STEPPED CARE targeting PSYCHOLOGICAL DISTRESS in HEAD and NECK and LUNG CANCER patients

A.M.H. KREBBER

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Funding for the studies included in this thesis was provided by The Netherlands Organisation for Health Research and Development (grant number 300020012) and by Fonds NutsOhra. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; nor in the preparation, review, or approval of the manuscripts.

Financial support for the printing of this thesis was kindly provided by VU University Amsterdam and the department of Otolaryngology/Head & Neck Surgery of VU Medical Center Amsterdam, The Netherlands.

Cover illustration: Jacqueline Houting
Design and layout: Esther Scheide
Photography: Mark van den Brink
Printed by: Gildeprint, The Netherlands

ISBN: 978-94-92332-14-1

VRIJE UNIVERSITEIT

STEPPED CARE targeting PSYCHOLOGICAL DISTRESS in HEAD and NECK and LUNG CANCER patients

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op vrijdag 2 december 2016 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

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geboren te Maastricht

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Voor Rover

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CHAPTER 1

General introduction

The World Cancer Report 2014, published by the World Health Organization's International Agency of Research on Cancer, warns that the global burden of cancer is growing at high velocity: in 2012 approximately 14 million new cases of cancer were diagnosed worldwide and this number is expected to climb to an estimated 22 million annually within the next 20 years due to ageing and growth of the population[1]. In the Netherlands, the cancer incidence curves have flattened out or slightly dropped during the last 5 years[2]. Survival rates for cancer patients have increased in the past decennia[1]. Reasons for this increase are the earlier detection of cancer due to better screening techniques and more successful cancer treatments. Cancer patients encounter a number of difficulties that can deteriorate quality of life, including fatigue, insomnia, cognitive impairment, loss of appetite, pain and decreased sexual functioning. Also, psychological comorbidity is often present[3-5].

This thesis addresses psychological comorbidity among cancer patients. This chapter provides background information on the principal matter of this thesis: improving access to high-quality and cost-effective psychosocial care for head and neck cancer (HNC) and lung cancer (LC) patients with psychological distress (symptoms of depression and/or anxiety).

EPIDEMIOLOGY OF HNC AND LC

HNC counts for 686,000 new cases worldwide every year[1]. LC is the most common diagnosed type of cancer with 1.8 million new cases every year, accounting for about 13% of total cancer diagnoses[1].

HNC originates in the head and neck region, and includes malignancies of the lips, oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses or salivary glands. Around 85% of HNC tumors is of squamous cell histology. The primary causes of HNC are tobacco and alcohol use, and human papillomavirus (HPV), which occurs primarily in the oropharynx[6]. Around the world, three times as many men as women are affected[7]. This difference is probably associated with higher rates of substance abuse, in particular tobacco use among men than women[8,9]. The risk of HNC also grows with age: most tumors are diagnosed in the late fifth and seventh decades of life[10]. Prognosis for HNC is determined by the basis of tumor site, stage and HPV tumor status[6,11]. In the Netherlands, five-year survival rates range from 41% among patients with a tumor originating in the paranasal sinuses, 31-59% in the pharynx, 61% in the oral cavity, 67% in the salivary glands, 68% in the larynx, 69% in the nasal cavity and to 91% in the lips[2].

LC refers to malignancies that originate in the airways or pulmonary parenchyma. Approximately 95% of all lung cancers are classified as either non-small cell lung cancer (NSCLC, 85%) or small cell lung cancer (SCLC, 10%). This distinction is essential for staging, treatment, and prognosis. Other cell types comprise about 5 percent of malignancies arising in the lung. The most important risk factor for LC is tobacco use, and consequently, similar to HNC, LC is twice as prevalent in men than in women[7,9,12]. Other known risk factors for LC include exposure to occupational and environmental carcinogens (such as asbestos), and outdoor pollution[13,14]. As it takes decades to develop LC after smoking initiation, diagnosis of LC before age 30 is rare and peaks in the elderly[10,15]. LC is the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five[10].

TREATMENT OF HNC AND LC

Surgery, radiation and chemotherapy in varying combinations are administered in the management of HNC and LC, depending on TNM (classification of malignant tumors) stage, primary tumor site and physical performance status. In HNC, limited or early-stage disease (stage I and II) occurs in approximately 40% of patients and is usually well treated with surgery or radiation alone. Advanced disease (stage III and IV) is associated with a high risk of both local recurrence and distant metastases. Therefore, in advanced disease, combined modality treatment is required to optimize the chances for long-term disease control. These combined modality approaches include primary surgery followed by postoperative (chemo)radiation or concurrent chemoradiation with salvage surgery if needed. The role of induction chemotherapy is limited and still under investigation[16,17].

For patients with NSCLC, surgery offers the best opportunity for cure for early stage disease[18]. In addition, stereotactic radiotherapy is nowadays considered as a good alternative[19,20]. Survival rates in advanced disease remain low, despite developments in systemic therapies (e.g., chemotherapy, biologics, and targeted agents)[21]. Because SCLC is disseminated at presentation in almost all patients, chemotherapy is an important component of treatment, with or without radiation[22].

IMPACT OF HNC AND LC AND ITS TREATMENT ON QUALITY OF LIFE

Cancer has a tremendous impact on people's life and is life disrupting at numerous levels. A diagnosis of cancer has significant psychological effects including uncertainty and fear. In addition, cancer treatment can have devastating acute and late consequences, negatively affecting health-related quality of life. Health-related quality of life is an important, multidimensional health outcome indicator, usually as perceived by the patient, and can be defined as "the extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment"[23]. Following treatment, many HNC or LC patients have to deal with deteriorating side effects, such as an altered appearance, respiratory, speech and swallowing problems, neuro- and nephrotoxicity, and high levels of symptomatology (fatigue, pain, hearing loss, dry mouth, shoulder dysfunction)[24,25]. Consequently, the implications of HNC and LC can give rise to psychological distress and social isolation[25-27], with fear of recurrence and fear regarding secondary cancers adding to the burden. Comorbid symptoms of depression and anxiety are highly prevalent among HNC and LC patients[28-31]. Among a cohort of various cancer types Brintzenhofe-Szoc et al. found that HNC and LC are in the top four of cancer types with the highest rates of mixed anxiety/depression symptoms[28].

PSYCHOLOGICAL COMORBIDITY IN CANCER PATIENTS

In literature on patients with somatic chronic diseases, the terms psychological distress and psychiatric disorder often appear under the heading "psychological comorbidity"[32]. In oncological settings the idiom distress is often applied, rather than psychiatric disorder as depression or anxiety, because it is thought to be less stigmatic[33]. Moreover, not every cancer patient who needs psychosocial care has a psychiatric disorder as diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)[34] or the International Classification of Diseases (ICD)[35]. Distress has been defined by the National Comprehensive Cancer Network (NCCN) as "a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears, to problems that can become disabling such as depression, anxiety, panic, social isolation, and existential and spiritual crisis."[36]. Psychological distress, by some referred to as the sixth vital sign in cancer care, can easily

be measured by self-report instruments, such as the Hospital Anxiety and Depression Scale[37,38] (HADS) or the Distress Thermometer[39]. Because self-report instruments do not allow case finding for anxiety and depressive disorders, screening for distress as a first step is recommendable, followed by proper diagnostic assessment.

As the cancer population is expanding, psychological comorbidity is expected to grow accordingly. A third or more of cancer patients suffer from a significant level of psychological distress following their diagnosis[40]. Major depression is prevalent in 13% of cancer patients and seems to be highest during treatment[41]; anxiety is prevalent in 10% of cancer patients[42]. In long-term cancer survivors the prevalence is estimated to be 12% and 18% respectively[43]. Depression and anxiety often occur concomitantly: more than half of cancer patients with depressive symptoms also suffer from anxiety symptoms[28,44]. When depression and anxiety coexist symptoms of depression are more severe, psychological functioning is worse, compliance and response to anti-depressive therapy is lower[44-46] and costs of health care utilization are higher[47]. Depression among cancer patients is associated with an elevated risk of mortality[48-52]. In their meta-analysis Satin et al. estimated a 26% greater mortality rate among cancer patients experiencing depressive symptoms and a 39% higher mortality rate among those diagnosed with major depression compared with non-depressed cancer patients[48].

PSYCHOLOGICAL TREATMENT OPTIONS IN CANCER CARE

In general, psychosocial intervention has shown to be effective in cancer patients with psychological distress[53,54]. In their review Fawzy et al. speak of four covering types of psychosocial interventions in cancer care: psycho-education, psychotherapy (individual), cognitive behavioral training and group interventions[55]. Cognitive behavioral therapy (CBT), problem-solving therapy (PST) and pharmacologic interventions appear to be superior in reducing depressive symptoms relative to control conditions for adults diagnosed with cancer[53]. Despite proven efficacy of psychosocial interventions in cancer patients, many distressed cancer patients do not make use of mental health care and as a result psychological comorbidity is often undertreated in cancer patients[56-60]. Barriers to referral to psychosocial care are insufficient screening for anxiety and depression at the often busy clinics, non-compliance, costs, and lacking knowledge about available psychosocial services on the part of both oncologists and patients[39,57,58,61-63]. These bottlenecks are in contradiction with the high prevalence of psychological distress and

the high intensity of psychosocial care needs among cancer patients[64-66]. The hiatus between the amount of patients experiencing distress and those getting psychological help has led to recommendations for implementing routine screening for psychological distress. In his review Mitchell stated that screening for distress and quality of life in cancer care is likely to benefit communication and referral for psychosocial help, and that it has the potential to influence patient well-being but only if barriers are addressed[67].

CURRENT ORGANIZATION OF PSYCHOSOCIAL SUPPORT IN CANCER CARE

The Dutch knowledge and quality institute for professionals and managers in oncological and palliative care, Netherlands Comprehensive Cancer Organisation (IKNL), recommends systematic screening of every adult cancer patient at the ambulant care department of a hospital for psychological distress using the so-called Lastmeter[39]. The Lastmeter consists of the Distress Thermometer, a problem list, and the question "Would you like to talk to an expert about your problems?". Internationally, other tools have emerged as well, such as Viewpoint, SupportScreen, ESRA-C, CHES, and OncoQuest[58,68]. After filling out the Lastmeter, the IKNL advises immediate review of the results by a care professional (attending physician or nurse), who is trained to interpret the outcome of the Lastmeter and to discuss the results with the patient. If needed the trained care professional can offer basic psychosocial care focused on strengthening the patient's ability to cope with and reducing the experienced burden, or refer to specialized psychosocial care for further assessment and help[69]. The presence of a professional "care navigator" has shown to lead to higher patient satisfaction, shorter hospital stays, fewer cancer-related problems, better mental health, and greater patient empowerment[69].

