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The effects of life review interventions on spiritual well-being, psychological distress, and quality of life in patients with terminal or advanced cancer: A systematic review and meta-analysis of randomized controlled trials

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Abstract:	Background: Life review interventions have been used to alleviate psycho-spiritual distress in people near the end of life. However, their effectiveness remains inconclusive. Aim: To evaluate the effects of therapeutic life review on spiritual well-being, psychological distress, and quality of life (QOL) in patients with terminal or advanced cancer. Design: A systematic review according to the PRISMA methodology. Data sources: Five databases were searched from their respective inception through August 2016 for relevant randomized controlled trials (RCTs). The effects of therapeutic life review were pooled across the trials. Standardized mean differences (SMDs) were calculated for the pooled effects. Heterogeneity was assessed using the I2 test. Study quality was assessed using the Cochrane criteria. Results: Eight RCTs met the inclusion criteria. The pooled results suggested a desirable effect of therapeutic life review on the meaning of life domain of spiritual well-being (SMD = 0.33; 95% CI, 0.12 to 0.53), general distress (SMD = -0.32; 95% CI, -0.55 to -0.09) and overall QOL (SMD = 0.35; 95% CI, 0.15 to 0.56) when compared to usual care only. Of the three outcomes examined, only the pooled effect on overall QOL remained statistically significant at follow-ups up to 3 months after the intervention (SMD = 0.82; 95% CI, 0.47 to 1.18). Conclusions: Therapeutic life review is potentially beneficial for people near the end of life. However, the results should be interpreted with caution due to the limited number of RCTs and associated methodological weaknesses. Further rigorously designed RCTs are warranted.

What is already known about the topic?

- Life review therapy has been applied for depression in the elderly for a long time; only in recent years has it been used to relieve psycho-existential suffering of people facing death.
- Therapeutic life review can delivered on the basis of different concepts such as dignity, meaning, forgiveness, and life completion.
- An increasing number of clinical trials have examined the efficacy and effectiveness of therapeutic life review in palliative care, but the findings are inconsistent.

What this paper adds?

- This paper presents the cumulative evidence from well-designed clinical trials of the effectiveness of therapeutic life review in palliative care.
- The available evidence suggest favorable effects of therapeutic life review on the meaning of life domain of spiritual well-being, general distress, and overall quality of life.
- This paper points out that further well-designed multi-centered studies are warranted.

Implications for practice, theory, or policy

- Therapeutic life review appears to hold promise as a psych-existential intervention for individuals near the end of life.
- It may be necessary to integrate therapeutic life review into end-of-life care practice so as to enhance the psycho-spiritual well-being of terminally ill patients.
- Given that therapeutic life review is often delivered in an individualized approach and a flexible way for terminally-ill individuals, a practical guideline to maintain an adequate degree of standardization may be required.

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The effects of life review interventions on spiritual well-being, psychological distress, and quality of life in patients with terminal or advanced cancer: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Life review interventions have been used to alleviate psycho-spiritual distress in people near the end of life. However, their effectiveness remains inconclusive.

Aim: To evaluate the effects of therapeutic life review on spiritual well-being, psychological distress, and quality of life (QOL) in patients with terminal or advanced cancer.

Design: A systematic review according to the PRISMA methodology.

Data sources: Five databases were searched from their respective inception through August 2016 for relevant randomized controlled trials (RCTs). The effects of therapeutic life review were pooled across the trials. Standardized mean differences (SMDs) were calculated for the pooled effects. Heterogeneity was assessed using the I^2 test. Study quality was assessed using the Cochrane criteria.

Results: Eight RCTs met the inclusion criteria. The pooled results suggested a desirable effect of therapeutic life review on the meaning of life domain of spiritual well-being (SMD = 0.33; 95% CI, 0.12 to 0.53), general distress (SMD = -0.32; 95% CI, -0.55 to -0.09) and overall QOL (SMD = 0.35; 95% CI, 0.15 to 0.56) when compared to usual care only. Of the three outcomes examined, only the pooled effect on overall QOL remained statistically significant at follow-ups up to 3 months after the intervention (SMD = 0.82; 95% CI, 0.47 to 1.18).

Conclusions: Therapeutic life review is potentially beneficial for people near the end of life. However, the results should be interpreted with caution due to the limited number of RCTs and associated methodological weaknesses. Further rigorously designed RCTs are warranted.

Keywords: cancer, end of life care, life review, oncology, palliative care, psychotherapy, quality of life, spirituality, systematic review

Background

Existential suffering is a major concern for many persons near the end of life, especially for those with a terminal illness and possible premature death.[1] It is "the distressed state of individuals confronting their own mortality and arising from the consequent feelings of powerlessness, hopelessness, meaninglessness, futility, remorse, death anxiety, and disruption of personal identity" (p.1022).[2] Thus, it is one of the most important factors that contribute to decreased QOL among those approaching death.[3] If left unattended, it may result in anxiety, depression, desire for a hastened death, and suicidal ideation.[1, 4] Existential or spiritual distress not only adds to patient and family suffering, but also presents a huge challenge for care professionals in the provision of end-of-life care.[2, 5, 6]

According to World Health Organization, relief of existential suffering in terminally ill patients is a major component of palliative care - an approach aiming to improve the QOL of patients and their families facing the problems associated with a life-threatening illness through prevention and relief of suffering as well as treatment of pain and other physical, psychosocial, and spiritual problems.[7] It is increasingly emphasized by care professionals, dying persons and family members. Practically, existential or spiritual concerns can be addressed using different approaches. In addition to the traditional approach which is often related to religious practice and connects human experience to nature and to the significant or sacred, therapeutic life review, which helps the patients to experience their connectedness to the moment, self and others so as to find meaning and purpose in one's life, is considered an effective psycho-spiritual intervention to alleviate existential/spiritual distress for people facing the challenge of death. It is a process of recalling, reevaluating, and reintegrating life experiences in the final stage of life.[8, 9] Unlike reminiscence which focuses on recalling memorable and pleasurable events from the past, therapeutic life review includes the intention of resolving and integrating past conflicts, thus giving new significance to an individual's life and bringing peace to the individual.[8-10] Various studies indicated that life review therapy might reduce depression in the elderly, enhance their life satisfaction, self-esteem, and QOL.[11-14]

According to a process model,[15] the beneficial effects of life review can be achieved through three different pathways: life completion, burden relief, and hope promotion. First, through

reviewing their life history, family lives, attainments and social roles, patients can achieve personally meaningful goals and confirm self-identity and/or self-continuity, resulting in increased feeling of life completion and peace as well as elevated spiritual well-being. Second, through reviewing memories of bringing up children and taking care of family members, patients can view their present state with balance, which may decrease their feeling of being a burden and thus relief psychological distress. Finally, life review interviews may improve patients' feelings about relationships with family members through a review of life history and allow patients to look forward to their progeny's future growth and increase their hope. The beneficial effect on hope has been evident among patients with advanced cancer.[16]

In recent years, an increasing number of clinical trials have examined the effects of therapeutic life review on different health outcomes among terminally ill patients, but the findings are inconsistent. Two systematic reviews have summarized relevant studies in the field,[9, 17] but the results of those studies have not been synthesized. The effectiveness of therapeutic life review on health for terminally ill patients remains inconclusive. To date, the literature lacks a systematic review and meta-analysis of the clinical trial evidence in this field. To facilitate evidence-based end-of-life care practices, results of relevant clinical trials must be pooled. Thus, the purpose of this systematic review was to critically assess and synthesize the clinical evidence available from RCTs of the effects of therapeutic life review interventions on spiritual well-being, psychological distress, and QOL among patients with terminal or advanced cancer.

Methods

This review followed the procedure recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18]

Eligibility criteria

The following criteria were applied for study selection. (1) Types of studies. All RCTs evaluating the effects of therapeutic life review on different health outcomes among patients with terminal or advanced cancer were included. Nonrandomized controlled trials and uncontrolled observational studies were excluded. (2) Types of participants. Study population of the intervention should be cancer patients near the end of life and aged 18 years and older.

Studies that included newly diagnosed cancer patients, usually at stage I or II, were excluded. Studies that included a substantial proportion of the patients with non-cancer terminal illness (>10%) were also excluded due to disparities in trajectories of decline leading to death and in physical and mental conditions.[19] (3) Types of intervention. Given the focus of this review on therapeutic life review in particular, rather than on spiritual interventions or psychotherapies in general, we excluded the studies that addressed here-and-now issues and the studies that connected the patients to nature or to the sacred, as well as the studies of reminiscence. As an individual approach was often applied in clinical practice to ensure that the patients felt free to reveal their life experiences, studies of group therapy were excluded. (4) Types of controls. All included studies had to include a control group of either no psychological intervention or a placebo intervention. (5) Types of outcomes. The included studies should include such outcomes as spiritual well-being, psychological distress, and/or QOL.

The literature search

The following electronic databases were searched initially in August 2016 and re-searched in February 2017: CINAHL, Cochrane Library, PsycINFO, PubMed, and Web of Science. The following terms were used with such a search string: "(life review or meaning of life intervention or meaning-making intervention or meaning reconstruction or narrative therapy or meaning-centered psychotherapy or preparation and life completion or dignity therapy or forgiveness therapy or legacy activities or reflective journaling or outlook or story-telling) and (terminally ill or seriously ill or life-threatening or end of life or palliative care or advanced cancer or advanced-stage cancer)." These terms were identified from relevant articles and review papers. We searched the databases for articles containing these terms in the title, abstract or keywords from their respective inception through February 2017. Although this review mainly included studies published in English, studies in other languages with abstracts in English were also examined if available. The reference lists of all included studies and relevant reviews were searched manually for other articles.

