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Existential distress in patients with advanced cancer and their caregivers: Study protocol of a longitudinal cohort study

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Abstract

Introduction

At the end of life, patients with advanced cancer and their informal caregivers may be confronted with many existential concerns. Despite the strong potential to alleviate existential distress through psychosocial interventions, existential distress and its impact on health care outcomes have not yet been studied systematically. We aim to investigate frequency, longitudinal trajectory and predictive impact of existential distress on relevant end-of-life outcomes. We further aim to determine patients' and caregivers' specific need for and utilization of psychosocial support.

Methods and Analysis

In this longitudinal cohort study we will consecutively recruit adult patients with advanced cancer and their caregivers from outpatient and inpatient clinics. Over a period of 12 months, particpants will complete self-report questionnaires at five points of assessment (sociodemographic and disease-related characteristics, existential distress, end-of-life outcomes, resources and support needs). At baseline and after six months, we will also conduct structured diagnostic interviews to assess mental disorders. Statistical analyses will include descriptive statistics to determine prevalence of existential distress, mental disorders and end-of-life outcomes; multiple linear and logistic regression analyses to calculate the predictive impact of existential distress on end-of-life outcomes; and growth mixture models to analyze longitudinal trajectories of existential distress.

Ethics and dissemination

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Results of this study will be presented at scientific conferences and published in peer-reviewed journals. Other forms of dissemination will include sharing results on the psychometric properties of the structured demoralization interview with international research groups and communication with health care professionals providing psychosocial treatment for patients and caregivers. Following scientific standards, our progress will be regularly updated on clinicaltrials.gov.

Study registration

NCT04600206

Strengths and limitations of this study

- longitudinal empirical data will allow for conclusions concerning frequency, persistence and course of existential distress throughout one year

- recruitment strategy includes enrolling a large, heterogeneous sample of patients with advanced cancer providing representative findings for a German healthcare setting
- profiles of existential distress can be applied by clinicians from multiple professions and may help to address these concerns easily and effectively in fast moving healthcare settings
- assessment of an extensive battery of instruments in highly distressed sample
- potentially high dropout rates due to patients' physical decline or death within the study period

Keywords

Advanced cancer, caregivers, death anxiety, demoralization, existential distress, longitudinal, mental disorders, palliative care, suicidal ideation and behavior

Introduction

In Germany, more than 230,000 individuals die from cancer each year. Due to an aging population and improvement in life-prolonging anticancer treatments, the number of patients and caregivers who face the existential consequences of living with advanced incurable cancer will strongly increase over the next years.[1,2] In about one third of the patients, multiple sources of distress lead to increased levels of depression, anxiety, and substantial physical symptom burden.[3–5] Informal caregivers are confronted with often conflicting demands of caring for a severely ill loved one and maintaining a focus on their own needs, resulting in high levels of psychological distress.[6–9] Although the existential domain of suffering has long been incorporated into a bio-psycho-social existential perspective in advanced cancer and palliative care,[10–12] existential distress has received little attention in systematic quantitative or prospective research in these populations.

Existential distress refers to a distinct domain of cancer-related distress. It may occur alongside other forms of distress, but can also arise independently, even when physical pain is treated, social support is available and no psychological disorder is present.[13,14] Due to the fundamental losses and changes advanced cancer can cause, emotional pain and despair may be experienced as "existential", similar to the distress described by existential philosophers, which arises from the finitude of life and the ramifications of existence.[15] Based on earlier reviews and conceptual literature,[15–21] we propose a taxonomy which integrates different expressions of existential concerns among patients and caregivers (Figure 1). Here, patients' and caregivers' existential distress is characterized as a fear of what will happen at death, uncertainty and unpreparedness, a sense of being a burden to others, a sense of profound loneliness, pointlessness, a violated sense of dignity, and grief about missed opportunities in life.

Operationalizations of existential distress[22] in cancer patients include, among other, demoralization[23], death anxiety[24,25], and dignity-related concerns[26] (Figure 1). Demoralization is defined by lowered morale and a perceived incapacity to cope that can become associated with a sense of helplessness and failure and a loss of self-worth, hope, and meaning in life. Current systematic reviews indicate that 20% of patients with advanced cancer experience demoralization.[27,28] Death anxiety refers to distress due to a shortened life expectancy, fears about uncontrollable suffering, worry about the impact of one's death on others and regret about missed opportunities in life.[24,25] A study in 382 outpatients with advanced cancer found significant death anxiety in 27% of the study participants.[29] Dignity-related concerns, such as perceived burdensomeness, were reported by up to 23% of the patients,[30,31] while 8% experienced a significantly impaired sense of dignity.[26] Other related categories of existential concerns include unpreparedness at the end of life (31%)[32], loss of control (16%), isolation (22%), uncompleted life tasks (7%) and loss of continuity (loss of role, loss of enjoyable activity and loss of being oneself) (10%)[33].

Especially spouses of cancer patients may experience identity-related existential concerns (20%)[34]. This may include role strain through the adoption of the caregiver-role and the associated changes in the relationship.[35] Caregivers may experience a change in their identity as a result of the extensive impact this often highly time-consuming function has on everyday life and the exertion of other important roles.[35–37] They may also suffer from the loss of the patient's identity, which is a frequent consequence of brain tumors.[38]

However, to date there is only limited research about the occurrence of existential distress in caregivers. While both, patients and caregivers, may be affected by demoralization and death anxiety, caregivers also face unique existential concerns including guilt, anticipatory grief[6,39] or despair about how to go on after their partner's death.[40] They often feel incompetent and unprepared for the task of caring for a loved one, which may lead to feelings of insufficiency and guilt for not providing appropriate care.[41] At the same time, caregivers often experience the pressure of maintaining hope and a positive attitude, preventing them from discussing own concerns.[42] Given this double challenge, caregivers may feel isolated and lonely. Whereas some couples manage to renegotiate roles and find ways to communicate about these issues, patients also tend to feel alienated by their caregivers' denial and avoidance of conflict.[43] Difficulties in coping with existential concerns has been associated with complicated grief.[44,45] Yet, there is a clear need for research on how caregivers may be affected by patients' existential distress and their own existential fears and hopelessness.[46] Especially because a lack of perceived relatedness in close relationships is a common source of existential distress for both, patients and caregivers.[47]

Cross-sectional studies do not only suggest a positive association between demoralization and an increased risk for adjustment, depressive and anxiety disorders, they also found positive associations between existential distress and suicidal ideation or the desire for hastened death.[48–50] Also, in the context of legalizing physician-assisted suicide in Canada, Li et al.[51] observed existential distress to be an important motive for these requests. A rare longitudinal study found an increase of existential distress over time.[52] Moreover, existential issues may contribute to receiving aggressive treatments in the last weeks of life.[53,54] Studies also indicate a positive relationship of religious coping and aggressive treatment at the end of life.[55,56] It is possible that existential distress is linked to a form of coping, which interferes with prognostic awareness and timely end-of-life discussions. Yet, the role of death anxiety, lack of preparedness, a strong hope for cure, and incongruence of patient and caregiver acceptance is currently unclear.[57]

Early palliative care interventions may respond to existential distress by increasing the use of approach-oriented coping,[58] which includes the acceptance of a difficult situation. The adoption of an upright, positive attitude toward unchangeable facts (e.g. incurable cancer) has been described as one possibility to discover meaning in life,[59] which in turn is associated with improved mental and physical health.[60] In contrast, a crisis of meaning has been shown to mediate the association between a stressor and health outcomes.[61] Although the importance of perceived meaning in life to the social and physical functioning, the psychosocial adaption and the experience of existential distress in cancer patients has thus been described in several studies,[60,62,63] little is known about the underlying mechanism that enables humans to find meaning in light of severe suffering.

Objectives

Existential distress may have profound consequences for health care outcomes of patients and their caregivers at the end of life. Despite their strong potential for alleviation through psychosocial interventions, clinicians struggle to recognize and address existential concerns.[64,65] In the shadow of prominent debates about autonomy at the end of life, research has fallen short of understanding the multifaceted factors that underlie existential distress. Due to the lack of systematic longitudinal studies, there is limited knowledge about the occurrence of existential distress, how it evolves over time, and its prospective impact on important end-of-life outcomes. Moreover, it is of substantial clinical relevance to assess caregivers' existential issues quantitatively, which have been mostly observed in qualitative research so far.