INNOVATION OF PSYCHOSOCIAL CARE

Facilitators to improve psychosocial care are organizing supportive cancer care according to efficient care models, incorporating self-management and eHealth in these care models, and implementing systems to monitor health related quality of life and psychological distress in clinical practice. Several meta-analyses have suggested that minimal contact therapies, such as web-based and self-help interventions, can be effective treatments for psychological distress with comparable effect sizes to face-to-face treatments[70-74]. In their meta-analysis on computerized CBT for anxiety and depressive disorders, Andrews et al.[70]

concluded that patients adhered and were satisfied with computerized CBT, especially when offered via the Internet. And thus, by increasing convenience and reducing clinician time that would otherwise be required by face-to-face treatment, web-based CBT has the capacity to increase access to mental health care[70].

A comprehensive and integrated organization of psychosocial care, such as stepped care, might be an effective method to tackle undertreatment of distress in cancer patients[75]. Stepped care is advocated in the National Institute for Health and Clinical Excellence (NICE) guidelines for common mental health problems, such as depression and anxiety[76]. Usually stepped care includes watchful waiting, (guided) self-help, brief face-to-face counselling, and specialized interventions. Patients start with the least intensive treatment that is most likely to work. Treatment response is systematically monitored and patients who do not benefit from current treatment step up to a subsequent treatment of higher intensity and costs[75]. Stepped care aims at effective and cost-efficient provision of therapeutic resources. There is evidence that, in primary care, stepped care is as effective as care as usual[77,78].

OBJECTIVES AND OUTLINE OF THIS THESIS

The main objective of this thesis is to investigate innovative psychosocial cancer care: screening for distress, stepped care, and self-management and eHealth. The focus is on HNC and LC patients.

The general outline of this thesis is as follows:
Chapter 2 describes a meta-analysis on the prevalence of depression and depressive symptoms in cancer patients during and after treatment. Chapter 3 outlines the added value of screening for psychological distress in follow-up care to identify HNC patients with untreated distress. Chapter 4 presents the study protocol of the randomized controlled trial on the (cost-)effectiveness of stepped care targeting head and neck cancer and lung cancer patients with psychological distress. In Chapter 5 the results of the randomized controlled trial testing the effectiveness of stepped care targeting psychological distress in HNC and LC patients are presented. Chapter 6 reveals the experiences with and perceived outcomes of step 2 of the stepped care program, the guided self-help intervention "Headlines", targeting psychological distress in head and neck cancer patients. Finally, Chapter 7 provides the conclusions of this thesis, their clinical implications and suggestions for future research.

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CHAPTER 2

Prevalence of depression in cancer patients during or after treatment: a meta-analysis

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Psycho-Oncology 2014; 23(2): 121-30

ABSTRACT

Objective. We aimed to investigate the prevalence of depression in cancer patients assessed by diagnostic interviews and self-report instruments, and to study differences in prevalence between type of instrument, type of cancer and treatment phase.

Methods. A literature search was conducted in four databases to select studies on the prevalence of depression among adult cancer patients during or after treatment. A total of 211 studies met the inclusion criteria. Pooled mean prevalence of depression was calculated using Comprehensive Meta-Analysis.

Results. Hospital Anxiety and Depression Scale—depression subscale (HADS-D) ≥ 8, HADS-D ≥ 11, Center for Epidemiologic Studies ≥ 16, and (semi-)structured diagnostic interviews were used to define depression in 66, 53, 35 and 49 studies, respectively. Respective mean prevalence of depression was 17% (95% CI = 16–19%), 8% (95% CI = 7–9%), 24% (95% CI = 21–26%), and 13% (95% CI = 11–15%) ($P < .001$). Prevalence of depression ranged from 3% in patients with lung cancer to 31% in patients with cancer of the digestive tract, on the basis of diagnostic interviews. Prevalence of depression was highest during treatment 14% (95% CI = 11–17%), measured by diagnostic interviews, and 27% (95% CI = 25–30%), measured by self-report instruments. In the first year after diagnosis, prevalence of depression measured with diagnostic interviews and self-report instruments were 9% (95% CI = 7–11%) and 21% (95% CI = 19–24%), respectively, and they were 8% (95% CI = 5–12%) and 15% (95% CI = 13–17%) ≥ 1 year after diagnosis.

Conclusions. Pooled mean prevalence of depression in cancer patients ranged from 8% to 24% and differed by the type of instrument, type of cancer and treatment phase. Future prospective studies should disentangle whether differences in prevalence of depression are caused by differences in the type of instrument, type of cancer or treatment phase.

INTRODUCTION

In 2008, nearly 12.7 million new cases of cancer (excluding non-melanoma skin cancer) were diagnosed worldwide, and this number is expected to increase to 21.3 million by 2030[1]. Of all cancer types, lung cancer (12.7%), breast cancer (10.9%), colorectal cancer (8%), stomach cancer (7.8%) and prostate cancer (7.1%) are the most common worldwide[1]. Recent advances in diagnosis and treatment of cancer patients have led to improved survival rates.

Many cancer patients and survivors suffer from psychological problems, such as depression[2,3]. This may interfere with the patient's ability to cope with the burden of the illness, it may decrease acceptance of treatment, extend hospitalization, reduce quality of life and increase suicide risk[4-6].

In the past decades, studies have evaluated the prevalence of depression in cancer patients. However, the overall prevalence rate of depression in cancer patients remains unclear; previous studies reported prevalence rates between 0% and 58%[7]. Several factors may contribute to this wide range of prevalence rates, including (i) the use of different instruments to assess depression with different psychometric properties; (ii) the use of different criteria to define depression; and (iii) differences between included cancer populations with respect to cancer type, stage and treatment modality[7,8]. Recently, Mitchell et al.[9] conducted a meta-analysis on 66 studies to determine the prevalence of depression in cancer patients in oncological, hematological and palliative care settings. They reported a pooled prevalence of major depression in non-palliative care settings of 16.3% (95% CI = 13–20%), as measured via psychiatric interviews according to the DSM-IV criteria[10] or International Classification of Diseases 10 (ICD-10)[11].

The detection of depression in cancer patients is difficult. Depression can easily be overlooked because symptoms of cancer and its treatment resemble neurovegetative symptoms of depression, such as fatigue, loss of appetite and sleep disturbance[12]. Nevertheless, because both physiological and psychological symptoms of depression can be diagnostically useful when looking for depression, excluding neurovegetative symptoms from depression assessment instruments may impair the ability to diagnose depression in cancer settings[13]. Other difficulties to detect depression in cancer patients are the lack of specific skills to diagnose mental disorders[14], lack of time in busy oncological settings, and reluctance of the patient to discuss emotional well-being[14,15]. In clinical practice, therefore, self-report instruments are often used to detect depressive symptoms and to assess severity of symptoms[16]. Self-report instruments have the advantage of

being quick, easy to administer, inexpensive and they rely on psychological and cognitive symptoms rather than physiological symptoms[8]. No meta-analysis has been published to quantitatively summarize prevalence of depression in cancer patients as measured by self-report instruments and psychiatric interviews.

This study is a meta-analysis to estimate the prevalence of depression in patients during or after cancer treatment, as assessed by diagnostic interviews and self-report instruments. We distinguish between depressive disorders assessed using diagnostic interviews and symptom prevalence as measured by self-report instruments. Furthermore, we aim to examine whether the prevalence of depression differs by the type of instrument used to assess depression, the type of cancer and treatment phase.

MATERIAL AND METHODS

SEARCH STRATEGY

A comprehensive literature search was performed up to December 2011 in four databases (PubMed, PsycINFO, EMBASE and CINAHL). Studies were identified by combining keywords and text words indicative of epidemiology (e.g., epidemiologic, epidemiological, epidemiol*, preval* and inciden*), depression (e.g., depressi*, depression emotion, distress, depressive disorder and major depression), and neoplasms (e.g., tumor, tumors, tumorous, tumor and carcino*). Pubmed was additionally scanned by using the following Mesh terms: 'depression/ epidemiology', 'psychological/epidemiology', 'depressive disorder/epidemiology' and 'neoplasms'. Detailed search profiles are available on request.

INCLUSION AND EXCLUSION CRITERIA

We included studies that (i) reported the prevalence of depression in adult patients in non-palliative care settings during or after cancer treatment; (ii) assessed depression by semi-structured or structured diagnostic interviews based on criteria by DSM-III(-R)/IV or ICD-10, or by self-report instruments with 'good' or 'excellent' psychometric quality as rated by Vodermaier et al.[8], that is, the Hospital Anxiety and Depression Scale—depression subscale (HADS-D)[17], the Center for Epidemiologic Studies— Depression Scale (CES-D)[18,19], Beck Depression Inventory (BDI), and Brief Symptom Inventory[20]; (iii) defined depression as a 'major depressive disorder' based on criteria by DSM-III(-R)/IV or ICD-10, and as 'increased risk of depression' by self-report instruments; and (iv) were written in English.

We excluded studies examining psychometric properties of instruments; intervention studies including randomized controlled trials, reviews, case reports, reports on the prevalence of depression in palliative cancer patients; studies in which depression could not be distinguished from distress; and studies that only reported mean and standard deviations (SD) of the sum scores of outcome measures of depression instead of numbers or percentages of depressed patients.

SELECTION PROCESS AND BIAS RISK ASSESSMENT

After eliminating duplicate studies of the identified references, the titles and available abstracts of the remaining studies were examined by three reviewers: AK, LB and IR. Studies that possibly met inclusion criteria, studies with no abstract and studies that could not clearly be excluded on the basis of the title and abstract were retrieved in full text and scrutinized more extensively for eligibility.

The bias risk of each study was assessed using a 13-item list adapted from existing criteria lists[21-23]. As the prevalence of depression depends on the population under study, this list focused on (i) the description of the study population and (ii) the representativeness of the study populations. Items for the description of the study population included sociodemographic characteristics (at least three of the following four: age, gender, marital status and education and employment or socioeconomic status), cancer type, tumor status, type of treatment, time since diagnosis, treatment phase, inclusion and exclusion criteria and information about (a history) of psychiatric problems of the participants. Items of the representativeness of the study population included sample size > 100, presentation of participation or response rate, reasons for non-response or non-participation presented, comparison of characteristics of responders and non-responders, and consecutive sampling method. A positive score was given if the study provided adequate information regarding the item of concern. In case of incomplete or unclear information or a lack of description, a negative score was given. If a study referred to another publication describing relevant information about the first study, the additional publication was obtained to score the item of concern.

The reviewers AK and GK or IR independently performed the bias assessments. In case of disagreement between the two reviewers on assigning scores, a third reviewer (LB) was consulted to discuss the item of concern until consensus was reached. For each study, a total bias score was calculated by counting the number of criteria scored positively, divided by the total number of bias items (i.e., 13). A study was considered

of low bias risk if the score was at least 9.75 (75%) of the total possible score and of medium bias risk if the score was between 6.5 and 9.75 (50–75%). A bias score lower than 6.5 (50%) was defined as high bias risk.