Data extraction and quality assessment

Study selection, data extraction and quality assessment were conducted by one main researcher

(CW) and then verified by other researchers (AC, CC). Any discrepancies were resolved by discussion. From each of the included trials, we extracted the following information: type of participants, number of participants, type of intervention; dosage of the intervention, duration of follow up, type of control, outcomes, and results. For the results of each trial, we extracted the data on mean, standard deviation and sample size for each outcome in each group at post-intervention and at follow-up for meta-analyses. Where median and range rather than mean and standard deviation were presented, the trial was not included in meta-analyses due to data incompatibility. Where the intervention group was compared with two different control groups (standard palliative care, client-centered care), we extracted the data of the control group with standard palliative care for meta-analysis. The data of another control group were not extracted since they might not be comparable with relevant data from other trials. Where outcomes were measured at more than one time-point during the follow-up, we used the data at the last time-point for meta-analyses of follow-up data. For expected but unavailable outcome data, we contacted the correspondence author via e-mail for more information.

The TIDieR (Template for Intervention Description and Replication) checklist[20] was used to assess the quality of intervention description in each article. The checklist contains 12 items, including the intervention name; intervention rationale; information materials used in the intervention, intervention procedures; intervention providers; mode of delivery of intervention; location of intervention delivery; frequency, intensity and dose of the intervention; intervention tailoring; intervention modifications; intervention fidelity assessment, and actual intervention adherence. The Cochrane Collaboration's assessment tool[21] was used to assess the quality of whole study for each trial. This tool assesses study quality based on seven criteria: adequate randomization; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data reporting; intention-to-treat analysis; selective outcome reporting; and other bias. Since blinding both participants and personnel are generally impossible for studies of face-to-face interventions, we only assessed if the outcome assessors were blind to the treatment allocation. Based on these criteria, four major categories of bias could be evaluated: selection bias (biased allocation), performance bias (unequal provision of care apart from the intervention), detection bias (biased assessment of outcomes), and attrition bias (biased occurrence of loss to follow up).[21] Reporting bias was assessed by examining

whether all expected outcome data were reported. "Other bias" was mainly assessed according to sample size justification, protocol registration, and other relevant information.

Data synthesis and analysis

The reported effects of intervention on each outcome in relevant RCTs were separately pooled using Review Manager 5.3 (http://ims.cochrane.org/revman). Standardized mean differences (SMDs) were calculated for the pooled effects, which were interpreted using the following rule of thumb: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.[22] A fixed-effects model was used when an outcome was measured by the same instrument in different studies, and a random-effects model was used for data synthesis when an outcome was measured by different measures. Heterogeneity was tested with the I^2 statistic. A I^2 value of less than 75% were considered as high degree of heterogeneity, 50-75% as moderate, and 25-50% as low degree of heterogeneity.[23] Sensitivity was examined by assessing the impact of a single study on the pooled overall effect through omitting one study in turn. Publication bias was not assessed due to the limited number of trials (< 10) included in each analysis.[21]

Results

Results of the literature search

Our searches identified 1387 records. After removal of duplications, 1012 records remained. Of them, 986 records were excluded after screening titles and abstracts. Full reports of 26 publications were acquired and 17 publications were further excluded, including 6 uncontrolled trials,[10, 24-28] 1 study with quasi experimental design,[29] 1 study with yoked control design,[30] and 9 RCTs that did not meet the inclusion criteria[31-39] (Figure 1).

Characteristics of included studies

Nine reports on 8 RCTs published between 2010 and 2014 met the inclusion criteria. They were conducted in Canada,[40, 41] Hong Kong,[42] Japan,[15] Mainland China,[43] Portugal,[44, 45] UK,[16] and USA.[46] All of them were published in English in peer-reviewed journals. Table 1 presents the characteristics of the included RCTs.

All included RCTs focused on patients with terminal or advanced cancer. The sample sizes ranged from 28 to 441, with a median of 80 and a total of 955 participants, including 427 in the intervention groups and 528 in the control groups, respectively. The types of intervention included short-term life-review,[15] life review,[43] dignity therapy,[16, 41, 44, 45] meaning-making intervention,[40] meaning of life intervention,[42] and meaning-centered psychotherapy.[46] Frequencies of intervention ranged from single session[40] to seven sessions,[46] with 2 sessions in four RCTs[15,16,42,44] and 3 sessions in two RCTs.[41,43] The participants were followed up in 6 RCTs[16,40,42-44,46] for a period of time ranging from 2 weeks[42] to 3 months.[40]

Nearly all of the included RCTs used a two-armed, parallel-group design, except one with three arms. The intervention groups were usually compared with standard palliative care or usual care groups. Only in one RCT, the life review intervention was compared to therapeutic massage.[46] Outcomes were measured at two time points (including baseline) in two RCTs,[15, 41] at three time points in 5 RCTs,[16, 40, 42, 43, 46] and at four time points in one RCT.[44] Spiritual well-being was assessed with the Functional Assessment of Chronic Illness Therapy-Spiritual (FACIT-Sp) Scale.[15, 40, 41, 46] Psychological distress was assessed with the Hospital Anxiety and Depression scale (HADS).[15, 16, 40, 44, 46] QOL was evaluated with different measures, including a single-item QOL scale,[43] a 2-item QOL scale,[16, 41] EuroQol five dimensions questionnaire (EQ-5D),[16] the McGill Quality of Life Questionnaire (MQOL),[40, 46] and Quality-of-Life Concerns in the End-of-Life questionnaire (QOLC-E).[42, 43]

Pooled effects of the life review therapies on different outcomes

Meta-analyses of the data were performed for 7 RCTs. Two publications on the same RCT were not included in the meta-analyses since the data with median and range rather than mean and standard deviation were presented in the publications.[44, 45] In another RCT,[46] the participants in the control group who received physical massage could be taken as those who received a placebo intervention. Although there is evidence that the use of massage therapy may reduce pain, anxiety and depression in oncological palliative care patients,[47] a RCT with terminally ill patients produced no evidence of benefit from massage, when evaluated with measures of global QOL and pain distress over the course of patient participation.[48] Moreover, there is no evidence of any effect of massage on spiritual well-being so far. Thus, the data of this group

were pooled with relevant data from other RCTs.

(1) Spiritual well-being

Four RCTs[15, 40, 41, 46] examined the effect of therapeutic life review on spiritual well-being. Of them, 3 RCTs[15, 40, 46] suggested a beneficial effect on the meaning domain and one RCT[46] suggested a beneficial effect on the faith domain of spiritual well-being immediately at post-intervention. Only one RCT suggested that the beneficial effect on the meaning domain remained 3 months later.[40] Their results were pooled, respectively. The pooled effect size was statistically significant only for the meaning domain at post-intervention (SMD = 0.33; 95% CI, 0.12 to 0.53; $p = 0.002$). There was a high degree of heterogeneity ($I^2 = 91\%$, Figure 2). After excluding the trial by Ando et al.,[15] the pooled effect become insignificant (SMD = 0.10; 95% CI, -0.12 to 0.32; $p = 0.36$; $I^2 = 30\%$). Exclusion of any other single trial did not significantly alter the pooled effect.

(2) Psychological distress

Six RCTs[15, 16, 40, 41, 44, 46] examined the effects of life review therapies on psychological distress. Of them, only one[15] suggested a desirable effect on general distress as indicated by the total score of HADS and another RCT[44] suggested beneficial effects on both anxiety and depression symptoms at post-intervention. No beneficial effect on psychological distress was observed at follow-up in any RCT. Apart from one RCT in which the data with median and range were presented,[44] the results of these trials were pooled for each outcome, and the pooled effect size was statistically significant only for general distress levels at post-intervention (SMD = -0.32; 95% CI, -0.55 to -0.09; $p = 0.007$). There was a high degree of heterogeneity ($I^2 = 93\%$, Figure 2). After excluding the trial by Ando et al.,[15] the pooled effect size become insignificant (SMD = -0.03; 95% CI, -0.29 to 0.22; $p = 0.79$, $I^2 = 4\%$). Exclusion of any other single trial did not significantly alter the pooled effect.

(3) Quality of life

Six RCTs[16, 40-43, 46] examined the effect of life review therapies on QOL. A single-item or 2-item scale was applied in 4 RCTs and a validated scale was applied in 5 RCTs (Table 1). The total

score of the validated scale was not available in one RCT.[43] The available results from these RCTs were pooled. The pooled effect size was statistically significant for overall QOL measured with single-item or 2-item scales at post-intervention (SMD = 0.35; 95% CI, 0.15 to 0.56; $p < 0.001$) and at follow-ups (SMD = 0.82; 95% CI, 0.47 to 1.18; $p < 0.0001$). There was a high degree of heterogeneity (I^2 = 91% and 90%, respectively, Figure 2). After excluding the trial by Xiao et al.,[43] the pooled effect sizes for overall QOL become insignificant at post-intervention (SMD = 0.10; 95% CI, -0.13 to 0.32; $p = 0.40$; I^2 = 0%) and at follow-ups (SMD = 0.04; 95% CI, -0.45 to 0.53; $p = 0.88$; I^2 = 0%). Exclusion of any other single trial did not significantly alter the pooled effect. The pooled effect size on the total scores of the validated QOL scales was marginally significant (SMD = 0.25; 95% CI, -0.03 to 0.54; $p = 0.08$).