This study will systematically assess existential distress and investigate its impact on patient- and caregiver-relevant outcomes at the end of life. Therefore, we aim

1) to investigate the frequency, longitudinal trajectory and predictive impact of existential distress on patient- and caregiver-relevant end-of-life outcomes,
2) to determine patients' and caregivers' specific need for and utilization of psychosocial support with respect to existential concerns, and
3) to explore typical profiles of existential distress in patients and their caregivers.

Methods and analysis

Study design

Starting October 2020, we will conduct a longitudinal cohort study over a period of 12 months. This study period includes five points of assessment at baseline (T1), 3 months (T2), 6 months (T3), 9 months (T4) and 12 months (T5). The study was registered on clinicaltrials.gov: NCT04600206.

Participants and recruitment

We will consecutively recruit patients and their informal caregivers from outpatient and inpatient clinics of the University Cancer Center Hamburg and affiliated clinics. Eligible patients are at least 18 years old and are diagnosed with advanced cancer as defined by Union for International Cancer Control (UICC) stage IV solid tumor or stage III lung or ovarian tumor. Eligible caregivers (spouse or partner, any family member or friend) are at least 18 years old and care for a relative who is diagnosed with advanced cancer. Assessment will include patients with advanced cancer and their caregivers across all phases of advanced disease from diagnosis to terminal stages to reflect a cross-section of treatment settings, tumor entities, and time since diagnosis. Exclusion criteria for patients and caregivers are severe cognitive or physical impairment and insufficient ability to speak German to give informed consent and to complete the self-report questionnaires.

Procedures

We will obtain written informed consent from patients and caregivers prior to participation. Participants may withdraw informed consent at all times without being subject to any disadvantages. Patients and caregivers will complete paper-pencil self-report questionnaires to measure existential distress and respective support needs at each point of assessment. At baseline (T1) and after 6 months (T3), we will conduct structured diagnostic interviews face-to-face or via telephone to assess mental disorders. We will assess sociodemographic characteristics of patients and caregivers (age, gender, education, and socioeconomic data) using a standardized self-report questionnaire. We will extract disease and medical care-related characteristics (tumor entity, tumor stage, time since diagnosis and anticancer and psychopharmacological treatments) from patients' medical charts. We will further review patients' medical charts regularly for record of deceased patients and extraction of medical care data. For post-bereavement assessment, we will approach caregivers of deceased patients 3 months after a patient's death. We will conduct follow-up assessments via mail, telephone or upon patients' and caregivers' appointments for medical treatment at the cancer centers. For non-responder analyses, we will collect basic demographic and medical data from non-participants on a voluntary basis.

Measures

Table 1 shows self-report questionnaires and observer-rated instruments that will be completed by patients, caregivers or both.

Existential distress

We will assess *demoralization*[23] in patients and caregivers using the *Demoralization Scale-II (DS-II).*[66,67] The 16-item revised scale measures feelings of hopelessness and helplessness, and loss of meaning and purpose on two subscales (Meaning and Purpose, Distress and Coping Ability). Items are scored on a 3-point Likert-scale ranging from 0 (never) to 2 (often). Sum scores range from 0 to 32 for the total scale and from 0 to 16 for the subscales. The subscales and the total scale (Cronbach's α = 0.89) show good internal consistency.[67] The original scale[68] was validated in German cancer patients and showed good internal consistency (Cronbach's α = 0.84).[69]

We will assess *death anxiety* for patients and caregivers using the *Death and Dying Distress Scale (DADDS).*[24,25] The 15-item scale measures clinically significant distress with regard to concerns surrounding the patient's death. This includes psychosocial and existential concerns about missed opportunities and the loss of time, past regrets and uncertainty about the future and the burden of death on others. It also measures practical concerns about the process of dying, including fears about dying alone or with suffering or worries about its timing. Items are scored on a 6-point Likert-scale ranging from 0 (no distress) to 5 (extreme distress). The sum score ranges from 0 to 75. High scores indicate high death anxiety. A modified version of the scale validated in German cancer patients showed excellent internal consistency (Cronbach's α = 0.91).[70]. The version for informal caregivers (C. Lo, personal communication, May 2020) includes a question asking for the caregiver's relationship with the patient (spouse or partner, child, sibling, parent or guardian, other family member or friend).

We will assess *perceived relatedness* for patients and caregivers using the subscales *Dependence and Relatedness* of the *Depressive Experiences Questionnaire (DEQ).*[71,72]. The 18- and 8-item scales are distinct aspects of an overall Dependency factor. They measure interpersonal issues like feelings of helplessness, fear of rejection, and feelings of loneliness due to disruption in a relationship.[72] Items are scored on a 7-point Likert-scale ranging from 1 (disagree) to 7 (agree). According to the procedure described by Blatt et al.,[73] we calculate scores based on the factor scores derived from a confirmatory factor analysis. The authors provided us with a syntax for SPSS (D. Zuroff, personal communication, May 2020). The validated German version[74] showed acceptable to good internal consistency (Cronbach's α = 0.74 to 0.83).[75]

We will assess *loss orientation and life engagement* in patients and caregivers using the *Revised Loss Orientation and Life Engagement in Advanced Cancer Scale (LOLES).*[76] The 20-item scale measures preoccupation with death and dying, engagement in personally meaningful activities, and coping efforts including end-of-life preparation, distraction and hoping for a positive outcome. Items are scored on a 5-point Likert-scale ranging from 0 (not at all) to 4 (nearly all the time). High scores indicate high levels of loss orientation, life engagement, and coping efforts, respectively. The pilot version of the scale showed good internal consistency (Cronbach's α = 0.80 to 0.88).

We will assess *dignity-related concerns* in patients using the *Sense of Dignity Item (SDI).*[26,77] The item measures the loss of dignity on a 7-point Likert-scale ranging from 0 (no sense of loss of dignity) to 6 (extreme sense of loss of dignity). A score > 3 indicates a fractured sense of dignity. Further, we will assess dignity-related and *identity-related concerns* using the *Patient Dignity Inventory (PDI)*.[78] The 25-item scale measures the loss of sense of dignity in patients with terminal illness. For our purposes, we will only use the subscales assessing physical symptom distress and body image and loss of autonomy, according to the validated German version.[79] Items are scored on a 5-point Likert-scale ranging from 1 (not a problem) to 5 (overwhelming problem). Scores ≥ 3 indicate that a relevant problem is experienced. The German version of the scale showed excellent internal consistency (Cronbach's α = 0.96).[79]

We will assess *anticipatory grief* in caregivers using the short version of the *Marwit–Meuser Caregiver Grief Inventory (MM-CGI-SF).*[80] The 18-item scale measures pre-death grief on the subscales Personal Sacrifice and Burden, Heartfelt Sadness and Longing, and Worry and Felt Isolation. Items are scored on a 5-point Likert-scale ranging from 1 (strongly disagree) to 5 (strongly agree). Three items, which referred to aspects specific to dementia, were adapted to cancer populations (S. Marwit, personal communication, June 2020). The total sum score ranges from 0 to 90. High scores indicate a higher level of grief level. Originally developed for caregivers of patients with Alzheimer's disease, its psychometric properties have been confirmed among caregivers of patients with cancer. The total scale and the subscales showed good to excellent internal consistency (Cronbach's α = 0.80 to 0.90).

We will assess *guilt* in caregivers using the *Caregiver Guilt Questionnaire (CGQ).*[81] The 22-item scale measures aspects of guilt experienced by caregivers on the subscales *Guilt about doing wrong by the care recipient*, *Guilt about not rising to the occasion as caregivers*, *Guilt about self-care*, *Guilt about neglecting other relatives*, and *Guilt about having negative feelings towards other people*. Items are scored on a 5-point Likert-scale ranging from 0 (never) to 4 (always or most always). The total sum score ranges from 0 to 88. High scores indicate greater guilt. The total scale and the subscales showed acceptable to good internal consistency (Cronbach's α = 0.63 to 0.89).

End-of-life outcomes and prevalence of mental disorders

Information about *aggressiveness of care* including receipt of chemotherapy in the last two weeks of life, emergency hospital admissions or intensive-care treatment during the last month of life[82] will be obtained from medical chart reviews for deceased patients. Further, we will document the involvement of specialized palliative care services or hospice services.