DATA EXTRACTION

The reviewers AK, IR and LB extracted the following data from the included studies: (i) mean/median age; (ii) sex; (iii) cancer type; (iv) time since diagnosis; (v) type of treatment; (vi) treatment phase: during treatment, < 1 year after treatment, ≥ 1 year after treatment, and mixed phases; (vii) instrument for assessment of depression; and (viii) sample size and number of cases of depression, more specifically major depressive disorder as measured by diagnostic interviews, and increased risk for depression as measured by self-report instruments. Unclear data were discussed until consensus was reached.

STATISTICAL ANALYSIS

To calculate pooled mean prevalence of depression, we used the computer program Comprehensive Meta-Analysis (version 2.2.064 by Borenstein et al., Biostat, Englewood (New Jersey, US), 2005). As we expected considerable heterogeneity among the studies, we decided to calculate the mean point prevalence and 95% CI by using a random effects model. In the random effects model, it is assumed that the included studies are drawn from 'populations' of studies that differ from each other systematically (heterogeneity). In this model, the prevalence resulting from the included studies not only differs because of the random error within studies (fixed effects model) but also because of true variation in prevalence from one study to the next.

Pooled mean prevalence was calculated for instruments that were used more than 25 times in the total number of cohorts. In addition, we performed subgroup analyses, in which we tested whether there were significant differences in prevalence of depression between different types of (i) depression measurement instruments; (ii) cancer type; and (iii) treatment phase (during diagnosis or treatment, < 1 year post-treatment, and ≥ 1 year post-treatment). Because studies with high bias might lead to underestimation or overestimation of overall prevalence of depression, we excluded these studies from analysis. We used the mixed effects model, which pooled studies within subgroups with the random effects model but tested for significant differences between subgroups with the fixed effects model. We tested the heterogeneity under the fixed model, using the I^2 statistic. I^2 describes the variance between studies as a proportion of the total

variance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity, with 0–25% as low, 25–50% as moderate and 50–75% as high heterogeneity[24]. We also calculated the Q-statistic but only report whether this was significant or not. The *P* values above .05 indicate that the total variance is due to variance within studies and not to variance between studies.

RESULTS

STUDY SELECTION

After removing duplicates, the literature searches yielded 2301 records. On the basis of the title and abstract, we excluded 1644 records that did not meet our inclusion criteria. Full text articles were retrieved for 657 potentially relevant records, of which 464 were excluded (Figure 1). Through reference search, an additional 18 studies were found eligible for inclusion. The 211 eligible studies described a total of 238 cohorts comprising 82,426 patients: 72 cohorts on cancer of the breast, 22 on cancer of the male genitalia, 21 on cancer of the head and neck, 16 on hematological malignancies, 15 on cancer of the female genitalia, 15 on cancer of the digestive tract, 10 on cancer of the respiratory tract, 7 on cancer of the brain, 3 on cancer of the skin, 2 on cancer of the bone and soft tissue, 2 on cancer of the urinary tract, and 2 on cancer of the endocrine system. A mixed group was investigated in 51 cohorts.

ASSESSMENT OF DEPRESSION

A structured or semi-structured diagnostic interview (Table 1) was used 49 times in the 238 cohorts. Self-report instruments were used 267 times, of which the HADS-D with cut-off ≥ 8 was used 78 times (in 66 studies), the HADS-D with cut-off ≥ 11 was used 59 times (in 53 studies), and CES-D with cut-off ≥ 16 was used 38 times (in 35 studies). Because they were used ≥ 25 times, diagnostic interviews, HADS-D (cut-offs ≥ 8 and ≥ 11), and CES-D (cut-off ≥ 16), which were embedded in 159 studies, were used for further analyses.

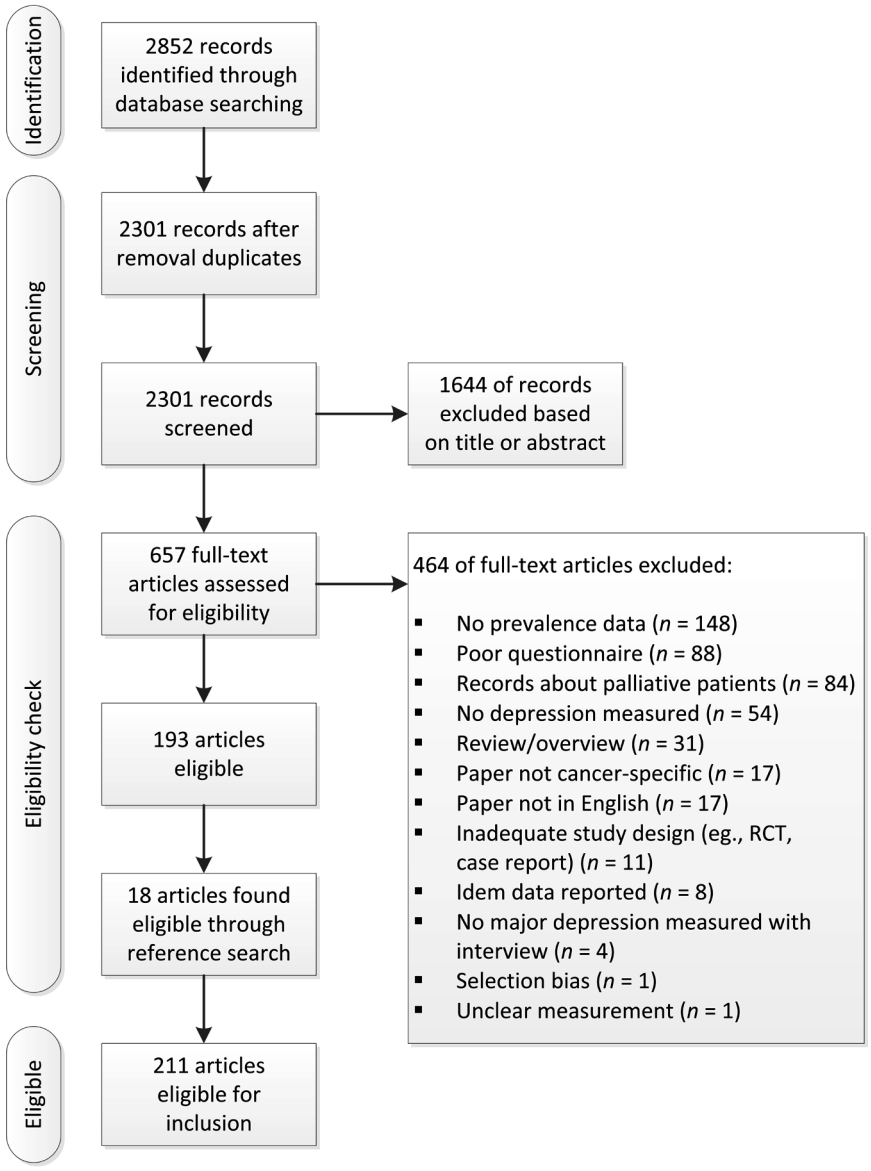


Figure 1. Selection of studies

Table 1. Number of times diagnostic interviews or self-report instruments were used in cohorts (n = 238)

Diagnostic interviews & self-report instruments	*n*		
All ratings	316		
Self-report instruments	267		
Diagnostic interviews	49		
Diagnostic interviews[a] only	*n*		
All ratings	**49**		
Interview DSM	18		
SCID (DSM)	16		
CIDI (ICD/DSM)	3		
DIS DSM	3		
MINI (DSM)	3		
SADS RDC (similar to DSM)	3		
MILP (DSM)	1		
mini-DIPS (ICD/DSM)	1		
DQPD (ICD)	1		
Self-report instruments[b] only		Cut-off	*n*
All ratings	267		
HADS-D	153		
		HADS-D ≥ 5	2
		HADS-D ≥ 7	2
		HADS-D ≥ 8	**78**
		HADS-D > 8	2
		HADS-D ≥ 10	2
		HADS-D ≥ 11	**59**
		HADS-D > 11	1
		HADS-D ≥ 15	3
		HADS-D ≥ 16	1
		HADS-D no cut-off	3
CES-D	54		
		CES-D ≥ 9	2
		CES-D ≥ 10	6
		CES-D > 10	2
		CES-D ≥ 15	1
		CES-D ≥ 16	**38**
		CES-D > 16	2
		CES-D ≥ 21	1
		CES-D ≥ 24	1
		CES-D no cut-off	1

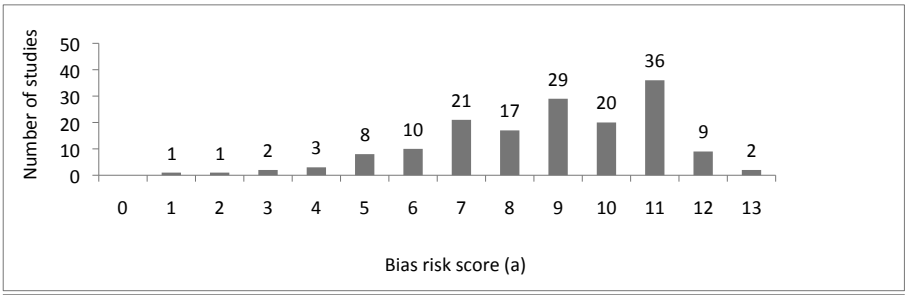
Table 1. Number of times diagnostic interviews or self-report instruments were used in cohorts (n = 238) *(continued)*

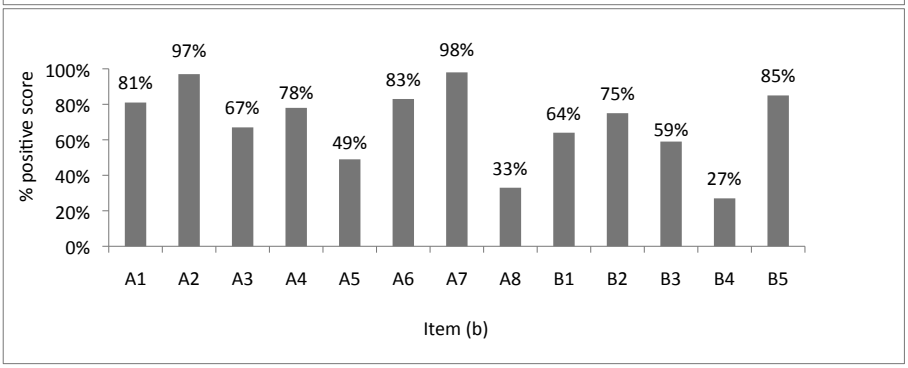
BDI	42	BDI ≥ 5	2
		BDI ≥ 9	1
		BDI ≥ 10	7
		BDI ≥ 11	1
		BDI ≥ 13	2
		BDI ≥ 14	6
		BDI ≥ 15	3
		BDI ≥ 16	2
		BDI ≥ 17	3
		BDI ≥ 18	3
		BDI ≥ 19	3
		BDI ≥ 20	3
		BDI ≥ 22	1
		BDI ≥ 24	1
		BDI ≥ 25	1
		BDI ≥ 29	1
		BDI ≥ 30	2
BSI	18	BSI 53 items	15
		BSI 18 items	3

Diagnostic interviews[a]: DSM = Diagnostic and Statistical Manual of Mental Disorders; SCID = Structured Clinical Interview for DSM; CIDI = Composite International Diagnostic Interview; ICD-10 = International Classification of Diseases; MILP = Monash Interview for Liaison Psychiatry; SADS = Schedule for Affective Disorders and Schizophrenia; RDC = Research Diagnostic Criteria; DQPD = Diagnostic Questionnaire for Depressive Patients (according to ICD-10).
Self-report instruments[b]: HADS-D = Hospital Anxiety and Depression Scale – Depression subscale; CES-D = Center for Epidemiological Studies – Depression Scale; BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory.