Study quality assessment and risk of bias

Of the included eight RCTs, three were reported to be pilot studies[40, 42, 46] and additional three were registered phase II RCTs.[16, 41, 44] The study phase was unclear for the remaining two.[15, 43] As assessed with the TIDieR checklist (Table 2), nearly all of the included studies described the intervention in sufficient detail. Only one study[16] did not report the location of the intervention and three studies[41-43] did not address planned measurement of adherence. Actual adherence to the intervention was measured in all studies. All described the information materials, intervention procedures, and the timeframe and frequency of the intervention. Table 3 presents the study quality assessment for each trial. One RCT[41] can be ranked as a high-quality study. Allocation concealment was unclear in two RCTs,[42, 43] and blinding of outcome assessors was unclear in most of the included RCTs, except two.[40, 41] Incomplete outcome data were evident in all of the included RCTs, and only one RCT[43] perform intention-to-treat analyses. Attrition rates in the included RCTs ranged from 12%[15] to 60%.[16] Only in two RCTs,[41, 46] sample size was larger than 100. Free of selective reporting was unclear in 3 RCTs,[42-44] and free of other bias was unsure in most of the included RCTs.

Discussion

In this review, clinical trial evidence of the effects of therapeutic life review on different health outcomes in patients with terminal or advanced cancer was examined and synthesized. A total

of 8 RCTs was included. Our results of meta-analysis suggested favorable effects of therapeutic life review on spiritual well-being, psychological distress, and overall QOL. These findings are in line with the results of systematic reviews of the effects of spiritual interventions in patients with cancer.[49,50] Similar to spiritual interventions, however, our results did not support long-term effects of therapeutic life review interventions on spiritual well-being and psychological distress, possibly due to the deteriorating physical and mental condition of terminally-ill cancer patients.[49] Maybe the favorable effects of therapeutic life review could be maintained through regular review of the life review document or album. None of the included studies have addressed this point, which should be verified in further studies.

Specifically, our results suggest a favorable effect of therapeutic life reviews on the meaning of life domain but not on the faith domain of spiritual well-being. This is in line with the hypothesis proposed by Ando and colleagues that an effect on faith issues seems impossible following a short period of psychological intervention.[15] Our results suggested a desirable effect of therapeutic life review on general distress level but not on anxiety and depressive symptoms. Furthermore, our results indicated a desirable effect of therapeutic life review on overall QOL measured with single-item or 2-item scales. The effect on the total scores of validated QOL measures was only marginally significant. Of the three outcomes examined in this review, only the pooled effect size of life review interventions on overall QOL remained statistically significant at follow-ups up to 3 months after the intervention. Although a single-item scale cannot completely replace comprehensive and multidimensional questionnaire, it is a valid, reliable, and responsive instrument and is recommended in clinical trials,[51] particularly for patients who are seriously ill as comprehensive assessment is not practical for them.[52] Thus, our results regarding the effect of life review interventions on QOL are still informative.

A strength of this review may be that it provides high-quality cumulative evidence from well-designed clinical trials that therapeutic life review interventions are potentially effective in facilitating a sense of life meaning, alleviating psycho-existential suffering, and improving QOL for terminally-ill patients. Given the limited number of clinical trials and high risk of bias inherent in these trials, however, the results should be interpreted and generalized with caution. First, the therapeutic life review was provided to the participants through different strategies that were based on various concepts such as dignity, meaning, forgiveness, and life completion.

Although these strategies shared a core component of life review, their focuses and intensity of performance might be different. Moreover, there was a great disparity in the frequency or dosage of intervention and in the duration of follow ups across the trials. It also remains unclear about the optimal time to deliver the interventions. All of these may make it a bit difficult to compare the results across the trials. Given that therapeutic life review is often delivered in an individualized approach and a flexible way, a practical guideline to maintain an adequate degree of standardization may be required in this field so as to minimize the patient's burden and performance bias and to maximize effectiveness.

Second, high risk of attrition bias might be a particular concern for the included RCTs due to high attrition rates as a result of death or deterioration of some participants. In addition, few of the included studies had screened the participants by distress levels. This might have weakened the evidence since participants with less distress had little room to improve following intervention than those with more distress.[41, 46] Moreover, sample size was relatively small in most of the included RCTs, which might have resulted in type-II errors or inadequate power.

Third, although sequence-generation and allocation concealment were adequate in most of the included trials, it was rare and difficult to blind the participants and investigators to the face-to-face interviews. Thus, the desirable changes of some outcomes in the intervention groups might result from Hawthorne effects such as the expectations of the participants and researchers.[43] Furthermore, blinding of outcome assessors was not confirmed in six RCTs. Thus it was possible that detection bias might have been introduced in these trials.

Lastly and notably, the pooled effect for each outcome was statistically significant mainly due to the very large effect reported in one relevant trial. As shown in Figure 2, Ando and colleagues[15] reported a very large interventional effect on the meaning domain of spiritual well-being and on the general distress level, respectively. Xiao and colleagues[43] reported a very large effect on overall QOL measured with a single-item scale. After removing the trial from relevant model of meta-analysis, the pooled effect become insignificant. Thus, the available evidence on the effectiveness of therapeutic life review is not robust, and needs to be further confirmed. Given that the two aforementioned studies were conducted within the socio-cultural contexts different from that of other studies, the effectiveness of therapeutic life review for

individuals of different ethnicities or within different sociocultural contexts needs to be further examined and differentiated.

Our review has some limitations. The first one may be that the effects of different dosages and intensity of the interventions and the effects of different strategies were not differentiated due to the limited number of the included trials. These issues should be addressed in the future. Another limitation may be the potential incompleteness of the evidence reviewed. It is a common concern for any systematic reviews. In addition, we have not contacted with relevant authors to identify unpublished or ongoing studies. Thus, publication bias might have existed for the included studies and the effect sizes of the therapeutic life reviews might have been overestimated or underestimated. Finally, we did not include the participants with other terminal illnesses, which may limit the generalizability of the findings. Despite these limitations, our review is the first to synthesize the available evidence on the effectiveness of therapeutic life review interventions on different outcomes among terminally ill patients, which may provide insight for further studies. Given that end of life care is being included in the global health agenda,[53] the findings of this review may be useful for or informative to a wide range of professionals and practitioners.

Conclusions

In conclusion, this review shows that therapeutic life review interventions may be potentially effective in facilitating a sense of life meaning, alleviating psycho-existential suffering, and improving QOL among cancer patients near the end of life. Given the risk of bias in the included trials, further rigorously designed RCTs that adhere to accepted standards of trial methodology, include large-scale, well-defined, multi-centered samples, and use sensitive outcome measures are warranted.

Clinical implications

Therapeutic life review as an effective approach has been applied for depression in the elderly for a long period of time.[12] Only in recent years has it been used as a palliative care approach to relieve psycho-existential suffering of terminally ill patients. To date, therapeutic life review is not widely used in end-of-life care practice yet.[9] Despite the risk of bias in the included trails,

our results indicate that therapeutic life review interventions may be potentially promise in helping terminally ill patients to address their existential suffering, improve their QOL, and promote good death. Although the available evidence, as indicted by the pooled effects of meta-analyses, is not robust, seven of the included eight RCTs have suggested a favorable effect of therapeutic life review on one or more outcomes. Thus, it may be necessary to promote therapeutic life review as a palliative care approach and integrate it into end-of-life care practice so as to enhance the psycho-spiritual well-being of terminally ill patients. As pointed out by Chochinov and colleagues, the purpose and potential benefit of therapeutic life review for terminally ill patients is not solely the symptomatic relief of stress, but also for the prevention of distress, promotion of wellbeing, and establishment of a sense of personal meaning and life purpose.[41] Such practice may help to improve the quality of end-of-life care for individuals facing death, and to support the patients and their families in the best way.

Competing interests:

The authors declared that they have no competing interests.