We will assess the prevalence of *affective and anxiety disorders* in patients and caregivers using the *Structured Clinical Interview for DSM-5 (SCID-5).*[83] The semi-structured clinical interview measures mental disorders according to the DSM-5.[84] The German version showed acceptable internal consistency (Cronbach's α ≥ 0.70).[85]

We will assess the prevalence of *adjustment disorders* in patients and caregivers using the new *Adjustment Disorder Module of the Composite International Diagnostic Interview (CIDI*).[86] The structured interview measures the disorder according to the International Classification of Diseases (ICD-11).[87] If participants name one or more stressful events during the past 12 months, they are asked about accompanying symptoms, duration of symptoms and impairments in their professional or social life. The diagnosis will be determined according to the criteria described by Perkonigg and colleagues.[86]

We will assess the *desire for hastened death* in patients using the short form of the *Schedule of Attitudes Toward Hastened Death (SAHD-A).*[88] The 6-item version of the original instrument[89] measures a wish to die sooner than might occur by natural disease. Items are scored with either being true (1) or false (0). For the total score, we count the number of endorsed items, ranging from 0 to 6. High scores indicate high levels of desire for hastened death. We selected the six relevant items out of the validated German version (SAHD-D).[90] The short version showed good internal consistency (Cronbach's α = 0.83).[88]

We will assess *suicidal ideation* in patients and caregivers using the *Beck Scale for Suicidal Ideation (BSS)*.[91,92] The 21-item scale measures the intensity of suicidal tendencies with three statements for each item (e.g., 0 = I have a moderate to strong wish to live, 1 = I have a weak wish to live, 2 = I have no wish to live). The first five items can be used to screen for suicidal ideation. If items 4 and 5, measuring active and passive suicidal ideation, are scored with 0, participants are asked to skip to the items regarding previous suicidal attempts. The sum score ranges from 0 to 38 for the total scale and from 0 to 10 for the screening score. Higher values indicate stronger suicidal tendencies. The German version showed high internal consistency for the screening items Cronbach's α = 0.89) and the total scale (Cronbach's α = 0.88).[92]

We will assess *coping and demoralization* in patients and caregivers using the *Structured Interview for Psychological Adjustment and Demoralization* developed by Kissane and colleagues (Bobevski. I. & Kissane, D., 2019, Structured Interview for Psychological Adjustment and Demoralisation, unpublished clinical interview). The 36-item interview measures participants' sense of coping with any stressful event, including cancer and its treatment, with regard to level of avoidance, symptoms of demoralization, preoccupation, value of life, and functional impairment. Items can be answered with yes or no.

We will assess *complicated grief* in caregivers after the patient's death using the *Inventory of Complicated Grief (ICG)*.[93] The 19-item scale measures symptoms of complicated grief on based on the proposed criteria for DSM-5[84] on a single factor. Items are scored on a 5-point Likert-scale ranging from 0 (never) to 4 (always). The sum score ranges from 0 to 76. Scores ≥ 25 indicate experiences of complicated grief. The German version of the scale shows good internal consistency (Cronbach's α = 0.87).[94]

We will assess the *quality of dying and death* from the caregivers' perspective using the *Quality of Dying and Death Questionnaire (QODD)*.[95] After a patient's death, the questionnaire is usually administered as an interview, asking caregivers to evaluate the patients' dying experience during their last seven days or last month. In this study, we will administer a short 20-item version[96] as a self-report instrument. Caregivers indicate how they would rate each experience for the patient on a scale from 0 (terrible experience) to 10 (almost perfect experience). The score is calculated by adding up the ratings and dividing them by the number of items answered. To obtain a total score between 0 and 100, the result is multiplied by 10. Higher scores indicate a better quality of the dying experience. The adapted German version showed good internal consistency (Cronbach's α = 0.85).[97]

Control variables, resources, and support needs

We will assess *symptom burden* in patients using the *Memorial Symptom Assessment Scale (MSAS-SF).*[98] The 28-item scale measures the frequency and the distress of physical symptoms that may occur as a result of cancer or its treatment. Items are scored on a five-point Likert-scale ranging from 0 (not at all distressed) to 4 (very much distressed). For the total score, we count the number of physical symptoms reported by the patients. The scale shows good internal consistency (Cronbach's α = 0.87).

We will assess self-reported symptoms of *depression* and *anxiety* in patients and caregivers using the *Patient Health Questionnaire (PHQ-9)*[99] and the *Generalized Anxiety Disorder Questionnaire (GAD-7)*[100]. Both instruments measure symptoms of depression and anxiety based on DSM-5[84] criteria. Items are scored on a four-point Likert-scale ranging from 0 (not at all) to 3 (nearly every day). Sum scores range from 0 to 27 and 0 to 21, respectively. Scores ≥ 10 indicate moderate, scores ≥ 15 severe depression or anxiety. Both German versions showed good internal consistency (Cronbach's α = 0.89).[101,102]

We will assess *meaningfulness in life* and *crisis of meaning* in patients and caregivers using the subscales of the *Sources of Meaning and Meaning in Life Questionnaire (LeBe).*[103] The 5-item subscales measure perceived meaningful fulfillment and crisis of meaning. Items are scored on a 6-point Likert-scale ranging from 0 (totally disagree) to 5 (totally agree). Sum scores for each subscale range from 0 to 25. High scores indicate a greater sense of meaningfulness or a greater lack of meaning, respectively. Both scales showed acceptable to good internal consistency (Cronbach's α = 0.72 to 0.87).

We will assess the *need for and utilization of psychosocial support* for existential concerns in patients and caregivers using a standardized self-report questionnaire. It measures whether participants are still thinking about the existential concerns mentioned in the overall questionnaire, including fear of death and dying, fear of suffering, sense of pointlessness or hopelessness, sense of loss of dignity, preparation for the end of life, anticipatory grief, and existential loneliness. It will further assess whether participants wish to receive support dealing with this subject and who would be their preferred source of support (partner, family, friends, treating physician, psychologist/psychotherapist, other patients or caregivers). Moreover, participants will be asked whether they have previously utilized psychosocial support services.

Statistical methods

Power calculation

To determine the relative risk for a binary end-of-life outcome after 12 months, we base our sample size calculation on a multiple logistic regression model. The model includes existential distress at baseline and the covariates age, gender, and socioeconomic status. Because the test statistic in logistic regression analysis is based on a χ^2-distribution, the number of degrees of freedom (df) is equal to the number of regression weights in the model. Accordingly, we calculate the required sample size to reliably estimate the model by multiplying the minimum number of observations needed per df (n = 15) with the number of df (df = 4) and dividing the product by the ratio of positive events expected for the binary outcomes. To predict receipt of aggressive treatment, we use the mean frequency reported by the German studies of Dasch et al.[53] (38%) and Radbruch et al.[54] (10%). Thus, we require a sample of n = 250 ($n = \frac{15 \times 4}{0.24}$) for our analyses at 12-month follow-up. Based on previous experiences, we expect a drop-out rate of 50% due to death or loss of interest in participation[104] resulting in a required sample size of n=500 at baseline.

Statistical analysis

We will calculate descriptive statistics to determine sample and medical characteristics as well as the prevalence of existential distress, mental disorders and palliative care outcomes. We will estimate frequencies with 95% confidence intervals. To analyse the impact of existential distress at baseline on binary and continuous end-of-life and palliative care outcomes after 12 months, we conduct multiple linear and logistic regression. After testing for multicollinearity, we will control for demographic, physical and psychosocial variables.

We will analyse the longitudinal trajectory of existential distress across the 12-month study period using growth mixture models. These models estimate distinct groups of existential distress trajectories based on a structural equation-modelling framework. We will use latent class analysis to explore whether the measured existential concerns form distinct types of existential distress. If more than 5% of the observed values are missing, we will replace missing data using multiple imputation. To account for potential bias in the caregiver estimates regarding the occurrence of existential distress, we will apply weighting procedures to statistically control for differences between patients with and without participating caregivers. We will perform statistical analyses in SPSS[105] and RStudio with R.[106,107]

Patient and public involvement

The research questions and outcome measures are based on previous findings on the concerns of patients with advanced cancer and their caregivers as well as health care outcomes that were found relevant in this sample. Patients or the public were not involved in the design of the study. Patients and their caregivers are involved in conducting the study. We will ask them to complete self-report questionnaires and interviews, in order to answer our research question. We inform patients and caregivers that they are provided with the final results of the study upon request.