BIAS RISK OF THE STUDIES

The average bias score was 8.8 (SD 2.3) on a 13-point scale, and the scores ranged from 1 (highest bias risk) to 13 (lowest bias risk) (Figure 2(a)). Of the 159 assessed studies, 25 studies had a high bias risk, 67 studies had a medium bias risk, and another 67 had a low bias risk. More than 95% of the assessed studies reported cancer type, and inclusion and exclusion criteria (Figure 2(b)). Half of the studies provided information on 'reasons for non-response or non-participation' and 'time since diagnosis'. A minority of the studies provided information on 'comparison of characteristics between responders and non-responders' (27%) and '(history of) psychiatric problems' (32%). The full bias risk assessment of the studies can be found in Table 3 (Appendix 1).





Bias risk items

A. Patient population
1. Socio-demographic characteristics are described:
   a. age; b. gender; c. marital status; d. education/employment status/socioeconomic status
2. Tumor type
3. Tumor location and status
4. Type of treatment and frequencies (%)
5. Time since diagnosis
6. Disease phase:
   before treatment, during treatment, 1-12 months after treatment, > 1 year after treatment
7. Inclusion and exclusion criteria
8. (History of) psychiatric problems

B. Sample recruitment
1. Sample size (≥ 100)
2. Participation rates or response rates
3. Reasons for non-response or non-participation
4. Comparison of characteristics between responders and non-responders
5. Consecutive sample

Figure 2. Bias risk assessment of 159 studies: number of studies per rating (a) and percentage of studies with a positive score at item level (b)

PREVALENCE OF DEPRESSION

Over all studies, pooled prevalence of major depressive disorder as measured by semi-structured and structured diagnostic interviews was 14% (95% CI = 11–16%). Pooled prevalence of depression was 18% (95% CI = 16–20%) in cohorts using HADS-D with cut-off ≥ 8, 7% (95% CI = 6–8%) in cohorts using HADS-D with cut-off ≥ 11, and 24% (95% CI = 21–26%) in cohorts using CES-D with cut-off ≥ 16 (Table 2). Characteristics of the analyzed studies are shown in Table 4 (Appendix 2).

After excluding studies with high bias risk (*n* = 25), we found a pooled prevalence of major depressive disorder as measured by semi-structured and structured diagnostic interviews of 13% (95% CI = 11–15%) (Table 2). Pooled prevalence of depression was 17% (95% CI = 16–19%) in cohorts using HADS-D with cut-off ≥ 8, 8% (95% CI = 7–9%) in cohorts using HADS-D with cut-off ≥ 11, and 24% (95% CI = 21–26%) in cohorts using CES-D with cut-off ≥ 16. Heterogeneity was high, ranging from 86 to 96% (Table 2).

On the basis of diagnostic interviews, the prevalence of depression ranged from 3% in patients with lung cancer to 28% in patients with cancer of the brain (Table 2). On the basis of self-report instruments (HADS-D with cut-off ≥ 8 and CES-D with cut-off ≥ 16) prevalence of depression ranged from 7% in patients with skin cancer to 31% patients with cancer of the digestive tract. Heterogeneity was high, ranging from 64 to 97% (Table 2).

Regarding treatment phase, as measured by diagnostic interviews, we found the highest prevalence of depression in the acute phase of disease with a pooled prevalence of 14% (95% CI = 11–17%) against a pooled prevalence of 9% (95% CI = 7–11%) in the first year post-treatment and 8% (95% CI = 5–12%) 1 year or more post-treatment. On the basis of self-report instruments, we also found the highest prevalence of depression in the acute phase of disease, with a pooled prevalence of 27% (95% CI = 25– 30%). Pooled prevalence in the first year post-treatment was 21% (95% CI = 19–24%) and it was 15% (95% CI = 13–17%) after the first year. Heterogeneity was high (68–95%, Table 2).

Table 2. Prevalence of depression

Instrument	Number of cohorts	Total sample	Pooled mean	95% CI	I^2	Between group difference
All cancer types						
All studies						
Diagnostic interviews	49	8747	0.14	0.11-0.16	91.45	
HADS-D ≥ 8	75	27384	0.18	0.16-0.20	95.68	
HADS-D ≥ 11	58	17920	0.07	0.06-0.08	92.92	
CES-D ≥ 16	38	6466	0.24	0.21-0.26	85.33	
Studies of medium/low bias risk						
Diagnostic interviews	39	7322	0.13	0.11-0.15	92.08	
HADS-D ≥ 8	68	26132	0.17	0.16-0.19	96.02	
HADS-D ≥ 11	49	16011	0.08	0.07-0.09	93.54	
CES-D ≥ 16	30	5583	0.24	0.21-0.26	86.37	
Subgroup analyses per cancer type						
Diagnostic interviews[a]						
Cancer type						
Breast	16	2297	0.11	0.08-0.16	88.77	
Mixed	11	3580	0.13	0.07-0.21	95.15	
Head and neck	5	591	0.11	0.03-0.34	95.11	
Respiratory tract	3	393	0.03	0.02-0.06	0.00	
Hematological	2	289	0.08	0.05-0.11	0.00	
Brain	1	89	0.28	0.20-0.38	0.00	
Female genitalia	1	83	0.23	0.15-0.33	0.00	
						< .001
Self-report instruments[a,b]						
Cancer type						
Breast	27	8964	0.20	0.16-0.24	93.87	
Mixed	18	9530	0.25	0.21-0.30	96.60	
Male genitalia	14	7115	0.10	0.08-0.13	89.34	
Head and neck	11	1336	0.20	0.16-0.25	71.15	
Hematological	7	695	0.25	0.20-0.31	64.10	
Female genitalia	7	2381	0.26	0.18-0.35	94.17	
Digestive tract	6	577	0.27	0.18-0.37	92.13	
Respiratory tract	4	641	0.21	0.11-0.37	91.97	
Bone and soft tissue	1	36	0.33	0.21-0.48	0.00	
Endocrine system	1	136	0.17	0.12-0.24	0.00	
Urinary tract	1	102	0.16	0.10-0.24	0.00	
Skin	1	202	0.07	0.04-0.11	0.00	
						< .001

Table 2. Prevalence of depression *(continued)*

Instrument	Number of cohorts	Total sample	Pooled mean	95% CI	I^2	Between group difference
Subgroup analyses per treatment phase						
Diagnostic interviews[a]						
Acute phase	11	1379	0.14	0.11-0.17	92.98	
< 1 year post-treatment	9	1138	0.09	0.07-0.11	67.48	
≥ 1 year post-treatment	7	1195	0.08	0.05-0.12	86.35	
						< .001
Self-report instruments[a,b]						
Acute phase	38	8134	0.27	0.25-0.30	92.42	
< 1 year post-treatment	32	7198	0.21	0.19-0.24	89.20	
≥ 1 year post-treatment	27	11206	0.15	0.13-0.17	94.62	
						< .001

CI = confidence interval. I^2 = the percentage of total variation across the studies that is due to heterogeneity rather than chance.
Outliers Montazeri et al. 2004, Mhaidat et al. 2009 and Tavoli et al. 2007 are left out of analysis.
Diagnostic interviews/Self-report instruments[a]: only medium and low bias risk studies.
Self-report instruments[b]: HADS-D ≥ 8 + CES-D ≥ 16.

DISCUSSION

In this meta-analysis, we found pooled mean prevalence of depression to be 8–24% in cancer patients in non-palliative care settings during or after treatment, and the prevalence differed by the type of instrument used to measure depression, cancer type and treatment phase. Prevalence of major depressive disorder appeared to be 13% as measured by DSM or ICD. In an earlier meta-analysis, Mitchell et al.[9] reported a pooled prevalence of 16.3% (95% CI = 13–20%) among 66 studies using diagnostic interviews. This small difference may be caused by the fact that we searched four databases and included more recently conducted studies up to December 2011, and we did not include studies examining psychometric properties of instruments, nor did we include studies with a high bias score in our analysis. In addition, we included 13 papers that were not included by Mitchell et al.[25-37].

Clearly, the prevalence of a major depressive disorder in cancer patients is much higher compared with the 4% found in the general population[38]. Prevalence of depression differed substantially according to the diagnostic instrument used and was substantially higher when self-report instruments were used as compared with the diagnostic instruments. An explanation for this difference might be that diagnostic interviews are standardized

tools and use more stringent criteria according to DSM or ICD for clinical depression than self-report instruments. Self-report instruments are designed to measure an increased risk for or severity of depression instead of diagnosing a depressive disorder[39,40]. Therefore, we note that the use of self-report instruments might overestimate the presence of depression and consequently overrate patients' need for psychological treatment.

Conversely, in patients with symptoms of depression, assessment by diagnostic interviews may lead to under- recognition of unmet needs for psychological support, as some oncologists may be insufficiently skilled to identify psychological distress and perceived social support in patients[14,41]. Under-recognition may result in undertreatment, as two-thirds of screen positive cases may develop a full-blown depression if left untreated[42]. Furthermore, standardized diagnostic interviews are time-consuming and thus relatively expensive, which hampers routine implementation in busy oncological settings. Consequently, Vodermaier et al.[8] previously recommended implementing routine self-report for symptoms of depression in cancer patients using valid and reliable self-report instruments, such as the HADS-D, the CES-D or the BDI. These recommendations are supported by Mitchell et al.[43], who also advised using a two-step procedure incorporating both screening (ruling out non-cases) and case-finding (ruling in probable cases) by two stem questions. For the use of these self-report instruments, no specific skills are required, and in case an increased risk of depression is detected, the patient should be able to be referred to a specialized psychosocial care provider.

We found differences in the prevalence of depression across patients treated for different cancer types. Although the prevalence of depression appeared to be highest in patients with cancer of the digestive tract, the brain, female genitalia and patients with hematological malignancies, the limited number of studies per cancer type and small sample sizes of specific cancer types hamper us to draw firm conclusions. Differences in prevalence of depression were not only found between patients treated for different cancer types, but also within patient populations treated for the same cancer type. For example, our results from a relatively large group of breast cancer patients, including 11,182 patients from 43 cohorts, showed pooled prevalence of depression of 11% (95% CI = 8–16%) as measured by diagnostic interviews and of 20% (95% CI = 16–24%) as measured by self-report instruments. These results are in accordance with the findings of Fann et al.[44], reporting the prevalence of major depressive disorder as measured by structured interviews among breast cancer patients ranging from 5% to 15%. Also, Massie et al.[7] reported wide ranges in the prevalence of depression in breast

cancer patients, that is, from 1.5% to 46%. Wide ranges in prevalence of depression within groups of patients with similar diagnosis may be caused by the time point of measurement, type of cancer treatment, number of side effects of cancer treatment, and gender[45,46]. Unfortunately, in the current study, we were unable to identify the influences of these factors on prevalence rates.