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Table 1. Summary of included studies

Studies	Participants	N (pre-/post-)	Dosage of intervention	Follow up	Control	Outcome measures	Results
Ando et al., 2010[15]	Terminal cancer patients from palliative care units 65±14 years	IG:38/34 CG: 39/34	Two sessions with a one-week interval 30-60 min/session	-	General support only	1. FACIT-Sp-M 2. HADS	1. P < 0.001 2. P < 0.001
Hall et al., 2011[16]	Patients with advanced cancer who were referred to palliative care teams 65±18 years	IG: 22/12/8 CG:23/15/10	Two sessions 30-60 min/session	4 weeks	Standard palliative care	1. HADS 2. QOL (2 items) 3. QOL (EQ-5D)	1. NS 2. NS 3. NS
Henry et al., 2010[40]	Advanced ovarian cancer patients (stage III or IV) 55±9.7 years	IG: 15/12/12 CG: 13/12/12	1-4 sessions 30-90 min/session	3 months	Usual care	1. FACIT-Sp-M 2. MQOL 3. HADS	1. P = 0.04 2. P = 0.07 3. P = 0.54
Chochinov et al., 2011[41]	Terminal cancer patients with a life expectancy of 6 months or less 65.1±14.4 years	IG: 165/108 CG1: 140/111 CG2: 136/107	Three sessions 30-60 min/session	-	CG1: standard palliative care CG2: client-centred care (focusing on here-and-now issues)	1. FACIT-Sp 2. HADS 3. QOL (2 items)	1. P = 0.006** 2. P = 0.009 3. P = 0.001
Mok et al., 2012[42]	Patients with advanced-stage cancer from oncology wards 64.6±11.6 years	IG: 44/34/29 CG:40/38/29	2 sessions with a 2-3-days interval 15-60 min/session	2 weeks	Usual care	1. Overall QOL(single-item) 2. QOLC-E	1. P < 0.05 2. P < 0.05
Xiao et al., 2013[43]	Patients with advanced cancer from a home-based hospice 59±11 years	IG: 40/35/31 CG:40/37/30	3 sessions Once a week	3 weeks	Routine care	1. Overall QOL(single-item) 2. QOLC-E	1. P < 0.01 2. P < 0.01 for 5/8 subscales
Julião et al., 2014[44, 45]	Terminal patients from a palliative care unit (cancer patients over 92%) 66.1±12.9 years	IG: 39/31/22/17 CG:41/37/28/19	Two sessions 30-60 min/session	1 month	Standard palliative care	HADS	P = 0.043 for depression P = 0.013 for anxiety
Breitbart et al., 2012[46]	Patients with advanced cancer (stage III or IV) 54.4±11.6 years	IG: 64/41/33 CG: 56/37/34	7 sessions Once a week 60 min/session	2 months	Therapeutic massage	1. FACIT-Sp 2. MQOL 3. HADS	1. P < 0.001 2. P = 0.013 3. NS

CG: control group; EQ-5D: EuroQol five dimensions questionnaire; FACIT-Sp: Functional Assessment of Chronic Illness Therapy-Spiritual scale; FACIT-Sp-M: Functional Assessment of Chronic Illness Therapy-Spiritual scale-Meaning of life subscale; HADS: Hospital Anxiety and Depression Scale; IG: intervention group; MQOL: McGill Quality of Life Questionnaire; GSES: General Self-Efficacy Scale; BHS: Beck Hopelessness Scale; QOLC-E: Quality-of-Life Concerns in the End-of-Life questionnaire;

Table 2: The Template for Intervention Description and Replication (TIDieR) checklist

Studies	Name	Why	Materials	Procedures	Who	How	Where	When and how much	Tailoring	Modifications	Planned adherence	Actual adherence
Ando et al., 2010[15]	√	√	√	√	√	√	√	√	√	NA	√	√
Hall et al., 2011[16]	√	√	√	√	√	√	NS	√	√	NA	√	√
Henry et al., 2010[40]	√	√	√	√	√	√	√	√	√	NA	√	√
Chochinov et al., 2011[41]	√	√	√	√	√	√	√	√	√	NA	NS	√
Mok et al., 2012[42]	√	√	√	√	√	√	√	√	√	NA	NS	√
Xiao et al., 2013[43]	√	√	√	√	√	√	√	√	√	NA	NS	√
Julião et al., 2014[44]	√	√	√	√	√	√	√	√	√	NA	√	√
Breitbart et al., 2012[46]	√	√	√	√	√	√	√	√	√	NA	√	√

NA: not applicable; NS: not specified

Table 3 Quality assessment for included randomized controlled trials

Studies	Adequate sequence generation	Allocation concealment	Blinding of outcome assessors	Incomplete outcome data	Intention-to-treat analysis	Free of selective reporting	Free of other bias
Ando et al., 2010[15]	Y	Y	unclear	Y	N	Y	unsure
Hall et al., 2011[16]	Y	Y	unclear	Y	N	Y	unsure
Henry et al., 2010[40]	Y	Y	Y	Y	N	Y	unsure
Chochinov et al., 2011[41]	Y	Y	Y	Y	N	Y	Y
Mok et al., 2012[42]	Y	unclear	unclear	Y	N	unsure	unsure
Xiao et al., 2013[43]	Y	unclear	unclear	Y	Y	unsure	unsure
Julião et al., 2014[44]	Y	Y	unclear	Y	N	unsure	unsure
Breitbart et al., 2012[46]	unclear	Y	unclear	Y	N	Y	Y

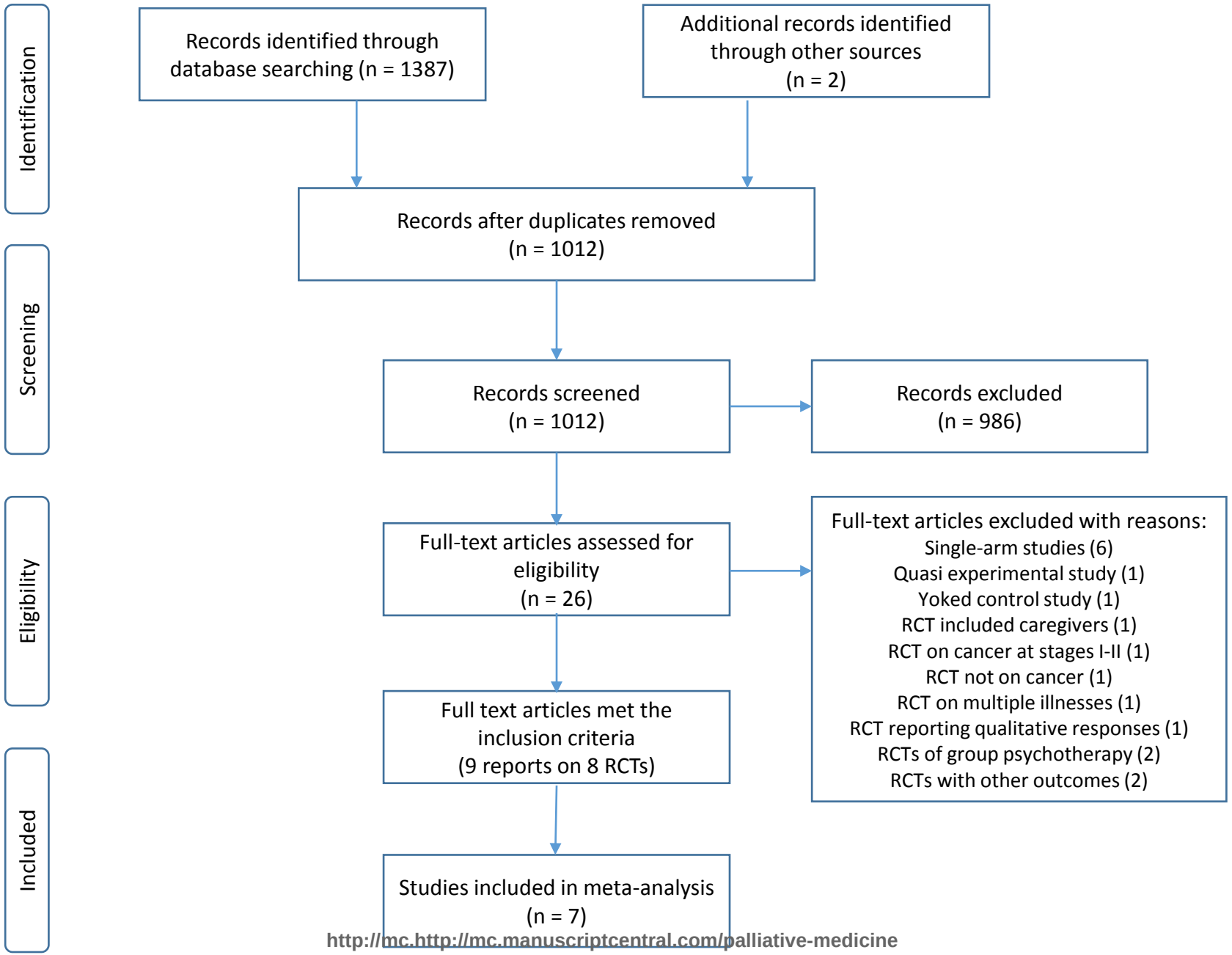
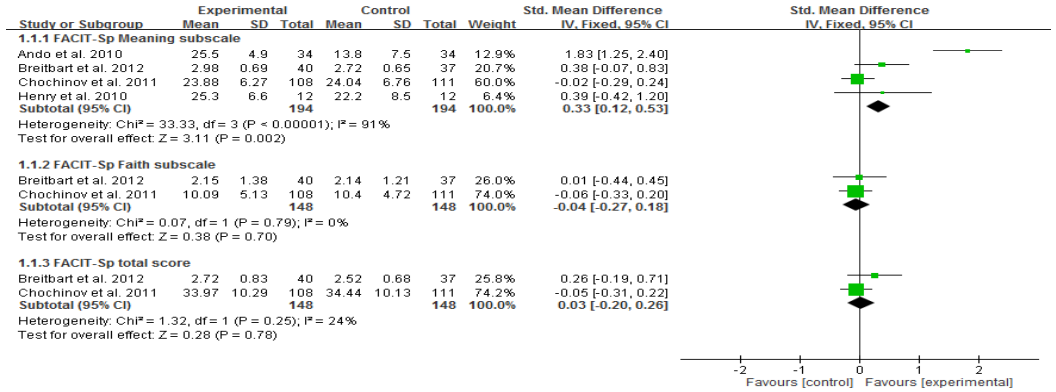
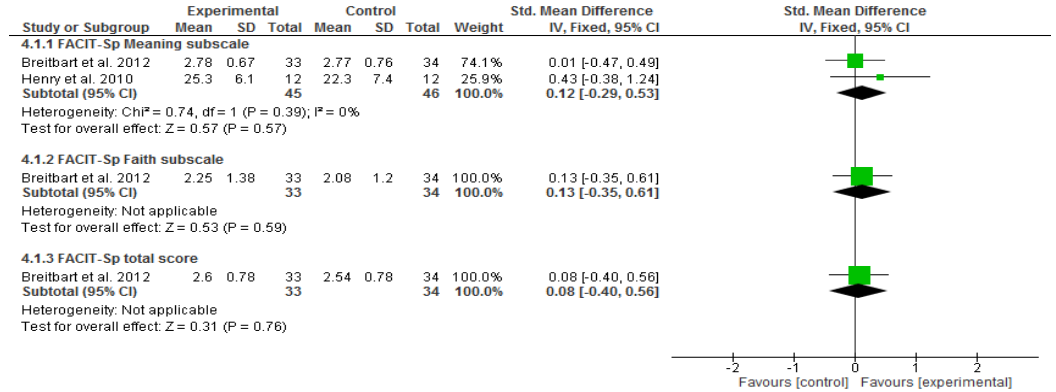


