrift laat zien dat LRT-MST effectief is voor het verbeteren van sommige aspecten van mentaal welzijn (ego-integriteit) bij patiënten met kanker in de palliatieve fase en hun naasten (zelfvertrouwen), maar niet effectief is voor het verminderen van symptomen van mentale ziekte (despair, symptomen van distress, angst en depressie of gezondheidsgerelateerde kwaliteit van leven). De resultaten zijn in een kader geplaatst van een nieuw model voor mentale gezondheid, welke voorstelt om in de klinische zorg aandacht te hebben voor zowel klachtgerichte als kracht/groeigerichte interventies. De uitkomsten van de kwantitatieve en kwalitatieve onderzoeken in dit proefschrift ondersteunen dat LRT-MST een kracht/groeigerichte interventie is. Verder geeft dit proefschrift inzicht in de ervaringen met en de ervaren uitkomsten van deelname aan LRT-MST welke gebruikt kunnen worden in toekomstig onderzoek om verschillende aspecten van LRT-MST verder te onderzoeken en LRT-MST nog passender te maken voor patiënten met kanker in de palliatieve fase. LRT-MST is een goede aanvulling voor de klinische praktijk en zal hopelijk gebruikt worden voor het (her)evalueren van vele levensverhalen.

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ABOUT THE AUTHOR

Gitta Kleijn was born on December 4th 1987 in Amsterdam, the Netherlands. She completed secondary education at Hermann Wesselink College in Amstelveen in 2006. After graduation she studied Psychology at the Vrije Universiteit Amsterdam. During her study she worked as a research-assistant at the university's department of Clinical, Neuro- and Developmental Psychology. In 2011 she obtained her master's degree in Clinical Psychology and started working as a PhD-student. She examined the efficacy of life review therapy combined with (autobiographical) memory specificity training (LRT-MST) targeting advanced cancer patients and their informal caregivers. This research was supervised by prof.dr. I.M. Verdonck – de Leeuw, prof.dr. W.J.M.J. Cuijpers and prof. dr. E.T. Bohlmeijer. In 2013 she started to combine her PhD with clinical work at Prezens, GGZ InGeest, where she completed a postdoctoral study in health care psychology (GZ-opleiding) in 2016. She continued working at Prezens until 2020. Currently, Gitta works as a health care psychologist for PsyQ and I-psy, Parnassia Group, where she combines clinical work, education and policy making.

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