Further, our findings show that prevalence of depression assessed by both diagnostic interviews and self-report instruments was highest in the acute phase of the disease (14% and 27%, respectively), and decreases afterwards. A similar drop has been found in early breast cancer patients by Burgess et al.[3] and Lee et al.[47]. Burgess et al. showed a point prevalence of depression, anxiety or both of 33% at diagnosis, 24% at 3 months after diagnosis, and 15% at 1 year after treatment. Lee et al. showed a point prevalence of depression of 7% preoperatively, 8% at 3 months postoperatively, and 2% at 1 year after treatment. Other prospective studies showed that there are distinct patterns regarding the course of psychological distress, ranging from resilience (no distress before or after treatment), recovery (elevated distress followed by return to normal), delayed recovery and persisting distress[48-50]. In the present study, we could not determine a clear pattern of depression rates at the different treatment phases of specific cancer types because we were unable to disentangle whether differences in prevalence rates were due to treatment phase or to types of cancer included. Future prospective trials should obtain insight in the course of depression at the different treatment phases of explicit cancer types, using preferably one standardized instrument to assess depression.

BIAS RISK SCORE

Of the 159 assessed studies, 84% had a medium and low bias risk, and 16% a high bias risk. The majority (73%) of the studies did not compare characteristics of responders and nonresponders, limiting insight in the generalizability of the results. In addition, only one third of the studies reported information on history of psychiatric problems. A history of depression increases the risk of recurrence of a depressive episode[51].

We excluded high bias risk studies from subgroup analysis, because these studies might lead to overestimation or underestimation of overall prevalence of depression. We found a minimal difference in prevalence of depression between analysis of all studies and analysis of medium and low bias risk studies only. Nevertheless, we recommend that criteria and demands regarding population and sample recruitment in studies should be standardized and followed conscientiously in future research in order to secure

psychometrical quality of trials. Larger samples of specific cancer types at a precise point in cancer treatment should be examined, and information on history of depression is preferable. Also, data on sample recruitment should be collected and reported rigorously.

STRENGTH AND LIMITATIONS

A strength of this study is the inclusion of both diagnostic interviews and self-report instruments. Because both instruments are frequently used in cancer research and clinical practice for the assessment of depression, we thought it was important to analyse both assessment methods. Another strength was the inclusion of a bias assessment and our focus on medium and low bias risk studies. Nevertheless, heterogeneity was high, and it remained high after analysing subgroups of different instruments, cancer types and treatment phase. Also, the equal weighing of the 13 items of the bias list may be to some extent arbitrary. The small number of cohorts hampered us to disentangle differences in prevalence caused by cancer type and differences caused by treatment phase, which may reduce the heterogeneity of studies. Also, we were unable to study influences of other variables such as age, gender or type of treatment because of lack of information in the majority of the included studies.

To determine major depression, ICD-10 uses similar criteria as DSM-III(-R)/IV, but adding higher threshold categories, which might have resulted in lower prevalences of major depression when assessed by ICD-10.

We acknowledge that cut-off points are to some extent arbitrary, and prevalence of depression depends on the chosen cut-off point(s) per questionnaire. An exploration at symptom level would have been preferable. Unfortunately, the prevalence of depression in the analyzed studies was mostly reported as exceeding a certain cut-off point rather than a score on the individual symptoms of depression. For that reason, we could not perform a depression analysis at symptom level.

For the pooled analysis, we focussed on the HADS-D and the CES-D, because prevalence of depression assessed by these instruments were reported more than 25 times in the total number of cohorts. Because the BDI and the Brief Symptom Inventory were not reported sufficiently ($n < 25$) in the total number of cancer patient cohorts, we could not incorporate these instruments in the pooled analysis.

CONCLUSION

Pooled mean prevalence of depression in cancer patients during or after treatment ranged between 8% and 24% and depended on the instruments used, type of cancer and treatment phase. The use of self-report instruments may overestimate the presence of depression. Future prospective trials investigating the prevalence of depression in cancer patients using valid and reliable instruments are needed.

ACKNOWLEDGEMENTS

We would like to thank search specialist R. H. J. Otten, MSc for supporting the database searches. The contribution of Dr. L. M. Buffart was supported by a fellowship granted by the EMGO Institute for Health and Care Research. A related randomized controlled trial has passed Ethical Committee Review.

APPENDIX 1

Table 3. Bias risk assessment of the studies (n = 159)

Study	A1	A1a	A1b	A1c	A1d	A2	A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5	total
Aass et al. 1997[52]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	13
Akechi et al. 2001 A[26]	1	1	1	1	1	1	1	0	0	0	1	0	1	1	1	0	1	8
Akechi et al. 2001 B[25]	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	11
Alexander et al. 1993[53]	1	1	1	1	0	0	0	0	1	0	1	0	0	1	1	0	1	6
Anderson et al. 1999[54]	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	11
Annunziata et al. 2010[55]	1	1	1	1	1	1	0	1	1	1	0	0	0	0	1	0	1	7
Aragona et al. 1996[56]	0	1	1	0	0	1	1	1	0	1	1	0	0	0	0	0	0	5
Atesci et al. 2004[57]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	11
Aukst-Margetic et al. 2004[58]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	10
Banou et al. 2009[59]	1	1	1	1	1	1	0	1	1	0	1	0	0	1	1	0	1	8
Berard et al. 1998[60]	1	1	1	1	0	1	1	0	0	1	1	0	1	0	0	0	1	7
Bergh van den et al. 2009[61]	1	1	1	1	1	1	1	0	1	0	1	0	1	1	0	0	0	7
Bisseling et al. 2009[62]	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	10
Bisson et al. 2002[63]	1	1	1	1	0	1	1	0	1	1	1	1	0	1	1	0	1	10
Bodurka-Bevers et al. 2000[64]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	11
Bonner et al. 2011[65]	1	1	1	1	1	1	0	1	0	0	1	0	0	1	0	0	1	6
Boyes et al. 2011[66]	0	1	1	0	0	1	1	1	1	1	1	0	1	1	0	0	1	9
Brain et al. 2006[67]	1	1	1	1	1	1	0	1	1	1	1	0	1	0	0	0	0	7
Breen et al. 2009[68]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	0	0	9
Bukberg et al. 1984[69]	1	1	1	1	1	1	1	1	0	1	1	0	0	1	1	0	0	8
Burris & Andrykowsky 2010[70]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	12
Carroll et al. 1993[71]	0	1	1	0	0	1	1	0	0	0	1	0	1	1	1	1	1	8
Carter et al. 2010[72]	1	1	1	1	1	1	0	1	0	1	1	0	0	1	0	0	0	6
Chaturvedi et al. 1996[73]	1	1	1	0	1	1	0	1	0	1	1	0	1	0	0	0	1	7
Chen et al. 2009 A[74]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	0	1	10
Chen et al. 2009 B[75]	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	1	1	10
Ciaramella & Poli 2001[76]	0	1	1	0	0	1	0	1	1	0	1	1	1	0	0	0	1	7
Colon et al. 1991[77]	0	1	1	0	0	1	0	1	0	1	1	0	1	0	0	0	0	5

Table 3. Bias risk assessment of the studies (*n* = 159) *(continued)*

Study	A1	A1a	A1b	A1c	A1d	A2	A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5	total
Coyne et al. 2004[78]	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	12
Dahl et al. 2005[79]	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	11
Dausch et al. 2004[27]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	9
De Graeff et al. 2000[80]	0	1	1	0	0	1	1	0	0	1	1	0	1	1	1	0	1	8
Derogatis et al. 1983[2]	1	1	1	1	0	1	1	0	0	1	1	1	1	0	1	1	1	10
Deshields et al. 2006[81]	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	1	10
Dodd et al. 2011[82]	1	1	1	1	1	1	0	1	0	1	1	0	1	1	1	0	1	8
Ellman & Thomas 1995[83]	1	1	1	0	1	1	1	1	0	1	1	0	1	1	1	1	1	11
Evans et al. 1986[84]	0	1	1	0	0	1	0	1	1	1	1	0	0	1	1	0	1	8
Farrell et al. 2005[85]	0	1	1	0	0	1	0	1	0	1	1	0	0	1	1	0	1	7
Fritzsche et al. 2004[28]	1	1	1	1	1	1	0	0	0	0	1	0	0	1	1	1	1	7
Gall et al. 2007[86]	1	1	1	0	1	1	1	0	0	1	1	0	1	0	0	0	0	6
Gandubert et al. 2009[87]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	12
Gil et al. 2010[29]	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	0	1	10
Gilbert et al. 2012[31]	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0	0	1	8
Ginsburg et al. 1995[88]	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	11
Given & Given 1992[89]	1	1	1	1	1	1	0	0	1	1	1	0	0	0	0	0	0	5
Grandi et al. 1987[90]	0	1	1	0	0	1	1	1	0	1	0	0	0	0	0	0	1	5
Grassi et al. 1993[91]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	11
Grassi et al. 1997[30]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	12
Grassi et al. 2004[92]	1	1	1	1	1	1	1	0	1	0	1	0	1	0	0	0	0	6
Groenvold et al. 1999[93]	0	1	1	0	0	1	1	1	0	1	1	0	1	1	1	1	1	10
Grulke et al. 2008[94]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	11
Hagedoorn et al. 2011[95]	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	11
Hammerlid et al. 1997[96]	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	11
Hammerlid et al. 1999[97]	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	1	9
Hervouet et al. 2005[98]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	9
Hipkins et al. 2004[99]	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	1	11
Hinz et al. 2009[100]	0	1	1	0	0	1	1	1	1	1	1	0	1	1	1	1	1	11