Figure 1. PRISMA Flow Diagram of study selection

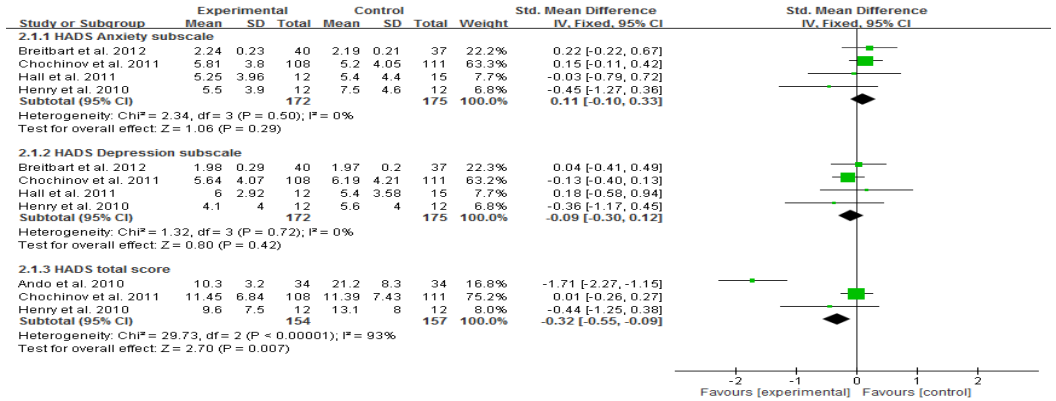
a. The effects on spiritual well-being at post-intervention



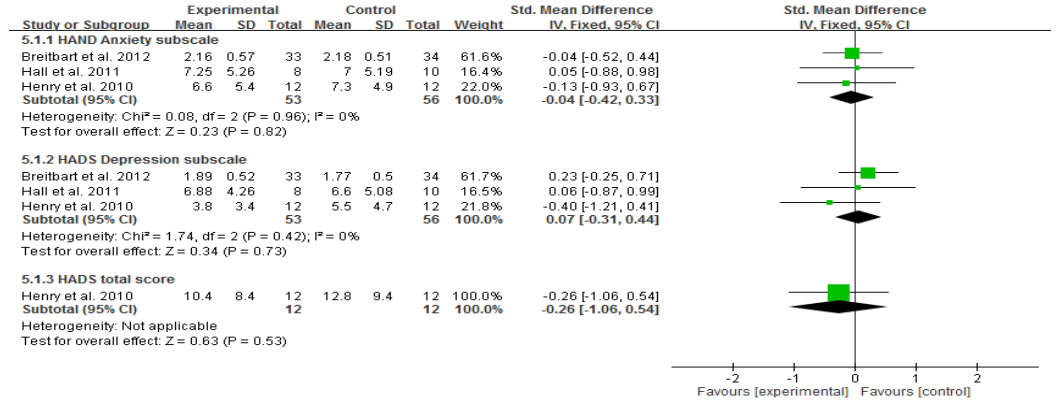
i. The effects on spiritual well-being at follow-ups



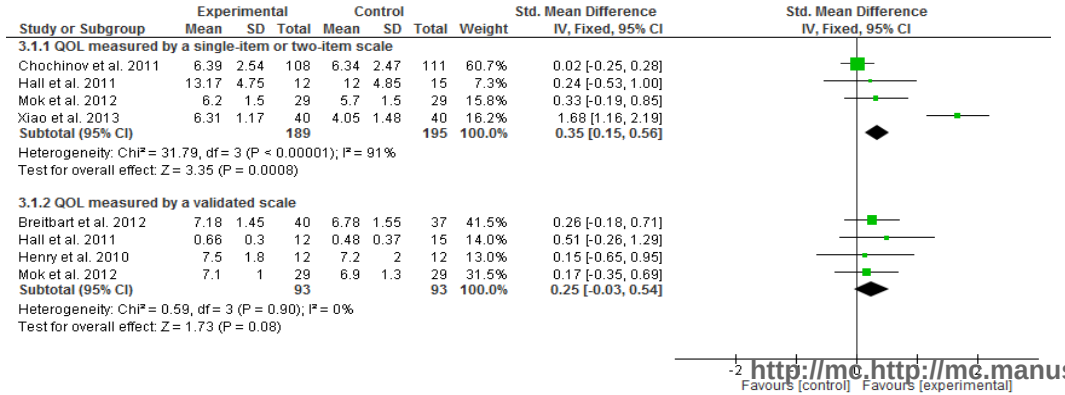
b. The effects on psychological distress at post-intervention



ii. The effects on psychological distress at follow-ups



c. The effects on quality of life at post-intervention



iii. The effects on quality of life at follow-ups

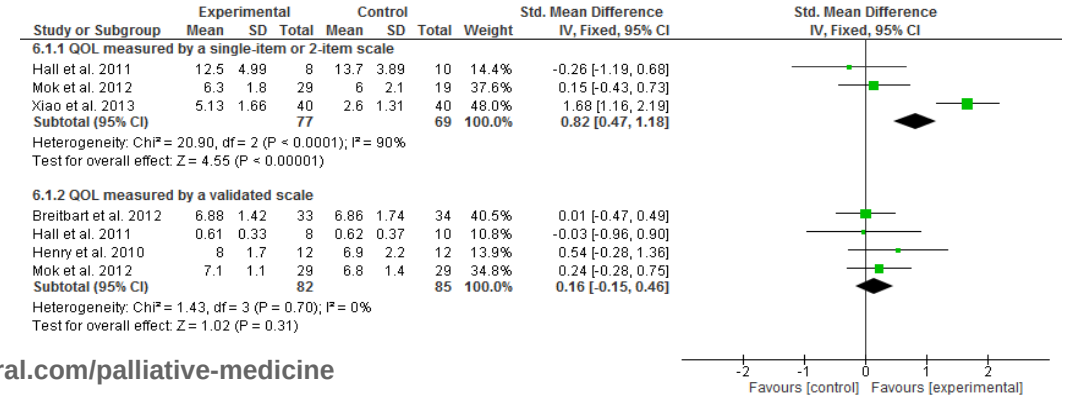


Figure 2 Forest plots of the meta-analyses of the data from relevant RCTs

Running title: *A review of therapeutic life review for terminal cancer patients*

4,278 words in the main text

246 words in the abstract

3 tables and 2 figures

The effects of life review interventions on spiritual well-being, psychological distress, and quality of life in patients with terminal or advanced cancer: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Life review interventions have been used to alleviate psycho-spiritual distress in people near the end of life. However, their effectiveness remains inconclusive.

Aim: To evaluate the effects of therapeutic life review on spiritual well-being, psychological distress, and quality of life (QOL) in patients with terminal or advanced cancer.

Design: A systematic review according to the PRISMA methodology.

Data sources: Five databases were searched from their respective inception through August 2016 for relevant randomized controlled trials (RCTs). The effects of therapeutic life review were pooled across the trials. Standardized mean differences (SMDs) were calculated for the pooled effects. Heterogeneity was assessed using the I^2 test. Study quality was assessed using the Cochrane criteria.

Results: Eight RCTs met the inclusion criteria. The pooled results suggested a desirable effect of therapeutic life review on the meaning of life domain of spiritual well-being (SMD = 0.33; 95% CI, 0.12 to 0.53), general distress (SMD = -0.32; 95% CI, -0.55 to -0.09) and overall QOL (SMD = 0.35; 95% CI, 0.15 to 0.56) when compared to usual care only. Of the three outcomes examined, only the pooled effect on overall QOL remained statistically significant at follow-ups up to 3 months after the intervention (SMD = 0.82; 95% CI, 0.47 to 1.18).

Conclusions: Therapeutic life review is potentially beneficial for people near the end of life. However, the results should be interpreted with caution due to the limited number of RCTs and associated methodological weaknesses. Further rigorously designed RCTs are warranted.