Ethics and dissemination

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional research ethics committee (Lokale Psychologische Ethikkommission am Zentrum für Psychosoziale Medizin, LPEK-0177). Informed consent will be obtained from all individual participants included in the study or their legal guardians.

This longitudinal study will provide unique systematic knowledge about patients' and caregivers' existential concerns. There is a need for quantitative studies focusing explicitly on existential concerns of caregivers, who in general tend to be overlooked and are also referred to as "hidden patients".[108,109] Accordingly, results of this study will be presented at scientific conferences and published in peer-reviewed journals. Other forms of dissemination will include sharing results on the psychometric properties of the structured demoralization interview with international research groups, in order to further examine the clinical relevance of using demoralization as a diagnostic category allowing for the diagnosis and treatment of demoralization alongside depression and adjustment disorder which has been proposed by Kissane et and colleagues.[110] Our clearly integrated data will contribute to the recognition of existential distress in these populations and provide the empirical foundation necessary to develop targeted interventions. In this context dissemination will include communication with health care professionals providing psychosocial treatment for patients and caregivers. Following scientific standards, our progress will be regularly updated on clinical trials.gov.

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Declarations

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Author contributions

SV, MH, CB, and KO designed the study and coordinate the research project. RP, AK and SV wrote the first draft of the manuscript. MH, CB, KO, and UK revised it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the study.

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Competing interests

All authors declare no conflict of interest.

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Figure 1. Taxonomy of existential concerns among patients and caregivers.

Table 1. Self-report questionnaires and observer-rated instruments

	Construct measured	**Patients**	**Caregivers**
Existential distress			
Demoralization Scale-II (DS-II)	Demoralization	●	●
Death Anxiety and Distress Scale (DADDS)	Death anxiety	●	●
Depressive Experiences Questionnaire (DEQ) Subscales: Dependence, Relatedness	Perceived relatedness	●	●
Revised Loss Orientation and Life Engagement in Advanced Cancer Scale (LOLES)	Loss orientation and life engagement	●	●
Dignity-Item (SDI)	Dignity-related concerns	●	
Patient Dignity Inventory (PDI)	Dignity-related concerns Identity-related concerns	●	
Marwit-Meuser Caregiver Grief Inventory (MM-CGI-SF)[a]	Anticipatory grief		●
Caregiver Guilt Questionnaire (CGQ)[a]	Guilt		●
End-of-Life outcomes and prevalence of mental disorders			
Disease- and medical care-related characteristics[b]	Aggressiveness of care	●	
Structured Clinical Interview for DSM-5 (SCID-5)[c]	Affective disorders Anxiety disorders	●	●
Adjustment Disorder-CIDI – New Module (AjD-CIDI)[c]	Adjustment disorder	●	●
Schedule of Attitudes Toward Hastened Death – Short Form (SAHD-A)	Desire for hastened death	●	
Beck Scale for Suicide Ideation (BSS)	Suicidal ideation	●	●
Structured Interview for Psychological Adjustment and Demoralisation[c]	Coping Demoralization	●	●
Inventory of Complicated Grief (ICG)[d]	Complicated grief		●
Quality of Dying and Death Questionnaire (QODD)[d]	Quality of dying and death		●
Control variables, resources, and support needs			
Memorial Symptom Assessment Scale – Short Form (MSAS-SF)	Symptom burden	●	
Patient Health Questionnaire-9 (PHQ-9)	Symptoms of depression	●	●
Generalized Anxiety Disorder Questionnaire-7 (GAD-7)	Symptoms of anxiety	●	●
Sources of Meaning and Meaning in Life Questionnaire (LeBe)	Meaningfulness in life Crisis of meaning	●	●
Need for and utilization of psychosocial support		●	●

[a] Not assessed after the patient's death
[b] Assessed via medical chart review
[c] Observer-rated interview
[d] Assessed only after the patients' death

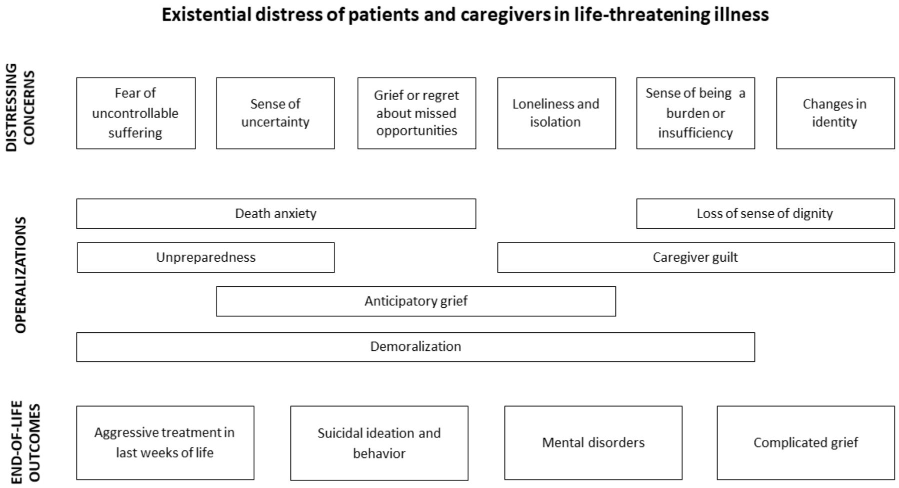

Figure 1. Taxonomy of existential concerns among patients and caregivers.

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Existential distress in patients with advanced cancer and their caregivers: study protocol of a longitudinal cohort study

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Abstract

Introduction

At the end of life, patients with advanced cancer and their informal caregivers may confront multiple existential concerns. Despite the strong potential to alleviate existential distress through psychosocial interventions, existential distress and its impact on health care outcomes have not yet been studied systematically. We aim to investigate the frequency, longitudinal trajectory, and predictive impact of existential distress on end-of-life outcomes. We further aim to determine patients' and caregivers' specific need for and utilization of psychosocial support for existential distress.

Methods

This longitudinal cohort study will consecutively recruit 500 patients with advanced cancer and 500 caregivers from oncological outpatient and inpatient clinics. Participants will complete self-report questionnaires (sociodemographic and disease-related characteristics, existential distress, end-of-life outcomes, resources, and support needs) at five points of assessment (at baseline and after 3, 6, 9, and 12 months). At baseline and 6-month follow-up, we will conduct structured diagnostic interviews to assess mental disorders. Statistical analyses will include descriptive statistics to determine the prevalence of existential distress, mental disorders and end-of-life outcomes; multiple linear and logistic regression analyses to calculate the predictive impact of existential distress on end-of-life outcomes; and growth mixture models to analyze longitudinal trajectories of existential distress.

Discussion

This study will provide comprehensive knowledge about patients' and caregivers' existential concerns. The longitudinal empirical data will allow for conclusions concerning the frequency and course of existential distress throughout one year. This important extension of existing cross-sectional research will contribute to further develop targeted psychosocial interventions. Profiles of existential distress may be applied by clinicians from multiple professions and help to address existential concerns effectively.

Strengths and limitations

- longitudinal empirical data will allow for conclusions concerning frequency and course of existential distress in patients and caregivers throughout one year
- recruitment strategy allows enrollment of a large, heterogeneous sample of patients with advanced cancer from a range of clinics and treatment facilities
- profiles of existential distress may be applied by clinicians from multiple professions and help to address existential concerns effectively
- extensive assessment of psychological distress in a potentially highly distressed and understudied sample
- potentially high dropout rates due to patients' physical decline or death within the study period

Ethics and dissemination

The study was approved by the institutional research ethics committee (reference number LPEK-0177). Results will be presented at scientific conferences and published in peer-reviewed journals. Other forms of dissemination will include sharing results on the psychometric properties of the structured demoralization interview with international research groups and communication with health care professionals providing psychosocial treatment for patients and caregivers. Following scientific standards, our progress will be regularly updated on clinicaltrials.gov.