Holmes & Williamson 2008[101]	0	1	0	0	0	1	0	1	0	1	1	0	0	1	0	0	0	5
Hopwood et al. 2010[102]	1	1	1	0	1	1	1	1	0	1	1	0	1	1	0	0	1	9
Horney et al. 2011[103]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	11
Hosaka et al 1994[104]	0	1	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	2
Hoyer et al. 2011[105]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	11
Huang et al. 2010[106]	1	1	1	1	1	1	1	0	1	0	1	0	1	1	1	0	1	9
Humphris et al. 2003[107]	0	1	1	0	0	1	1	1	0	1	1	0	1	0	0	0	1	7
Hung et al. 2011[108]	1	1	1	0	1	1	1	1	0	1	1	0	1	1	1	1	1	11
Iconomou et al. 2004[109]	1	1	1	1	1	1	1	1	0	1	1	0	0	1	1	1	0	9
Joffe et al. 1986[110]	0	1	1	0	0	1	1	0	0	0	0	1	0	0	0	0	0	4
Jones et al. 2000[111]	0	0	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	11
Kagawa-Singer et al. 1997[112]	1	1	1	1	1	1	1	1	0	1	1	1	0	1	0	0	0	8
Kangas et al. 2005[113]	1	1	1	1	1	1	1	0	1	1	1	1	0	1	0	0	1	9
Katz et al. 2004[114]	1	1	1	1	0	1	1	1	0	1	1	0	0	1	1	0	1	9
Kelly et al. 2007[115]	0	0	1	0	0	1	0	1	0	1	1	0	1	1	1	0	1	8
Kennedy et al. 2010[116]	1	1	1	1	0	1	1	1	1	0	1	0	0	1	1	0	1	9
Kettmann & Altmaier 2008[117]	0	1	1	0	0	1	0	1	0	1	1	0	0	1	1	0	1	7
Kilbride et al. 2007[118]	1	1	1	1	0	1	1	1	0	1	1	0	0	1	1	0	1	9
Kim et al. 2010[119]	1	1	1	1	1	1	1	1	0	0	1	0	1	1	1	1	1	11
Kim et al. 2011[120]	1	1	1	1	1	1	1	0	1	0	1	0	1	1	1	0	1	9
Kirsh et al. 2004[121]	1	1	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	5
Kissane et al. 2004[32]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	12
Klepin et al. 2011[122]	1	1	1	0	1	1	0	1	0	1	1	0	0	1	1	0	1	7
Krespi et al. 2010[123]	1	1	1	1	1	1	0	1	0	1	1	0	1	1	1	0	1	9
Kugaya et al. 2000[124]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	12
Kurtz et al. 2002[125]	0	1	1	0	0	1	1	1	0	1	1	0	1	1	1	0	1	9
Lechner et al. 2006[126]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	11
Li et al. 2011[127]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	0	0	0	8
Liu et al. 2009[128]	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	0	1	10
Livingston et al. 2010[129]	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	1	1	9
Lueboonthavatchai et al. 2007[130]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	6

Table 3. Bias risk assessment of the studies (*n* = 159) *(continued)*

Study	A1	A1a	A1b	A1c	A1d	A2	A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5	total
Matsuoka et al. 2002[131]	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	11
Maunsell et al. 1992[132]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	11
Mccaffrey et al. 2007[33]	1	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	9
Mccorkle et al. 2006[133]	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	11
Mehnert et al. 2007[134]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	13
Mehnert et al. 2008[135]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	11
Mehnert et al. 2010[136]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1	10
Merckaert et al. 2010[137]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	11
Mhaidat et al. 2009[138]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	0	9
Mohan et al. 2009[139]	1	1	1	0	1	1	0	0	0	1	1	0	1	1	1	0	0	7
Montazeri et al. 2005[140]	1	1	1	1	1	1	0	0	1	1	1	0	1	0	0	0	0	6
Morasso et al. 2001[141]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	0	1	11
Morrill et al. 2008[142]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	11
Murphy et al 1996[143]	0	1	1	0	0	1	0	1	0	0	0	0	0	0	0	0	1	3
Neilson et al. 2010[144]	1	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	9
Nelson et al. 2010[145]	1	1	1	1	1	1	1	0	1	0	1	0	1	1	1	0	1	9
Okamura et al. 2000[146]	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	0	1	10
Ozalp et al. 2008[147]	1	1	1	1	1	1	1	1	0	0	1	0	1	1	1	0	1	9
Palmer et al. 2004[34]	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	11
Pamuk et al. 2008[148]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	11
Paredes et al. 2011[149]	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	8
Partridge et al. 2008[150]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	12
Pasacreta et al. 1997[151]	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	12
Pascoe et al. 2000[152]	1	1	1	1	1	0	0	0	0	0	1	0	1	1	0	0	0	4
Pirl et al. 2009[35]	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	0	1	9
Popoola et al. 2011[36]	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	0	1	10
Price et al. 2010[153]	1	1	1	1	1	1	1	0	1	0	1	1	1	1	0	1	1	10
Prieto et al. 2002[4]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	11
Rasic et al. 2008[154]	1	1	1	1	1	0	0	0	0	0	1	1	1	0	0	0	1	5

Reuter et al. 2006[155]	1	1	1	1	1	1	1	1	0	1	1	0	1	0	0	0	0	7
Reuter et al. 2007[156]	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	1	9
Rijken et al. 1995[157]	1	1	1	1	1	1	1	1	0	1	1	0	1	0	0	0	0	7
Rogers et al. 2009[158]	1	1	1	0	1	1	1	1	0	1	1	0	0	1	1	0	0	8
Roopnarinesingh et al. 2003[159]	0	1	1	0	0	1	0	0	0	0	1	1	0	0	0	0	0	3
Saevarsdottir et al. 2010[160]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	9
Sarna et al. 2010[161]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	9
Schlegel et al. 2009[162]	1	1	1	1	1	1	1	1	0	1	1	0	1	0	0	0	1	9
Schmid-Buchi et al. 2011[163]	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	0	1	8
Schrier et al. 2011[37]	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	9
Schwarz et al. 2008[164]	0	1	1	0	0	1	1	1	1	1	1	0	1	1	1	0	1	9
Shim et al. 2011[165]	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	11
Singer et al. 2008[166]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	11
Skoogh et al. 2010[167]	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	1	10
So et al. 2010[168]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	11
Spiegel et al. 1994[169]	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	6
Steel et al. 2007[170]	0	1	1	0	0	1	1	1	0	1	1	1	1	1	1	1	1	11
Stommel et al. 2004[171]	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	1	10
Storey et al. 2012 A[172]	1	1	1	1	0	1	1	1	0	1	1	0	1	1	1	1	1	11
Storey et al. 2012 B[173]	0	1	1	0	0	1	1	1	0	1	1	0	1	1	1	1	1	10
Strong et al. 2007[174]	0	1	1	0	0	1	1	1	0	0	1	0	1	1	1	0	1	8
Suzuki et al. 2011[175]	0	1	1	0	0	1	0	0	1	1	1	0	1	0	0	0	1	6
Tagay et al. 2006[176]	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	0	1	10
Tavoli et al. 2007[177]	1	1	1	1	1	1	0	1	1	0	1	0	1	0	0	0	1	8
Tercyak et al. 2007[178]	1	1	1	1	1	1	1	0	1	0	1	0	1	0	0	0	1	7
Thorsen et al. 2005[179]	1	1	1	1	1	1	0	0	0	1	1	0	1	1	0	1	1	8
Thuné-Boyle et al. 2006[180]	1	1	1	1	1	1	0	1	0	1	1	1	0	1	0	0	0	7
Tuinman et al. 2010[181]	1	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	9
Uchitomi et al. 2003[182]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	12
Vahdaninia et al. 2010[183]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	0	1	10
Van Onselen et al. 2010[184]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	11

Table 3. Bias risk assessment of the studies (*n* = 159) *(continued)*

Study	A1	A1a	A1b	A1c	A1d	A2	A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5	total
Van Wilgen et al. 2006[185]	0	1	1	0	0	1	0	1	0	1	1	0	1	0	0	0	0	5
Verdonck et al. 2009[48]	0	1	1	0	0	1	1	1	1	1	1	0	0	0	0	0	1	7
Verdonck-de Leeuw et al. 2010[186]	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	1	7
Vistad et al. 2007[187]	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	11
Ward et al. 1992[188]	1	1	1	1	1	1	1	1	0	1	1	0	0	1	0	0	0	7
Watson et al. 1999[189]	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1	10
Wellisch et al. 1996[190]	0	1	1	0	0	1	0	1	1	1	1	0	0	1	0	0	1	7
Wellisch et al. 2002[191]	1	1	1	1	1	1	0	1	0	1	1	1	0	0	0	0	1	7
Wronska et al. 2003[192]	1	1	1	1	1	1	0	1	0	1	1	0	0	0	0	0	1	6
Yen et al. 2006[193]	1	1	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	4
Zonderman et al. 1989[194]	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1

Bias risk items

A. Patient population

1. Socio-demographic characteristics are described:
   a. age; b. gender; c. marital status; d. education/employment status/socioeconomic status
2. Tumor type
3. Tumor location and status
4. Type of treatment and frequencies (%)
5. Time since diagnosis
6. Disease phase:
   before treatment, during treatment, 1-12 months after treatment, > 1 year after treatment
7. Inclusion and exclusion criteria
8. (History of) psychiatric problems

B. Sample recruitment

1. Sample size (≥ 100)
2. Participation rates or response rates
3. Reasons for non-response or non-participation
4. Comparison of characteristics between responders and non-responders
5. Consecutive sample

APPENDIX 2

Table 4. Characteristics of analyzed studies (n = 159) examining prevalence of depression in cancer patients during or after treatment

Study	Bias risk	Tumor type (n)	Total sample (n)	Definition of depression	Diagnostic instrument[a]	Age (SD)	% Female	Country
Aass et al. 1997[52]	Low	Gynaecological (163), breast (161), urological (102), hematological (66), gastrointestinal (56), lung (39), other (129)	716	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Median 58.3 (NR)	63	Norway
Akechi et al. 2001 A[26]	Medium	Mixed	1721	MDD	Interview DSM-IV	NR (NR)	NR	Japan
Akechi et al. 2001 B[25]	Low	Lung	129	MDD	Interview DSM-III-R	Mean 62, median 64 (9)	26	Japan
Alexander et al. 1993[53]	High	Mixed	60	MDD	Interview DSM-III-R	Mean 53.2 (13.9)	40	India
Anderson et al. 1999[54]	Low	Brain	40	Depression	HADSD ≥ 11	Mean 44 (NR)	40	United Kingdom
Annunziata et al. 2010[55]	Medium	Mixed	85	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Median 42 (NR)	43.5	Italy
Aragona et al. 1996[56]	High	Breast	85	MDD	Interview DSM-III-R	Median 54 (12)	100	Italy
Atesci et al. 2004[57]	Low	Mixed	117	MDD	SCID for DSM-IV	Mean 53.7 (14.2)	51.3	Turkey
Aukst-Margetic et al. 2004[58]	Low	Breast	115	Depression, MDD	CES-D ≥ 16, DQPD (ICD-10)	Mean 61.8 (11.2)	100	Croatia
Banou et al. 2009[59]	Medium	Mixed	64	Depression	CES-D ≥ 16	Mean 53.4 (11.27)	100	United States
Berard et al. 1998[60]	Medium	Mixed	456	Depression, MDD	HADS-D ≥ 8, Interview DSM-IV	Mean 51.8 (13.34)	75-84	South Africa
Bergh, van den et al. 2009[61]	Medium	Prostate	129	Depression	CES-D ≥ 16	Mean 64.9 (6.89)	0	The Netherlands
Bisseling et al. 2009[62]	Low	Ovarium	62	Depression	HADSD ≥ 11	Mean 36.5 (7.5)	100	Australia
Bisson et al. 2002[63]	Low	Prostate	88	Depression	HADS-D ≥ 8	Mean 64.5 (6.7)	0	United Kingdom
Bodurka-Bevers et al. 2000[64]	Low	Ovarium	246	Depression	CES-D ≥ 16	Mean 56.7 (NR)	100	United States