Keywords: cancer, end of life care, life review, oncology, palliative care, psychotherapy, quality of life, spirituality, systematic review

Background

Existential suffering is a major concern for many persons near the end of life, especially for those with a terminal illness and possible premature death.[1] It is "the distressed state of individuals confronting their own mortality and arising from the consequent feelings of powerlessness, hopelessness, meaninglessness, futility, remorse, death anxiety, and disruption of personal identity" (p.1022).[2] Thus, it is one of the most important factors that contribute to decreased QOL among those approaching death.[3] If left unattended, it may result in anxiety, depression, desire for a hastened death, and suicidal ideation.[1, 4] Existential or spiritual distress not only adds to patient and family suffering, but also presents a huge challenge for care professionals in the provision of end-of-life care.[2, 5, 6]

According to World Health Organization, relief of existential suffering in terminally ill patients is a major component of palliative care - an approach aiming to improve the QOL of patients and their families facing the problems associated with a life-threatening illness through prevention and relief of suffering as well as treatment of pain and other physical, psychosocial, and spiritual problems.[7] It is increasingly emphasized by care professionals, dying persons and family members. Practically, existential or spiritual concerns can be addressed using different approaches. In addition to the traditional approach which is often related to religious practice and connects human experience to nature and to the significant or sacred, therapeutic life review, which helps the patients to experience their connectedness to the moment, self and others so as to find meaning and purpose in one's life, is considered an effective psycho-spiritual intervention to alleviate existential/spiritual distress for people facing the challenge of death. It is a process of recalling, reevaluating, and reintegrating life experiences in the final stage of life.[8, 9] Unlike reminiscence which focuses on recalling memorable and pleasurable events from the past, therapeutic life review includes the intention of resolving and integrating past conflicts, thus giving new significance to an individual's life and bringing peace to the individual.[8-10] Various studies indicated that life review therapy might reduce depression in the elderly, enhance their life satisfaction, self-esteem, and QOL.[11-14]

According to a process model,[15] the beneficial effects of life review can be achieved through three different pathways: life completion, burden relief, and hope promotion. First, through

reviewing their life history, family lives, attainments and social roles, patients can achieve personally meaningful goals and confirm self-identity and/or self-continuity, resulting in increased feeling of life completion and peace as well as elevated spiritual well-being. Second, through reviewing memories of bringing up children and taking care of family members, patients can view their present state with balance, which may decrease their feeling of being a burden and thus relief psychological distress. Finally, life review interviews may improve patients' feelings about relationships with family members through a review of life history and allow patients to look forward to their progeny's future growth and increase their hope. The beneficial effect on hope has been evident among patients with advanced cancer.[16]

In recent years, an increasing number of clinical trials have examined the effects of therapeutic life review on different health outcomes among terminally ill patients, but the findings are inconsistent. Two systematic reviews have summarized relevant studies in the field,[9, 17] but the results of those studies have not been synthesized. The effectiveness of therapeutic life review on health for terminally ill patients remains inconclusive. To date, the literature lacks a systematic review and meta-analysis of the clinical trial evidence in this field. To facilitate evidence-based end-of-life care practices, results of relevant clinical trials must be pooled. Thus, the purpose of this systematic review was to critically assess and synthesize the clinical evidence available from RCTs of the effects of therapeutic life review interventions on spiritual well-being, psychological distress, and QOL among patients with terminal or advanced cancer.

Methods

This review followed the procedure recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18]

Eligibility criteria

The following criteria were applied for study selection. (1) Types of studies. All RCTs evaluating the effects of therapeutic life review on different health outcomes among patients with terminal or advanced cancer were included. Nonrandomized controlled trials and uncontrolled observational studies were excluded. (2) Types of participants. Study population of the intervention should be cancer patients near the end of life and aged 18 years and older.

Studies that included newly diagnosed cancer patients, usually at stage I or II, were excluded. Studies that included a substantial proportion of the patients with non-cancer terminal illness (>10%) were also excluded due to disparities in trajectories of decline leading to death and in physical and mental conditions.[19] (3) Types of intervention. Given the focus of this review on therapeutic life review in particular, rather than on spiritual interventions or psychotherapies in general, we excluded the studies that addressed here-and-now issues and the studies that connected the patients to nature or to the sacred, as well as the studies of reminiscence. As an individual approach was often applied in clinical practice to ensure that the patients felt free to reveal their life experiences, studies of group therapy were excluded. (4) Types of controls. All included studies had to include a control group of either no psychological intervention or a placebo intervention. (5) Types of outcomes. The included studies should include such outcomes as spiritual well-being, psychological distress, and/or QOL.

The literature search

The following electronic databases were searched initially in August 2016 and re-searched in February 2017: CINAHL, Cochrane Library, PsycINFO, PubMed, and Web of Science. The following terms were used with such a search string: "(life review or meaning of life intervention or meaning-making intervention or meaning reconstruction or narrative therapy or meaning-centered psychotherapy or preparation and life completion or dignity therapy or forgiveness therapy or legacy activities or reflective journaling or outlook or story-telling) and (terminally ill or seriously ill or life-threatening or end of life or palliative care or advanced cancer or advanced-stage cancer)." These terms were identified from relevant articles and review papers. We searched the databases for articles containing these terms in the title, abstract or keywords from their respective inception through February 2017. Although this review mainly included studies published in English, studies in other languages with abstracts in English were also examined if available. The reference lists of all included studies and relevant reviews were searched manually for other articles.

Data extraction and quality assessment

Study selection, data extraction and quality assessment were conducted by one main researcher

(CW) and then verified by other researchers (AC, CC). Any discrepancies were resolved by discussion. From each of the included trials, we extracted the following information: type of participants, number of participants, type of intervention; dosage of the intervention, duration of follow up, type of control, outcomes, and results. For the results of each trial, we extracted the data on mean, standard deviation and sample size for each outcome in each group at post-intervention and at follow-up for meta-analyses. Where median and range rather than mean and standard deviation were presented, the trial was not included in meta-analyses due to data incompatibility. Where the intervention group was compared with two different control groups (standard palliative care, client-centered care), we extracted the data of the control group with standard palliative care for meta-analysis. The data of another control group were not extracted since they might not be comparable with relevant data from other trials. Where outcomes were measured at more than one time-point during the follow-up, we used the data at the last time-point for meta-analyses of follow-up data. For expected but unavailable outcome data, we contacted the correspondence author via e-mail for more information.

The TIDieR (Template for Intervention Description and Replication) checklist[20] was used to assess the quality of intervention description in each article. The checklist contains 12 items, including the intervention name; intervention rationale; information materials used in the intervention, intervention procedures; intervention providers; mode of delivery of intervention; location of intervention delivery; frequency, intensity and dose of the intervention; intervention tailoring; intervention modifications; intervention fidelity assessment, and actual intervention adherence. The Cochrane Collaboration's assessment tool[21] was used to assess the quality of whole study for each trial. This tool assesses study quality based on seven criteria: adequate randomization; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data reporting; intention-to-treat analysis; selective outcome reporting; and other bias. Since blinding both participants and personnel are generally impossible for studies of face-to-face interventions, we only assessed if the outcome assessors were blind to the treatment allocation. Based on these criteria, four major categories of bias could be evaluated: selection bias (biased allocation), performance bias (unequal provision of care apart from the intervention), detection bias (biased assessment of outcomes), and attrition bias (biased occurrence of loss to follow up).[21] Reporting bias was assessed by examining

whether all expected outcome data were reported. "Other bias" was mainly assessed according to sample size justification, protocol registration, and other relevant information.

Data synthesis and analysis

The reported effects of intervention on each outcome in relevant RCTs were separately pooled using Review Manager 5.3 (http://ims.cochrane.org/revman). Standardized mean differences (SMDs) were calculated for the pooled effects, which were interpreted using the following rule of thumb: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.[22] A fixed-effects model was used when an outcome was measured by the same instrument in different studies, and a random-effects model was used for data synthesis when an outcome was measured by different measures. Heterogeneity was tested with the I^2 statistic. A I^2 value of less than 75% were considered as high degree of heterogeneity, 50-75% as moderate, and 25-50% as low degree of heterogeneity.[23] Sensitivity was examined by assessing the impact of a single study on the pooled overall effect through omitting one study in turn. Publication bias was not assessed due to the limited number of trials (< 10) included in each analysis.[21]

Results

Results of the literature search

Our searches identified 1387 records. After removal of duplications, 1012 records remained. Of them, 986 records were excluded after screening titles and abstracts. Full reports of 26 publications were acquired and 17 publications were further excluded, including 6 uncontrolled trials,[10, 24-28] 1 study with quasi experimental design,[29] 1 study with yoked control design,[30] and 9 RCTs that did not meet the inclusion criteria[31-39] (Figure 1).

Characteristics of included studies

Nine reports on 8 RCTs published between 2010 and 2014 met the inclusion criteria. They were conducted in Canada,[40, 41] Hong Kong,[42] Japan,[15] Mainland China,[43] Portugal,[44, 45] UK,[16] and USA.[46] All of them were published in English in peer-reviewed journals. Table 1 presents the characteristics of the included RCTs.