Study registration

clinicaltrials.gov: NCT04600206

Keywords

Advanced cancer, caregivers, death anxiety, demoralization, existential distress, longitudinal, mental disorders, palliative care, suicidal ideation and behavior, desire for hastened death

Introduction

In Germany, more than 230,000 individuals die from cancer each year. Due to an aging population and improvement in life-prolonging anticancer treatments, the number of patients and caregivers who face the existential consequences of living with advanced incurable cancer will strongly increase over the next years.[1, 2] In about one third of cancer patients, multiple sources of distress are associated with increased levels of depression and anxiety.[3, 4] Informal caregivers are confronted with often conflicting demands of caring for a severely ill loved one and maintaining a focus on their own needs, resulting in high levels of psychological distress.[5–8] Although the existential domain of suffering has long been incorporated into a bio-psycho-social perspective in advanced cancer and palliative care,[9–11] existential distress has received little attention in systematic quantitative or prospective research in these populations.

Existential distress refers to a distinct domain of cancer-related distress. It may occur alongside other forms of distress, but can also arise independently, even when physical pain is treated, social support is available and no mental disorder is present.[12, 13] Due to the fundamental losses and changes advanced cancer can cause, emotional pain and despair may be experienced as "existential", similar to the distress described by existential philosophers, which arises from the finitude of life and the ramifications of existence.[14] Based on earlier reviews and conceptual literature,[15–20] we propose a taxonomy that integrates different existential concerns among patients and caregivers and links them to operationalizations of existential distress (Figure 1, first and middle part). According to this taxonomy, frequently described existential concerns including fear of what will happen at death, uncertainty, unpreparedness, a sense of being a burden to others, or a sense of profound loneliness, can be systematically measured by clearly defined concepts. Operationalizations of existential distress concepts in cancer patients include for example death anxiety,[21, 22] demoralization,[23] and dignity-related concerns[24, 25] (Figure 1, middle part). Figure 1 (middle and lower part) further illustrates the research model for association of these concepts with end-of-life outcomes.

Demoralization is defined by lowered morale and a perceived incapacity to cope that can become associated with a sense of helplessness and failure and a loss of self-worth, hope, and meaning in life.[26] Systematic reviews indicate that 20% of patients with advanced cancer experience demoralization.[27, 28] Death anxiety refers to distress due to a shortened life expectancy, fears about uncontrollable suffering, worry about the impact of one's death on others and regret about missed opportunities in life.[21, 22] A study in 382 outpatients with advanced cancer found significant death anxiety in 27% of the study participants.[29] Dignity-related concerns, such as perceived burdensomeness, were reported by up to 23% of the patients,[30, 31] while 8% experienced a significantly impaired sense of dignity.[25] Other related categories of existential concerns include unpreparedness at the end of life (31%),[32] loss of control (16%), isolation (22%), uncompleted life tasks (7%) and loss of continuity (loss of role, loss of enjoyable activity and loss of being oneself) (10%).[33]

Especially spouses of cancer patients may experience identity-related existential concerns (20%).[34] This may include role strain through the adoption of the caregiver-role and associated changes in the relationship.[35] Caregivers may experience a change in their identity as a result of the extensive impact of caregiving on everyday life and the exertion of other important roles.[35, 36] They may also suffer from the patient's perceived loss of identity.[37]

However, to date there is only limited research about the occurrence of existential distress in caregivers. While both patients and caregivers may be affected by demoralization and death anxiety, caregivers also face unique existential concerns including guilt, anticipatory grief,[5, 38] or despair about how to go on after their partner's death.[39] They often feel incompetent and unprepared for the task of caring for a loved one, which may lead to feelings of insufficiency and guilt for not providing appropriate care.[40] At the same time, caregivers often experience the pressure of maintaining hope and a positive attitude, preventing them from discussing own concerns.[41] Given this double challenge, caregivers may feel isolated and lonely. Whereas some couples manage to renegotiate roles and find ways to communicate about these issues, patients also tend to feel alienated by their caregivers' denial and avoidance of conflict.[42] This lack of perceived relatedness in close relationships is a common source of existential distress for patients and caregivers.[43] Moreover, difficulties in coping with existential concerns have been associated with complicated grief.[44, 45] Yet little is known on the extent to which caregivers are affected by their own existential fears and hopelessness.[46]

Among patients with advanced cancer, cross-sectional studies do not only suggest a positive association between demoralization and an increased risk for adjustment, depressive and anxiety disorders, they also found positive associations between existential distress and suicidal ideation or the desire for hastened death.[47–49] In the context of legalizing physician-assisted suicide in Canada, Li et al.[50] observed existential distress to be an important motive for these requests. A rare longitudinal study found an increase of existential distress over time.[51] Moreover, existential issues may contribute to receiving aggressive treatments in the last weeks of life.[52, 53] Studies also indicate a positive association of religious coping with aggressive treatment at the end of life.[54, 55] It is possible that existential distress is linked to a form of coping that interferes with prognostic awareness and timely end-of-life discussions. There is growing evidence that the ability to maintain a sense of meaning, acceptance and use of approach-oriented coping may contribute to better end-of-life outcomes.[56, 57] However, the role of death anxiety, lack of preparedness, a strong hope for cure, and incongruence of patient and caregiver acceptance for end-of-life care outcomes is currently unclear.[58] Although the impact of caregiver existential distress on patient end-of-life outcomes may be partially mediated by patient existential distress, a relevant impact may be expected.[7]

Objectives

Existential distress may have profound consequences for health care outcomes of patients and their caregivers at the end of life. Despite their strong potential for alleviation through psychosocial interventions, clinicians struggle to recognize and address existential concerns.[59, 60] In the shadow of prominent debates about autonomy at the end of life, research has fallen short of understanding the multifaceted factors that underlie existential distress. Due to the lack of systematic longitudinal studies, there is limited knowledge about the occurrence of existential distress, how it evolves over time, and its prospective impact on important end-of-life outcomes. Moreover, it is of substantial clinical relevance to assess caregivers' existential issues quantitatively, which have been predominantly studied qualitatively so far.

This study will systematically assess existential distress and investigate its impact on patient- and caregiver-relevant outcomes at the end of life. Therefore, we aim

1) to investigate the frequency and longitudinal trajectory of existential distress in patients with advanced cancer and their caregivers,
2) to examine the predictive impact of existential distress on patient- and caregiver-relevant end-of-life outcomes,
3) to determine patients' and caregivers' specific need for and utilization of psychosocial support with respect to existential concerns, and
4) to explore typical profiles of existential distress in patients and caregivers.

Methods and analysis

Study design

Starting October 2020, we will conduct a longitudinal cohort study over a period of 12 months. This study period includes five points of assessment at baseline (T1), 3 months (T2), 6 months (T3), 9 months (T4) and 12 months (T5). The study was registered at clinicaltrials.gov: NCT04600206.

Participants and recruitment

We will consecutively recruit 500 patients and 500 informal caregivers from outpatient and inpatient clinics including oncological and palliative care units at the University Cancer Center Hamburg (UCCH, University Medical Center Hamburg and affiliated hospitals located in the Hamburg metropolitan region). Eligible patients are at least 18 years old and diagnosed with advanced cancer as defined by Union for International Cancer Control (UICC) stage IV solid tumors. Eligible caregivers (spouse or partner, family member or close friend) are at least 18 years old. Assessment will include patients with advanced cancer and caregivers across all phases of advanced disease from diagnosis to terminal stages to reflect a cross-section of treatment settings, tumor entities, and time since diagnosis. Recruitment is not limited to patient-caregiver dyads; patients and caregivers can participate individually. Exclusion criteria for patients and caregivers are severe cognitive or physical impairment and insufficient ability to speak German to give informed consent and to complete the self-report questionnaires.

Procedures

Patients and caregivers will be approached on occasion of treatment at the respective clinic by trained research assistants. We will obtain written informed consent from patients and caregivers prior to participation. Participants may withdraw informed consent at any time. Patients and caregivers will complete paper-pencil self-report questionnaires to measure existential distress and respective support needs at each point of assessment. At baseline (T1) and after 6 months (T3), we will conduct structured diagnostic interviews with patients and caregivers face-to-face or via telephone to assess mental disorders.