Table 4. Characteristics of analyzed studies (*n* = 159) examining prevalence of depression in cancer patients during or after treatment *(continued)*

Study	Bias risk	Tumor type (*n*)	Total sample (*n*)	Definition of depression	Diagnostic instrument[a]	Age (SD)	% Female	Country
Bonner et al. 2011[65]	High	Female genitalia	13	Depression	HADS-D ≥ 8	Mean 53 (9.9)	100	Australia
Boyes et al. 2011[66]	Medium	Hematological (181), breast (207), head and neck (93), skin (202), lung (133), prostate (343), colorectal (157)	1316	Depression	HADS-D ≥ 8	NR (NR)	NR	Australia
Brain et al. 2006[67]	Medium	Breast	161	Depression	HADS-D ≥ 11	Mean 67 (11.93)	0	United Kingdom
Breen et al. 2009[68]	Medium	Mixed	192	Depression	HADS-D ≥ 8	Mean 52.4 (12.8)	65	Australia
Bukberg et al. 1984[69]	Medium	Mixed	62	MDD	Interview DSM-III	Mean 51 (NR)	28	United States
Burris & Andrykowsky 2010[70]	LowH	Mixed	116	Depression	HADS-D ≥ 11	Median 56.9 (9.3)	69	United States
Carroll et al. 1993[71]	Medium	Mixed	809	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 57.8 (15)	51.4	United States
Carter et al. 2010[72]	High	Female genitalia	88	Depression	CES-D ≥ 16	Mean 39.6 (NR)	100	United States
Chaturvedi et al. 1996[73]	Medium	Mixed	100	Depression	HADS-D ≥ 8	NR (NR)	79	India
Chen et al. 2009 A[74]	Low	Head and neck	112	Depression	HADS-D ≥ 11	53.4 (10.5)	3.6	Taiwan
Chen et al. 2009 B[75]	Low	Breast	1400	Depression	CES-D ≥ 10	Mean 55.2 (9.8)	100	United States & China
Ciaramella & Poli 2001[76]	Medium	Mixed	100	MDD	SCID for DSM-III-R	Mean 64 (NR)	50	Italy
Colon et al. 1991[77]	High	Hematological	100	MDD	Interview DSM-III	Mean 30 (NR)	35	USA
Coyne et al. 2004[78]	Low	Breast	113	MDD	SCID DSM-IV	Mean 55.8 (NR)	100	United States
Dahl et al. 2005[79]	Low	Testicular	1408	Depression	HADS-D ≥ 8	Mean 44.6 (10.2)	0	Norway

Dausch et al. 2004[27]	Medium	Breast	207	MDD	Interview DSM-IV	Mean 52.9 (10.6)	100	United States
De Graeff et al. 2000[80]	Medium	Head and neck	153	Depression	CES-D ≥ 16	NR (NR)	20	The Netherlands
Derogatis et al. 1983[2]	Low	Mixed	215	Depression	Interview DSM-III	Mean 50.3 (15.5)	51	United States
Deshields et al. 2006[81]	LowH	Breast	84	Depression	CES-D ≥ 16	Mean 55.6 (11.4)	100	United States
Dodd et al. 2011[82]	Medium	Mixed	187	Depression	CES-D ≥ 16	Mean 52 (11)	0	United States
Ellman & Thomas 1995[83]	Low	Breast	290	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	100	United Kingdom
Evans et al. 1986[84]	Medium	Female genitalia	83	MDD	Interview DSM-III	Mean 53.1 (15.6)	100	United States
Farrell et al. 2005[85]	Medium	Mixed	33	Depression	HADS-D ≥ 11	Mean 50 (NR)	100	United Kingdom
Fritzsche et al. 2004[28]	Medium	Hematological	69	Depression	Mini-DIPS (ICD-10/ DSM-IV)	Mean 48.23 (15.39)	46	Germany
Gall et al. 2007[86]	High	Colorectal	336	Depression	HADS-D ≥ 11	NR (NR)	NR	Australia
Gandubert et al. 2009[87]	Low	Breast	144	MDD	MINI DSM-IV	Mean 53 (NR)	100	France
Gil et al. 2010[29]	Low	Mixed	703	MDD	DSM-IV	53 (NR)	50	Spain
Gilbert et al. 2012[31]	Medium	Head and neck	94	MDD	SCID for DSM-IV	55.4 (9.7)	16	United States
Ginsburg et al. 1995[88]	Low	Lung	52	MDD	DIS DSM-III	NR (NR)	25	Canada
Given & Given 1992[89]	High	Breast	28	Depression	CES-D ≥ 16	Mean 58 (12)	100	United States
Grandi et al. 1987[90]	High	Breast	18	MDD	Interview DSM-III	Mean 53 (NR)	100	Italy
Grassi et al. 1993[91]	Low	Mixed	157	MDD	Interview DSM-III-R	Mean 52.3 (NR)	80.3	Italy
Grassi et al. 1997[30]	Low	Mixed	113	MDD	CIDI + ICD-10	Mean 52.31 (11.47)	80.5	Italy
Grassi et al. 2004[92]	High	Mixed	277	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 57.46 (12.59)	72.2	Italy

Table 4. Characteristics of analyzed studies (*n* = 159) examining prevalence of depression in cancer patients during or after treatment *(continued)*

Study	Bias risk	Tumor type (*n*)	Total sample (*n*)	Definition of depression	Diagnostic instrument[a]	Age (SD)	% Female	Country
Groenvold et al. 1999[93]	Low	Breast	463	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	100	Denmark
Grulke et al. 2008[94]	Low	Hematological	138	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 40.9 (11.3)	40.6	Germany
Hagedoorn et al. 2011[95]	Low	Colorectal	64	Depression	CES-D ≥ 16	Mean 61 (10)	28	The Netherlands
Hammerlid et al. 1997[96]	Low	Head and neck	44	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 63 (NR)	29.5	Sweden
Hammerlid et al. 1999[97]	Medium	Head and neck	356	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 63 (NR)	28	Sweden
Hervouet et al. 2005[98]	Medium	Prostate	861	Depression	HADS-D ≥ 8	Mean 55 (10.6)	0	Canada
Hipkins et al. 2004[99]	Low	Ovarium	63	Depression	HADS-D ≥ 8	Mean 58.2 (11.5)	100	United Kingdom
Hinz et al. 2009[100]	Low	Mixed	1529	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 60.3 (12.1)	40.8	Germany
Holmes & Williamson 2008[101]	High	Mixed	68	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	NR	United Kingdom
Hopwood et al. 2010[102]	Medium	Breast	2177	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	NR	United Kingdom
Horney et al. 2011[103]	Low	Head and neck	102	Depression	HADS-D ≥ 8	NR (NR)	NR	United Kingdom
Hosaka et al 1994[104]	High	Hematological	31	MDD	Interview DSM-III	Mean 52.35 (NR)	26	Japan
Hoyer et al. 2011[105]	Low	Breast	1086	Depression	HADS-D ≥ 11	Mean 61.8 (12.6)	100	Sweden
Huang et al. 2010[106]	Medium	Breast	150	Depression	CES-D ≥ 16	Mean 51.6 (10.4)	100	Taiwan
Humphris et al. 2003[107]	Medium	Head & neck	100	Depression	HADS-D ≥ 8	Mean 58.3 (11.4)	32	United Kingdom
Hung et al. 2011[108]	Low	Lung	350	Depression	HADS-D ≥ 8	Mean 68.8 (9.8)	63.4	United States
Iconomou et al. 2004[109]	Medium	Mixed	80	Depression	HADS-D ≥ 11	Mean 60.8 (10.7)	56.2	Greece

Joffe et al. 1986[110]	High	Mixed	21	MDD	SADS interview RDC	Mean 54.8 (2.1)	29	United States
Jones et al. 2000[111]	Low	Testicular	47	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	0	United Kingdom
Kagawa-Singer et al. 1997[112]	Medium	Breast	34	Depression	CES-D ≥ 16	NR (NR)	100	United States
Kangas et al. 2005[113]	Medium	Mixed	49	MDD	SCID DSM-IV	NR (NR)	NR	Australia
Katz et al. 2004[114]	Medium	Head and neck	60	MDD	SADS interview RDC (similar to DSM-IV)	Mean 60.5 (13)	22.7	Canada
Kelly et al. 2007[115]	Medium	Head and neck	194	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	NR	United Kingdom
Kennedy et al. 2010[116]	Medium	Breast	43	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Median 60.2 (NR)	100	United Kingdom
Kettmann & Altmaier 2008[117]	Medium	Hematological	86	Depression	CES-D ≥ 16	Mean 35.32 (10.22)	45.4	United States
Kilbride et al. 2007[118]	Medium	Brain	38	Depression	HADS-D ≥ 11	Median 55 (NR)	42.1	United Kingdom
Kim et al. 2010[119]	Medium	Mixed	295	Depression	HADS-D ≥ 8	Mean 55.2 (13.2)	29.8	South Korea
Kim et al. 2011[120]	Low	Female genitalia	828	Depression	HADS-D ≥ 8	Mean 50.4 (13.7)	100	South Korea
Kirsh et al. 2004[121]	High	Hematological	95	MDD	Interview DSM-IV	Mean 45.76 (11.72)	43.2	United States
Kissane et al. 2004[32]	Low	Breast	303	MDD	MILP interview DSM-IV	Mean 46 (8)	100	Australia
Klepin et al. 2011[122]	Medium	Hematological	54	Depression	CES-D ≥ 16	Mean 70.8 (6.4)	40.7	United States
Krespi et al. 2010[123]	Medium	Breast	296	Depression, MDD	HADS-D ≥ 8 & HADS-D ≥ 11, SADS DSM-IV	Mean 58 (NR)	100	United Kingdom
Kugaya et al. 2000[124]	Low	Head and neck	107	MDD	SCID DSMIII-R	Mean 61 (11.8)	24	Japan
Kurtz et al. 2002[125]	Medium	Colorectal	154	Depression	CES-D ≥ 16	Mean 73 (NR)	51.3	United States

Table 4. Characteristics of analyzed studies (*n* = 159) examining prevalence of depression in cancer patients during or after treatment *(continued)*