All included RCTs focused on patients with terminal or advanced cancer. The sample sizes ranged from 28 to 441, with a median of 80 and a total of 955 participants, including 427 in the intervention groups and 528 in the control groups, respectively. The types of intervention included short-term life-review,[15] life review,[43] dignity therapy,[16, 41, 44, 45] meaning-making intervention,[40] meaning of life intervention,[42] and meaning-centered psychotherapy.[46] Frequencies of intervention ranged from single session[40] to seven sessions,[46] with 2 sessions in four RCTs[15,16,42,44] and 3 sessions in two RCTs.[41,43] The participants were followed up in 6 RCTs[16,40,42-44,46] for a period of time ranging from 2 weeks[42] to 3 months.[40]

Nearly all of the included RCTs used a two-armed, parallel-group design, except one with three arms. The intervention groups were usually compared with standard palliative care or usual care groups. Only in one RCT, the life review intervention was compared to therapeutic massage.[46] Outcomes were measured at two time points (including baseline) in two RCTs,[15, 41] at three time points in 5 RCTs,[16, 40, 42, 43, 46] and at four time points in one RCT.[44] Spiritual well-being was assessed with the Functional Assessment of Chronic Illness Therapy-Spiritual (FACIT-Sp) Scale.[15, 40, 41, 46] Psychological distress was assessed with the Hospital Anxiety and Depression scale (HADS).[15, 16, 40, 44, 46] QOL was evaluated with different measures, including a single-item QOL scale,[43] a 2-item QOL scale,[16, 41] EuroQol five dimensions questionnaire (EQ-5D),[16] the McGill Quality of Life Questionnaire (MQOL),[40, 46] and Quality-of-Life Concerns in the End-of-Life questionnaire (QOLC-E).[42, 43]

Pooled effects of the life review therapies on different outcomes

Meta-analyses of the data were performed for 7 RCTs. Two publications on the same RCT were not included in the meta-analyses since the data with median and range rather than mean and standard deviation were presented in the publications.[44, 45] In another RCT,[46] the participants in the control group who received physical massage could be taken as those who received a placebo intervention. Although there is evidence that the use of massage therapy may reduce pain, anxiety and depression in oncological palliative care patients,[47] a RCT with terminally ill patients produced no evidence of benefit from massage, when evaluated with measures of global QOL and pain distress over the course of patient participation.[48] Moreover, there is no evidence of any effect of massage on spiritual well-being so far. Thus, the data of this group

were pooled with relevant data from other RCTs.

(1) Spiritual well-being

Four RCTs[15, 40, 41, 46] examined the effect of therapeutic life review on spiritual well-being. Of them, 3 RCTs[15, 40, 46] suggested a beneficial effect on the meaning domain and one RCT[46] suggested a beneficial effect on the faith domain of spiritual well-being immediately at post-intervention. Only one RCT suggested that the beneficial effect on the meaning domain remained 3 months later.[40] Their results were pooled, respectively. The pooled effect size was statistically significant only for the meaning domain at post-intervention (SMD = 0.33; 95% CI, 0.12 to 0.53; $p = 0.002$). There was a high degree of heterogeneity ($I^2 = 91\%$, Figure 2). After excluding the trial by Ando et al.,[15] the pooled effect become insignificant (SMD = 0.10; 95% CI, -0.12 to 0.32; $p = 0.36$; $I^2 = 30\%$). Exclusion of any other single trial did not significantly alter the pooled effect.

(2) Psychological distress

Six RCTs[15, 16, 40, 41, 44, 46] examined the effects of life review therapies on psychological distress. Of them, only one[15] suggested a desirable effect on general distress as indicated by the total score of HADS and another RCT[44] suggested beneficial effects on both anxiety and depression symptoms at post-intervention. No beneficial effect on psychological distress was observed at follow-up in any RCT. Apart from one RCT in which the data with median and range were presented,[44] the results of these trials were pooled for each outcome, and the pooled effect size was statistically significant only for general distress levels at post-intervention (SMD = -0.32; 95% CI, -0.55 to -0.09; $p = 0.007$). There was a high degree of heterogeneity ($I^2 = 93\%$, Figure 2). After excluding the trial by Ando et al.,[15] the pooled effect size become insignificant (SMD = -0.03; 95% CI, -0.29 to 0.22; $p = 0.79$, $I^2 = 4\%$). Exclusion of any other single trial did not significantly alter the pooled effect.

(3) Quality of life

Six RCTs[16, 40-43, 46] examined the effect of life review therapies on QOL. A single-item or 2-item scale was applied in 4 RCTs and a validated scale was applied in 5 RCTs (Table 1). The total

score of the validated scale was not available in one RCT.[43] The available results from these RCTs were pooled. The pooled effect size was statistically significant for overall QOL measured with single-item or 2-item scales at post-intervention (SMD = 0.35; 95% CI, 0.15 to 0.56; $p < 0.001$) and at follow-ups (SMD = 0.82; 95% CI, 0.47 to 1.18; $p < 0.0001$). There was a high degree of heterogeneity (I^2 = 91% and 90%, respectively, Figure 2). After excluding the trial by Xiao et al.,[43] the pooled effect sizes for overall QOL become insignificant at post-intervention (SMD = 0.10; 95% CI, -0.13 to 0.32; $p = 0.40$; I^2 = 0%) and at follow-ups (SMD = 0.04; 95% CI, -0.45 to 0.53; $p = 0.88$; I^2 = 0%). Exclusion of any other single trial did not significantly alter the pooled effect. The pooled effect size on the total scores of the validated QOL scales was marginally significant (SMD = 0.25; 95% CI, -0.03 to 0.54; $p = 0.08$).

Study quality assessment and risk of bias

Of the included eight RCTs, three were reported to be pilot studies[40, 42, 46] and additional three were registered phase II RCTs.[16, 41, 44] The study phase was unclear for the remaining two.[15, 43] As assessed with the TIDieR checklist (Table 2), nearly all of the included studies described the intervention in sufficient detail. Only one study[16] did not report the location of the intervention and three studies[41-43] did not address planned measurement of adherence. Actual adherence to the intervention was measured in all studies. All described the information materials, intervention procedures, and the timeframe and frequency of the intervention. Table 3 presents the study quality assessment for each trial. One RCT[41] can be ranked as a high-quality study. Allocation concealment was unclear in two RCTs,[42, 43] and blinding of outcome assessors was unclear in most of the included RCTs, except two.[40, 41] Incomplete outcome data were evident in all of the included RCTs, and only one RCT[43] perform intention-to-treat analyses. Attrition rates in the included RCTs ranged from 12%[15] to 60%.[16] Only in two RCTs,[41, 46] sample size was larger than 100. Free of selective reporting was unclear in 3 RCTs,[42-44] and free of other bias was unsure in most of the included RCTs.

Discussion

In this review, clinical trial evidence of the effects of therapeutic life review on different health outcomes in patients with terminal or advanced cancer was examined and synthesized. A total

of 8 RCTs was included. Our results of meta-analysis suggested favorable effects of therapeutic life review on spiritual well-being, psychological distress, and overall QOL. These findings are in line with the results of systematic reviews of the effects of spiritual interventions in patients with cancer.[49,50] Similar to spiritual interventions, however, our results did not support long-term effects of therapeutic life review interventions on spiritual well-being and psychological distress, possibly due to the deteriorating physical and mental condition of terminally-ill cancer patients.[49] Maybe the favorable effects of therapeutic life review could be maintained through regular review of the life review document or album. None of the included studies have addressed this point, which should be verified in further studies.

Specifically, our results suggest a favorable effect of therapeutic life reviews on the meaning of life domain but not on the faith domain of spiritual well-being. This is in line with the hypothesis proposed by Ando and colleagues that an effect on faith issues seems impossible following a short period of psychological intervention.[15] Our results suggested a desirable effect of therapeutic life review on general distress level but not on anxiety and depressive symptoms. Furthermore, our results indicated a desirable effect of therapeutic life review on overall QOL measured with single-item or 2-item scales. The effect on the total scores of validated QOL measures was only marginally significant. Of the three outcomes examined in this review, only the pooled effect size of life review interventions on overall QOL remained statistically significant at follow-ups up to 3 months after the intervention. Although a single-item scale cannot completely replace comprehensive and multidimensional questionnaire, it is a valid, reliable, and responsive instrument and is recommended in clinical trials,[51] particularly for patients who are seriously ill as comprehensive assessment is not practical for them.[52] Thus, our results regarding the effect of life review interventions on QOL are still informative.

A strength of this review may be that it provides high-quality cumulative evidence from well-designed clinical trials that therapeutic life review interventions are potentially effective in facilitating a sense of life meaning, alleviating psycho-existential suffering, and improving QOL for terminally-ill patients. Given the limited number of clinical trials and high risk of bias inherent in these trials, however, the results should be interpreted and generalized with caution. First, the therapeutic life review was provided to the participants through different strategies that were based on various concepts such as dignity, meaning, forgiveness, and life completion.

Although these strategies shared a core component of life review, their focuses and intensity of performance might be different. Moreover, there was a great disparity in the frequency or dosage of intervention and in the duration of follow ups across the trials. It also remains unclear about the optimal time to deliver the interventions. All of these may make it a bit difficult to compare the results across the trials. Given that therapeutic life review is often delivered in an individualized approach and a flexible way, a practical guideline to maintain an adequate degree of standardization may be required in this field so as to minimize the patient's burden and performance bias and to maximize effectiveness.