We will assess sociodemographic characteristics of patients and caregivers (age, gender, education, and socioeconomic data) using a standardized self-report questionnaire. We will extract disease and medical care-related characteristics (tumor entity, tumor stage, time since diagnosis and anticancer and psychopharmacological treatments) from patients' medical charts. We will further review patients' medical charts regularly for record of deceased patients and extraction of medical care data. For post-bereavement assessment, we will approach caregivers of deceased patients 3 months after a patient's death. We will conduct follow-up assessments via mail, telephone or upon patients' and caregivers' appointments for medical treatment at the cancer centres. For non-responder analyses, we will collect basic demographic and medical data from non-participants on a voluntary basis. The COVID-19-pandemic has led to limited access of caregivers to oncological treatment facilities. We will adapt the recruitment strategy accordingly and approach caregivers via phone upon the patient’s approval.

Measures

Table 1 shows self-report questionnaires and observer-rated instruments that will be completed by patients, caregivers or both.

Existential distress

We will assess *death anxiety* in patients and caregivers using the *Death and Dying Distress Scale (DADDS).*[21, 22] The 15-item scale measures clinically significant distress with regard to concerns surrounding the patient's death. This includes psychosocial and existential concerns about missed opportunities and the loss of time, past regrets and uncertainty about the future and the burden of death on others. It also measures practical concerns about the process of dying, including fears about dying alone or with suffering or worries about its timing. Items are scored on a 6-point Likert-scale ranging from 0 (no distress) to 5 (extreme distress). The sum score ranges from 0 to 75; scores ≥ 45 indicate moderate to high levels death anxiety. A modified version of the scale validated in German cancer patients showed excellent internal consistency (Cronbach's α = 0.91).[61] The caregiver version (unpublished) will be validated in the current study (C. Lo, personal communication, May 2020).

We will assess *demoralization* in patients and caregivers using the *Demoralization Scale-II (DS-II).*[62, 63] The 16-item revised scale measures feelings of hopelessness and helplessness, and loss of meaning and purpose on two subscales (Meaning and Purpose, Distress and Coping Ability). Items are scored on a 3-point Likert-scale ranging from 0 (never) to 2 (often). Sum scores range from 0 to 32 for the total scale and from 0 to 16 for the subscales. The subscales and the total scale (Cronbach's α = 0.89) show good internal consistency.[62] The original scale[64] was validated in German cancer patients and showed good internal consistency (Cronbach's α = 0.84).[65] Although the scale is mostly used in cancer patients, it has been validated in different non-cancer populations and is applicable to caregivers.

We will assess *perceived relatedness* for patients and caregivers using the subscales *Dependence and Relatedness* of the *Depressive Experiences Questionnaire (DEQ).*[66, 67] The 18- and 8-item scales are distinct aspects of an overall Dependency factor. They measure interpersonal issues like feelings of helplessness, fear of rejection, and feelings of loneliness due to disruption in a relationship. Items are scored on a 7-point Likert-scale ranging from 1 (disagree) to 7 (agree). According to the procedure described by Blatt et al.,[68] we calculate scores based on the factor scores derived from a confirmatory factor analysis. The authors provided us with a syntax for SPSS (D. Zuroff, personal communication, May 2020). The German version was validated in clinical and non-clinical samples and showed acceptable to good internal consistency (Cronbach's α = 0.74 to 0.83).[69, 70]

We will assess *end-of-life-preparation and adjustment processes* in patients and caregivers using the *Loss Orientation and Life Engagement in Advanced Cancer Scale (LOLES).*[71] The 20-item scale measures preoccupation with death and dying, engagement in personally meaningful activities, and coping efforts including end-of-life preparation, distraction and hoping for a positive outcome. Items are scored on a 5-point Likert-scale ranging from 0 (not at all) to 4 (nearly all the time). High scores indicate high levels of loss orientation, life engagement, and coping efforts, respectively. The pilot version of the scale showed good internal consistency (Cronbach's α = 0.80 to 0.88). A parallel caregiver version (unpublished) will be validated in the present study.

We will assess *dignity-related distress* in patients using the *Sense of Dignity Item (SDI).*[25] The item measures subjective loss of dignity on a 7-point Likert-scale ranging from 0 (no sense of loss of dignity) to 6 (extreme sense of loss of dignity). A score > 3 indicates a fractured sense of dignity. Further, we will assess dignity- and *identity-related concerns* using the *Patient Dignity Inventory (PDI)*.[72] The 25-item scale measures the loss of sense of dignity in patients with terminal illness. For our purposes, we will only use the subscales assessing physical symptom distress and body image and loss of autonomy, according to the validated German version.[73] Items are scored on a 5-point Likert-scale ranging from 1 (not a problem) to 5 (overwhelming problem). Scores ≥ 3 indicate that a relevant problem is experienced. The German version of the scale showed excellent internal consistency (Cronbach's α = 0.96).[73]

We will assess *demoralization* in patients and caregivers using the *Structured Interview for Psychological Adjustment and Demoralization* developed by Kissane and colleagues (Bobevski I. & Kissane, D., 2019, Structured Interview for Psychological Adjustment and Demoralisation, unpublished clinical interview). The 36-item interview measures participants' sense of coping with any stressful event, including cancer and its treatment, with regard to level of avoidance, symptoms of demoralization, preoccupation, value of life, and functional impairment. It also assesses suicidal ideation. Items are answered with yes or no. The diagnostic algorithm is based on the proposed criteria for adjustment disorder with demoralization.[23, 74]

As part of the structured interview, patients' and caregivers *goals of care* and recall of *goals of care discussions*[75] with physicians will be assessed.

We will assess *anticipatory grief* in caregivers using the short version of the *Marwit–Meuser Caregiver Grief Inventory (MM-CGI-SF)*.[76] The 18-item scale measures pre-death grief on the subscales Personal Sacrifice and Burden, Heartfelt Sadness and Longing, and Worry and Felt Isolation. Items are scored on a 5-point Likert-scale ranging from 1 (strongly disagree) to 5 (strongly agree).

Three items, which referred to aspects specific to dementia, were adapted to cancer populations (S. Marwit, personal communication, June 2020). The total sum score ranges from 0 to 90. High scores indicate a higher level of grief level. Originally developed for caregivers of patients with Alzheimer's disease, its psychometric properties have been confirmed among caregivers of patients with cancer. The total scale and the subscales showed good to excellent internal consistency (Cronbach's α = 0.80 to 0.90).

We will assess *guilt* in caregivers using the *Caregiver Guilt Questionnaire (CGQ).*[77] The 22-item scale measures aspects of guilt experienced by caregivers on the subscales *Guilt about doing wrong by the care recipient*, *Guilt about not rising to the occasion as caregivers*, *Guilt about self-care*, *Guilt about neglecting other relatives*, and *Guilt about having negative feelings towards other people*. Items are scored on a 5-point Likert-scale ranging from 0 (never) to 4 (always or most always). The total sum score ranges from 0 to 88. High scores indicate greater guilt. The total scale and the subscales showed acceptable to good internal consistency (Cronbach's α = 0.63 to 0.89).

End-of-life outcomes and prevalence of mental disorders

Information about *aggressiveness of care* will include receipt of chemotherapy in the last two weeks of life, emergency hospital admissions or intensive-care treatment during the last month of life[78] will be obtained from medical chart reviews for deceased patients. Further, we will document the uptake and duration of specialized palliative care or hospice services received and place of death. We will further assess documentation of end-of-life care discussions as well as medical orders for life sustaining treatment in the electronic health record.