Second, high risk of attrition bias might be a particular concern for the included RCTs due to high attrition rates as a result of death or deterioration of some participants. In addition, few of the included studies had screened the participants by distress levels. This might have weakened the evidence since participants with less distress had little room to improve following intervention than those with more distress.[41, 46] Moreover, sample size was relatively small in most of the included RCTs, which might have resulted in type-II errors or inadequate power.

Third, although sequence-generation and allocation concealment were adequate in most of the included trials, it was rare and difficult to blind the participants and investigators to the face-to-face interviews. Thus, the desirable changes of some outcomes in the intervention groups might result from Hawthorne effects such as the expectations of the participants and researchers.[43] Furthermore, blinding of outcome assessors was not confirmed in six RCTs. Thus it was possible that detection bias might have been introduced in these trials.

Lastly and notably, the pooled effect for each outcome was statistically significant mainly due to the very large effect reported in one relevant trial. As shown in Figure 2, Ando and colleagues[15] reported a very large interventional effect on the meaning domain of spiritual well-being and on the general distress level, respectively. Xiao and colleagues[43] reported a very large effect on overall QOL measured with a single-item scale. After removing the trial from relevant model of meta-analysis, the pooled effect become insignificant. Thus, the available evidence on the effectiveness of therapeutic life review is not robust, and needs to be further confirmed. Given that the two aforementioned studies were conducted within the socio-cultural contexts different from that of other studies, the effectiveness of therapeutic life review for

individuals of different ethnicities or within different sociocultural contexts needs to be further examined and differentiated.

Our review has some limitations. The first one may be that the effects of different dosages and intensity of the interventions and the effects of different strategies were not differentiated due to the limited number of the included trials. These issues should be addressed in the future. Another limitation may be the potential incompleteness of the evidence reviewed. It is a common concern for any systematic reviews. In addition, we have not contacted with relevant authors to identify unpublished or ongoing studies. Thus, publication bias might have existed for the included studies and the effect sizes of the therapeutic life reviews might have been overestimated or underestimated. Finally, we did not include the participants with other terminal illnesses, which may limit the generalizability of the findings. Despite these limitations, our review is the first to synthesize the available evidence on the effectiveness of therapeutic life review interventions on different outcomes among terminally ill patients, which may provide insight for further studies. Given that end of life care is being included in the global health agenda,[53] the findings of this review may be useful for or informative to a wide range of professionals and practitioners.

Conclusions

In conclusion, this review shows that therapeutic life review interventions may be potentially effective in facilitating a sense of life meaning, alleviating psycho-existential suffering, and improving QOL among cancer patients near the end of life. Given the risk of bias in the included trials, further rigorously designed RCTs that adhere to accepted standards of trial methodology, include large-scale, well-defined, multi-centered samples, and use sensitive outcome measures are warranted.

Clinical implications

Therapeutic life review as an effective approach has been applied for depression in the elderly for a long period of time.[12] Only in recent years has it been used as a palliative care approach to relieve psycho-existential suffering of terminally ill patients. To date, therapeutic life review is not widely used in end-of-life care practice yet.[9] Despite the risk of bias in the included trails,

our results indicate that therapeutic life review interventions may be potentially promise in helping terminally ill patients to address their existential suffering, improve their QOL, and promote good death. Although the available evidence, as indicted by the pooled effects of meta-analyses, is not robust, seven of the included eight RCTs have suggested a favorable effect of therapeutic life review on one or more outcomes. Thus, it may be necessary to promote therapeutic life review as a palliative care approach and integrate it into end-of-life care practice so as to enhance the psycho-spiritual well-being of terminally ill patients. As pointed out by Chochinov and colleagues, the purpose and potential benefit of therapeutic life review for terminally ill patients is not solely the symptomatic relief of stress, but also for the prevention of distress, promotion of wellbeing, and establishment of a sense of personal meaning and life purpose.[41] Such practice may help to improve the quality of end-of-life care for individuals facing death, and to support the patients and their families in the best way.

Competing interests:

The authors declared that they have no competing interests.

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Table 1. Summary of included studies

Studies	Participants	N (pre-/post-)	Dosage of intervention	Follow up	Control	Outcome measures	Results
Ando et al., 2010[15]	Terminal cancer patients from palliative care units 65±14 years	IG:38/34 CG: 39/34	Two sessions with a one-week interval 30-60 min/session	-	General support only	1. FACIT-Sp-M 2. HADS	1. P < 0.001 2. P < 0.001
Hall et al., 2011[16]	Patients with advanced cancer who were referred to palliative care teams 65±18 years	IG: 22/12/8 CG:23/15/10	Two sessions 30-60 min/session	4 weeks	Standard palliative care	1. HADS 2. QOL (2 items) 3. QOL (EQ-5D)	1. NS 2. NS 3. NS
Henry et al., 2010[40]	Advanced ovarian cancer patients (stage III or IV) 55±9.7 years	IG: 15/12/12 CG: 13/12/12	1-4 sessions 30-90 min/session	3 months	Usual care	1. FACIT-Sp-M 2. MQOL 3. HADS	1. P = 0.04 2. P = 0.07 3. P = 0.54
Chochinov et al., 2011[41]	Terminal cancer patients with a life expectancy of 6 months or less 65.1±14.4 years	IG: 165/108 CG1: 140/111 CG2: 136/107	Three sessions 30-60 min/session	-	CG1: standard palliative care CG2: client-centred care (focusing on here-and-now issues)	1. FACIT-Sp 2. HADS 3. QOL (2 items)	1. P = 0.006** 2. P = 0.009 3. P = 0.001
Mok et al., 2012[42]	Patients with advanced-stage cancer from oncology wards 64.6±11.6 years	IG: 44/34/29 CG:40/38/29	2 sessions with a 2-3-days interval 15-60 min/session	2 weeks	Usual care	1. Overall QOL(single-item) 2. QOLC-E	1. P < 0.05 2. P < 0.05
Xiao et al., 2013[43]	Patients with advanced cancer from a home-based hospice 59±11 years	IG: 40/35/31 CG:40/37/30	3 sessions Once a week	3 weeks	Routine care	1. Overall QOL(single-item) 2. QOLC-E	1. P < 0.01 2. P < 0.01 for 5/8 subscales
Julião et al., 2014[44, 45]	Terminal patients from a palliative care unit (cancer patients over 92%) 66.1±12.9 years	IG: 39/31/22/17 CG:41/37/28/19	Two sessions 30-60 min/session	1 month	Standard palliative care	HADS	P = 0.043 for depression P = 0.013 for anxiety
Breitbart et al., 2012[46]	Patients with advanced cancer (stage III or IV) 54.4±11.6 years	IG: 64/41/33 CG: 56/37/34	7 sessions Once a week 60 min/session	2 months	Therapeutic massage	1. FACIT-Sp 2. MQOL 3. HADS	1. P < 0.001 2. P = 0.013 3. NS

CG: control group; EQ-5D: EuroQol five dimensions questionnaire; FACIT-Sp: Functional Assessment of Chronic Illness Therapy-Spiritual scale; FACIT-Sp-M: Functional Assessment of Chronic Illness Therapy-Spiritual scale-Meaning of life subscale; HADS: Hospital Anxiety and Depression Scale; IG: intervention group; MQOL: McGill Quality of Life Questionnaire; GSES: General Self-Efficacy Scale; BHS: Beck Hopelessness Scale; QOLC-E: Quality-of-Life Concerns in the End-of-Life questionnaire;

Table 2: The Template for Intervention Description and Replication (TIDieR) checklist

Studies	Name	Why	Materials	Procedures	Who	How	Where	When and how much	Tailoring	Modifications	Planned adherence	Actual adherence
Ando et al., 2010[15]	√	√	√	√	√	√	√	√	√	NA	√	√
Hall et al., 2011[16]	√	√	√	√	√	√	NS	√	√	NA	√	√
Henry et al., 2010[40]	√	√	√	√	√	√	√	√	√	NA	√	√
Chochinov et al., 2011[41]	√	√	√	√	√	√	√	√	√	NA	NS	√
Mok et al., 2012[42]	√	√	√	√	√	√	√	√	√	NA	NS	√
Xiao et al., 2013[43]	√	√	√	√	√	√	√	√	√	NA	NS	√
Julião et al., 2014[44]	√	√	√	√	√	√	√	√	√	NA	√	√
Breitbart et al., 2012[46]	√	√	√	√	√	√	√	√	√	NA	√	√

NA: not applicable; NS: not specified

Table 3 Quality assessment for included randomized controlled trials

Studies	Adequate sequence generation	Allocation concealment	Blinding of outcome assessors	Incomplete outcome data	Intention-to-treat analysis	Free of selective reporting	Free of other bias
Ando et al., 2010[15]	Y	Y	unclear	Y	N	Y	unsure
Hall et al., 2011[16]	Y	Y	unclear	Y	N	Y	unsure
Henry et al., 2010[40]	Y	Y	Y	Y	N	Y	unsure
Chochinov et al., 2011[41]	Y	Y	Y	Y	N	Y	Y
Mok et al., 2012[42]	Y	unclear	unclear	Y	N	unsure	unsure
Xiao et al., 2013[43]	Y	unclear	unclear	Y	Y	unsure	unsure
Julião et al., 2014[44]	Y	Y	unclear	Y	N	unsure	unsure
Breitbart et al., 2012[46]	unclear	Y	unclear	Y	N	Y	Y

Appendix 1: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6, Tables 1-3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Appendix 1: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10, Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14