We will assess the prevalence of *mental disorders* including affective and anxiety disorders, posttraumatic stress disorder and adjustment disorder in patients and caregivers using the *Structured Clinical Interview for DSM-5 (SCID-5)*.[79] The semi-structured clinical interview measures mental disorders according to the DSM-5.[80] The German version showed acceptable internal consistency (Cronbach's α ≥ 0.70).[81]

We will assess the prevalence of *adjustment disorders* according to ICD-11 in patients and caregivers using the new *Adjustment Disorder Module of the Composite International Diagnostic Interview (CIDI*).[82] The structured interview measures the disorder according to the revised conceptualization in the International Classification of Diseases-11 (ICD-11). If participants name one or more stressful events during the past 12 months, they are asked about accompanying symptoms, duration of symptoms and impairments in their professional or social life. The diagnosis will be determined according to the criteria described by Perkonigg and colleagues.[82]

We will assess the *desire for hastened death* in patients using the short form of the *Schedule of Attitudes Toward Hastened Death (SAHD-A)*.[83] The 6-item version of the original instrument[84] measures a wish to die sooner than might occur by natural disease. Items are scored with either being true (1) or false (0). For the total score, we count the number of endorsed items, ranging from 0 to 6. High scores indicate high levels of desire for hastened death. We selected the six relevant items out of the validated German version (SAHD-D).[85] The short version showed good internal consistency (Cronbach's α = 0.83).[83]

We will assess *suicidal ideation* in patients and caregivers using the *Beck Scale for Suicidal Ideation (BSS)*. [86, 87] The 21-item scale measures the intensity of suicidal tendencies with three statements for each item (e.g., 0 = I have a moderate to strong wish to live, 1 = I have a weak wish to live, 2 = I have no wish to live). The first five items can be used to screen for suicidal ideation. If items 4 and 5, measuring active and passive suicidal ideation, are scored with 0, participants are asked to skip to the items regarding previous suicidal attempts. The sum score ranges from 0 to 38 for the total scale and from 0 to 10 for the screening score. Higher values indicate stronger suicidal tendencies. The German version showed high internal consistency for the screening items Cronbach's α = 0.89) and the total scale (Cronbach's α = 0.88).[87]

We will assess *complicated grief* in caregivers after the patient's death using the *Inventory of Complicated Grief (ICG)*.[88] The 19-item scale measures symptoms of complicated grief on based on the originally proposed criteria for DSM-5[80] on a single factor. Items are scored on a 5-point Likert-scale ranging from 0 (never) to 4 (always). The sum score ranges from 0 to 76. Scores ≥ 25 indicate experiences of complicated grief. The German version of the scale shows good internal consistency (Cronbach's α = 0.87).[89]

We will assess the *quality of dying and death* from the caregivers' perspective using the *Quality of Dying and Death Questionnaire (QODD)*.[90] After a patient's death, the questionnaire is usually administered as an interview, asking caregivers to evaluate the patients' dying experience during their last seven days or last month. In this study, we will administer a short 20-item version[91] as a self-report instrument. Caregivers indicate how they would rate each experience for the patient on a scale from 0 (terrible experience) to 10 (almost perfect experience). The score is calculated by adding up the ratings and dividing them by the number of items answered. To obtain a total score between 0 and 100, the result is multiplied by 10. Higher scores indicate a better quality of the dying experience. The adapted German version showed good internal consistency (Cronbach's α = 0.85).[92]

Symptom burden and resources

We will assess *symptom burden* in patients using the *Memorial Symptom Assessment Scale (MSAS-SF).*[93] The 28-item scale measures the frequency and the distress of physical symptoms that may occur as a result of cancer or its treatment. Items are scored on a five-point Likert-scale ranging from 0 (not at all distressed) to 4 (very much distressed). For the total score, we count the number of physical symptoms reported by the patients. The scale shows good internal consistency (Cronbach's α = 0.87).

We will assess self-reported symptoms of *depression* and *anxiety* in patients and caregivers using the *Patient Health Questionnaire (PHQ-9)*[94] and the *Generalized Anxiety Disorder Questionnaire (GAD-7).*[95] Both instruments measure symptoms of depression and anxiety based on DSM-5 criteria. Items are scored on a four-point Likert-scale ranging from 0 (not at all) to 3 (nearly every day). Sum scores range from 0 to 27 and 0 to 21, respectively. Scores ≥ 10 indicate moderate, scores ≥ 15 severe depression or anxiety. Both German versions showed good internal consistency (Cronbach's α = 0.89).[96, 97]

We will assess *meaning in life* and *crisis of meaning* in patients and caregivers using the subscales of the *Sources of Meaning and Meaning in Life Questionnaire (*LeBe).[98] The 5-item subscales measure perceived meaningful fulfillment and crisis of meaning. Items are scored on a 6-point Likert-scale ranging from 0 (totally disagree) to 5 (totally agree). Sum scores for each subscale range from 0 to 25. High scores indicate a greater sense of meaningfulness or a greater lack of meaning, respectively. Both scales showed acceptable to good internal consistency (Cronbach's α = 0.72 to 0.87).

Support needs

We will assess the *need for and utilization of psychosocial support* for existential distress in patients and caregivers using a standardized self-report questionnaire. It measures whether participants are still thinking about the existential concerns mentioned in the overall questionnaire, including fear of death and dying, fear of suffering, sense of pointlessness or hopelessness, sense of loss of dignity, preparation for the end of life, anticipatory grief, and existential loneliness. It will further assess whether participants wish to receive support dealing with this subject and who would be their preferred source of support (partner, family, friends, treating physician, psychologist/psychotherapist, other patients or caregivers). Moreover, participants will be asked whether they have previously utilized psychosocial support services.

Statistical methods

Power calculation

To determine the relative risk for a binary end-of-life outcome after 12 months, we base our sample size calculation on a multiple logistic regression model. The model includes existential distress at baseline and the covariates age, gender, and socioeconomic status. Because the test statistic in logistic regression analysis is based on a χ^2-distribution, the number of degrees of freedom (df) is equal to the number of regression weights in the model. Accordingly, we calculate the required sample size to reliably estimate the model by multiplying the minimum number of observations needed per df (n = 15) with the number of df (df = 4) and dividing the product by the ratio of positive events expected for the binary outcomes.[99] To predict receipt of aggressive treatment, we use the mean frequency reported by the German studies of Dasch et al.[52] (38%) and Radbruch et al.[53] (10%). Thus, we require a sample of $n = \frac{15 * 4}{0.24} = 250$ for our analyses at 12-month follow-up. Based on previous experiences, we expect a drop-out rate of 50% due to death or loss of interest in participation[100] resulting in a required sample size of n=500 at baseline.

Statistical analysis

We will calculate descriptive statistics to determine sample and medical characteristics as well as the prevalence of existential distress, mental disorders and palliative care outcomes. We will estimate frequencies with 95% confidence intervals. To analyse the impact of existential distress at baseline on binary and continuous end-of-life and palliative care outcomes after 12 months, we conduct multiple linear and logistic regression. After testing for multicollinearity, we will control for demographic, physical and psychosocial variables. Analyses will be conducted separately for patients and caregivers.

We will analyse the longitudinal trajectory of existential distress across the 12-month study period using growth mixture models. These models estimate distinct groups of existential distress trajectories based on a structural equation-modelling framework. The expected longitudinal dropout of patients with a prognosis of less than 12 months will be handled by full information maximum likelihood estimation.[101] We will use latent class analysis to explore whether the measured existential concerns form distinct types of existential distress. If more than 5% of the observed values are missing, we will replace missing data using multiple imputation. Existential distress may be higher among caregivers of patients who are physically too weak to participate and close to death. We will account for this effect by including patient participation as a control variable in caregiver models. We will perform statistical analyses in SPSS[102] and RStudio with R.[103, 104]

Patient and public involvement

The research questions and outcome measures are based on previous findings on concerns of patients with advanced cancer and their caregivers as well as patient- and caregiver-centered health care outcomes. Patients or the public were not involved in the design of the study. Patients and their caregivers are involved through completion of self-report questionnaires and interviews. We inform patients and caregivers that they are provided with the study results upon request.

Ethics and dissemination

The study was approved by the institutional research ethics committee (Lokale Psychologische Ethikkommission am Zentrum für Psychosoziale Medizin, reference number LPEK-0177). Informed consent will be obtained from all individual participants included in the study or their legal guardians. All procedures performed in this study are in accordance with the 1964 Helsinki Declaration and its later amendments. Results of this study will be presented at scientific conferences and published in peer-reviewed journals. Other forms of dissemination will include sharing results on the psychometric properties of the structured demoralization interview with international research groups to further examine demoralization as a diagnostic category as proposed by Kissane et and colleagues.[74] Dissemination will further include communication with health care professionals providing psychosocial treatment for patients and caregivers. Study progress will be regularly updated on ClinicalTrials.gov.

Strengths and limitations

This longitudinal study will provide unique systematic knowledge about patients' and caregivers' existential concerns. The empirical data will allow for conclusions concerning frequency and course of existential distress throughout one year. There is a need for quantitative studies focusing explicitly on existential concerns of caregivers, who are sometimes referred to as ‘hidden patients’ whose distress tends to be overlooked.[105] The recruitment strategy will allow enrollment of a large, heterogeneous sample of patients with advanced cancer from a range of clinics and treatment facilities. Limitations include potentially high dropout rates due to patients' physical decline or death within the study period. Heterogeneous patient and caregiver samples will limit subgroup-specific interpretations. Despite these limitations, the extensive assessment of psychological distress in a potentially highly distressed and understudied sample will contribute to the recognition of existential distress in patients and caregiver populations and to development of targeted interventions. Profiles of existential distress may be applied by clinicians from multiple professions and help to address existential concerns effectively.

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Declarations

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Author contributions

SV, MH, CB, and KO designed the study and coordinate the research project. RP, AK and SV wrote the first draft of the manuscript. MH, CB, KO, and UK revised it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the study.

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Competing interests

All authors declare no conflict of interest.

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Figure 1. Research model of existential distress in life-threatening illness. The figure shows a proposed taxonomy of existential concerns and their operationalization by existential distress concepts, as well as the potential association of these concepts with end-of-life outcomes among patients with advanced cancer and their caregivers.

Table 1. Self-report questionnaires and observer-rated instruments

	Construct measured	**Patients**	**Caregivers**
Existential distress (predictor)			
Death Anxiety and Distress Scale (DADDS)	Death anxiety	●	●
Depressive Experiences Questionnaire (DEQ) Subscales: Dependence, Relatedness	Perceived relatedness	●	●
Revised Loss Orientation and Life Engagement in Advanced Cancer Scale (LOLES)	End-of-life preparation and adaptation	●	●
Dignity-Item (SDI)	Dignity-related distress	●	
Patient Dignity Inventory (PDI)	Dignity-related distress	●	
Demoralization Scale-II (DS-II)	Demoralization	●	●
Structured Interview for Psychological Adjustment and Demoralisation[c]	Demoralization, suicidal ideation	●	●
Marwit-Meuser Caregiver Grief Inventory (MM-CGI-SF)[a]	Anticipatory grief		●
Caregiver Guilt Questionnaire (CGQ)[a]	Caregiver guilt		●
End-of-life outcomes and prevalence of mental disorders (outcome)			
Disease- and medical care-related characteristics[b]	Aggressiveness of care	●	
Structured Clinical Interview for DSM-5 (SCID-5)[c]	Affective disorders Anxiety disorders Posttraumatic stress disorder Adjustment disorder	●	●
Adjustment Disorder-CIDI – New Module (AjD-CIDI)[c]	ICD-11 adjustment disorder	●	●
Schedule of Attitudes Toward Hastened Death – Short Form (SAHD-A)	Desire for hastened death	●	
Beck Scale for Suicide Ideation (BSS)	Suicidal ideation	●	●
Inventory of Complicated Grief (ICG)[d]	Complicated grief		●
Quality of Dying and Death Questionnaire (QODD)[d]	Quality of dying and death		●
Symptom burden and resources (covariate)			
Memorial Symptom Assessment Scale – Short Form (MSAS-SF)	Physical symptom burden	●	
Patient Health Questionnaire-9 (PHQ-9)	Symptoms of depression	●	●
Generalized Anxiety Disorder Questionnaire-7 (GAD-7)	Symptoms of anxiety	●	●
Sources of Meaning and Meaning in Life Questionnaire (LeBe)	Meaningfulness in life, crisis of meaning	●	●
Support needs			
Structured questionnaire of psychosocial support needs for existential distress	Need for and utilization of psychosocial support for existential distress	●	●

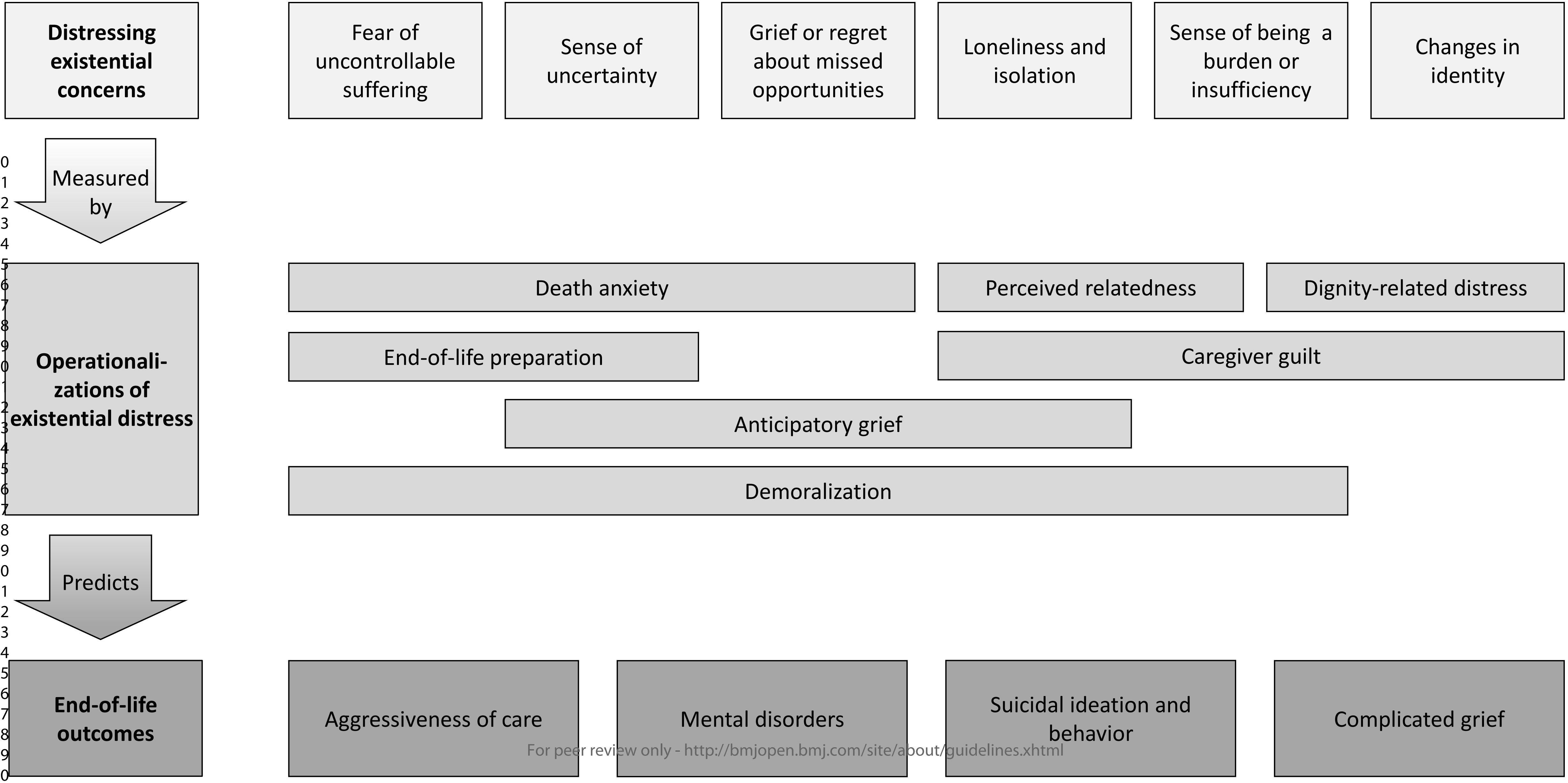
[a] Not assessed after the patient's death

[b] Assessed via medical chart review

[c] Observer-rated interview

[d] Assessed after the patients' death only

Research model of patient and caregiver existential distress in life-threatening illness



Distressing existential concerns

Fear of uncontrollable suffering

Sense of uncertainty

Grief or regret about missed opportunities

Loneliness and isolation

Sense of being a burden or insufficiency

Changes in identity

Measured by

Operationalizations of existential distress

Death anxiety

Perceived relatedness

Dignity-related distress

End-of-life preparation

Caregiver guilt

Anticipatory grief

Demoralization

Predicts

End-of-life outcomes

Aggressiveness of care

Mental disorders

Suicidal ideation and behavior

Complicated grief