Study	Bias risk	Tumor type (*n*)	Total sample (*n*)	Definition of depression	Diagnostic instrument[a]	Age (SD)	% Female	Country
Lechner et al. 2006[126]	Low	Breast	230	Depression	CES-D ≥ 16	Mean 53.5 (12.3)	100	United States
Li et al. 2011[127]	Medium	Breast	252	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 46 (8.76)	100	China
Liu et al. 2009[128]	Low	Breast	76	Depression	CES-D ≥ 16	Mean 51.1 (9.1)	100	United States
Livingston et al. 2010[129]	Medium	Colorectal	45	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	NR	Australia
Lueboonthavatchai et al. 2007[130]	High	Borst	300	Depression	HADS-D ≥ 11	Mean 50.9 (11.1)	100	Thailand
Matsuoka et al. 2002[131]	Low	Breast	74	MDD	SCID DSM-IV	48.1 (5.7)	100	Japan
Maunsell et al. 1992[132]	Low	Breast	205	MDD	DIS DSM-III	NR (NR)	100	Canada
Mccaffrey et al. 2007[33]	Medium	Head and neck	22	MDD	SCID DSM-IV	Mean 73 (NR)	16.7	United States
Mccorkle et al. 2006[133]	Low	Cervix	208	Depression	CES-D ≥ 16	Mean 55.2 (11.9)	100	United States
Mehnert et al. 2007[134]	Low	Breast	127	Depression	HADS-D ≥ 8 & HADS-D ≥ 11, SCID DSM-IV	Mean 54.9 (10.74)	100	Germany
Mehnert et al. 2008[135]	Low	Breast	1083	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 61.8 (9.8)	100	Germany
Mehnert et al. 2010[136]	Low	Breast	511	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 64.3 (6)	100	Germany
Merckaert et al. 2010[137]	Low	Mixed	381	Depression	HADS-D ≥ 8	Mean 54.2 (NR)	64.8	Belgium
Mhaidat et al. 2009[138]	Medium	Mixed	208	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 49 (NR)	48	Jordan
Mohan et al. 2009[139]	Medium	Prostate	178	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 61.5 (7.9)	0	United States

Montazeri et al. 2005[140]	High	Breast	120	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 46.9 (14.7)	100	Iran
Morasso et al. 2001[141]	Low	Breast	132	MDD	SCID for DSM-III-R	NR (NR)	100	Italy
Morrill et al. 2008[142]	Low	Breast	161	Depression	CES-D ≥ 16	Mean 59 (10.6)	100	United States
Murphy et al 1996[143]	High	Hematological	56	MDD	CIDI DSM-III-R	Mean 35.4 (15)	48	United Kingdom
Neilson et al. 2010[144]	Medium	Head and neck	102	Depression	HADS-D ≥ 8	Mean 62.5 (10)	15.7	United States
Nelson et al. 2010[145]	Medium	Prostate	686	Depression	HADS-D ≥ 8	Mean 63 (10)	0	United States
Okamura et al. 2000[146]	Low	Breast	55	MDD	SCID DSM-III-R	Mean 53, median 50 (9)	100	Japan
Ozalp et al. 2008[147]	Medium	Breast	204	MDD	SCID DSM-IV	Mean 50.8 (11.9)	100	Turkey
Palmer et al. 2004[34]	Low	Breast	115	MDD	SCID DSM-IV	Mean 55.6 (NR)	100	United States
Pamuk et al. 2008[148]	Low	Hematological	140	Depression	HADS-D ≥ 8	Mean 55.1 (14.5)	46.4	Turkey
Paredes et al. 2011[149]	Medium	Bone and soft tissue	61	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 48.3 (18.5)	52.4	Portugal
Partridge et al. 2008[150]	Low	Breast	487	Depression	HADS-D ≥ 11	Mean 53.9 (10.9)	100	United States
Pasacreta et al. 1997[151]	Low	Breast	79	Depression, MDD	CES-D ≥ 16, DIS DSM-III-R	Mean 54.9 (12.7)	100	United States
Pascoe et al. 2000[152]	High	Mixed	504	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	55	Australia
Pirl et al. 2009[35]	Medium	Mixed	243	MDD	Interview DSM-IV	Mean 63.2 (NR)	24	United States
Popoola et al. 2011[36]	Low	Breast	124	MDD	MINI DSM-IV	NR (NR)	100	Nigeria
Price et al. 2010[153]	Low	Ovarium	794	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	100	Australia
Prieto et al. 2002[4]	Low	Hematological	220	MDD	Interview DSM-IV	Mean 38.4	41.4	Spain
Rasic et al. 2008[154]	High	Mixed	863	MDD	CIDI DSM-IV	NR (NR)	56.5	Canada
Reuter et al. 2006[155]	Medium	Breast	353	Depression	HADS-D ≥ 11	Mean 49.8 (10.8)	100	Germany

Table 4. Characteristics of analyzed studies (*n* = 159) examining prevalence of depression in cancer patients during or after treatment *(continued)*

Study	Bias risk	Tumor type (*n*)	Total sample (*n*)	Definition of depression	Diagnostic instrument[a]	Age (SD)	% Female	Country
Reuter et al. 2007[156]	Medium	Breast	132	Depression	HADS-D ≥ 11	Mean 54 (NR)	100	Germany
Rijken et al. 1995[157]	Medium	Breast	112	Depression	CES-D ≥ 16	NR (NR)	100	The Netherlands
Rogers et al. 2009[158]	Medium	Head and neck	65	Depression	CES-D ≥ 16	Mean 60 (13)	20	United States
Roopnarinesingh et al. 2003[159]	High	Mixed	29	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 27.3 (NR)	0	Ireland
Saevarsdottir et al. 2010[160]	Medium	Mixed	109	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	NR (NR)	NR	Iceland
Sarna et al. 2010[161]	Medium	Lung	119	Depression	CES-D ≥ 16	Mean 67.7 (10.7)	100	United States
Schlegel et al. 2009[162]	Medium	Breast	223	Depression	CES-D ≥ 16	Mean 59.2 (12.7)	100	United States
Schmid-Buchi et al. 2011[163]	Medium	Breast	72	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 57.5, median 60 (11.8)	100	Switzerland
Schrier et al. 2011[37]	Medium	Breast	40	MDD	MINI DSM-IV	Mean 55.3 (7.3)	100	Israel
Schwarz et al. 2008[164]	Medium	Mixed	367	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 57.1 (13.6)	100	Germany
Shim et al. 2011[165]	Low	Mixed	116	Depression	HADS-D ≥ 8	Mean 52.5 (12.1)	39.7	South Korea
Singer et al. 2008[166]	Low	Head and neck	308	MDD	SCID DSM-IV	NR (NR)	9	Germany
Skoogh et al. 2010[167]	Low	Testicular	974	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 41, median 39 (NR)	0	Sweden
So et al. 2010[168]	Low	Breast	218	Depression	HADS-D ≥ 8	Mean 51.7 (10.3)	100	China
Spiegel et al. 1994[169]	High	Mixed	96	MDD	SCID DSM-III	Mean 53 (NR)	75	United States
Steel et al. 2007[170]	Low	Hepatobiliary	101	Depression	CES-D ≥ 16	Mean 60 (NR)	25	United States
Stommel et al. 2004[171]	Low	Mixed	802	Depression	CES-D ≥ 16	NR (NR)	NR	United States

Storey et al. 2012 A[172]	Low	Prostate	160	Depression	HADS-D ≥ 8	Mean 78 (NR)	0	United Kingdom
Storey et al. 2012 B[173]	Low	Prostate	377	Depression	HADS-D ≥ 8	Mean 72 (6.1)	0	United Kingdom
Strong et al. 2007[174]	Medium	Mixed	3071	Depression	HADS-D ≥ 8	Median 62 (NR)	66	United Kingdom
Suzuki et al. 2011[175]	High	Female genitalia	214	Depression	HADS-D ≥ 11	Mean 54.8 (NR)	100	Japan
Tagay et al. 2006[176]	Low	Thyroid	136	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 52.2 (16.4)	72	Germany
Tavoli et al. 2007[177]	Medium	Gastrointestinal	142	Depression	HADS-D ≥ 8	Mean 54.1 (14.8)	44.4	Iran
Tercyak et al. 2007[178]	Medium	Breast	147	Depression	CES-D ≥ 16	Median 52 (NR)	100	United States
Thorsen et al. 2005[179]	Medium	Testicular	1260	Depression	HADS-D ≥ 8	Mean 41 (NR)	0	Norway
Thuné-Boyle et al. 2006[180]	Medium	Mixed	72	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 56 (NR)	54	United Kingdom
Tuinman et al. 2010[181]	Medium	Testicular	93	Depression	CES-D ≥ 16	Mean 29.4 (7.5)	0	The Netherlands
Uchitomi et al. 2003[182]	Low	Lung	212	MDD	SCID DSM-III-R	Mean 62.1, median 63.5 (10.8)	39.6	Japan
Vahdaninia et al. 2010[183]	Low	Breast	167	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 47.4 (13.3)	100	Iran
Van Onselen et al. 2010[184]	Low	Mixed	179	Depression	CES-D ≥ 16	60.1 (NR)	47.5	United States
Van Wilgen et al. 2006[185]	High	Breast (189), head and neck (154), colorectal (104), female genitalia (62)	509	Depression	CES-D ≥ 16	Mean 55 (13)	99	The Netherlands
Verdonck et al. 2009[48]	Medium	Head and neck	55	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 63 (NR)	31	The Netherlands
Verdonck-de Leeuw et al. 2010[186]	Medium	Head and neck	85	Depression	HADS-D ≥ 8	Median 59 (NR)	36	The Netherlands
Vistad et al. 2007[187]	Low	Cervix	79	Depression	HADS-D ≥ 8	Mean 59.1 (11.4)	100	Norway

Table 4. Characteristics of analyzed studies (*n* = 159) examining prevalence of depression in cancer patients during or after treatment *(continued)*

Study	Bias risk	Tumor type (*n*)	Total sample (*n*)	Definition of depression	Diagnostic instrument[a]	Age (SD)	% Female	Country
Ward et al. 1992[188]	Medium	Breast	38	Depression	CES-D ≥ 16	Mean 49 (10.2)	100	United States
Watson et al. 1999[189]	Low	Breast	578	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 55 (10.6)	100	United Kingdom
Wellisch et al. 1996[190]	Medium	Hematological	30	Depression	CES-D ≥ 16	NR (NR)	50	United States
Wellisch et al. 2002[191]	Medium	Brain	89	MDD	Interview DSM-IV	Mean 43.2 (NR)	45	United States
Wronska et al. 2003[192]	High	Breast	61	Depression	HADS-D ≥ 8 & HADS-D ≥ 11	Mean 58 (NR)	100	Poland
Yen et al. 2006[193]	High	Breast	73	Depression	CES-D ≥ 16	NR (NR)	100	Taiwan
Zonderman et al. 1989[194]	High	Mixed	192	Depression	CES-D ≥ 16	NR (NR)	NR (NR)	United States

NR = Not Reported.

MDD = Major depressive disorder.

Diagnostic instrument[a]: BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; CES-D = Center for Epidemiological Studies – Depression Scale; CIDI = Composite International Diagnostic Interview; DSM-III/IV = Diagnostic and Statistical Manual of Mental Disorders; DQPD = Diagnostic Questionnaire for Depressive Patients (according to ICD-10); HADS-D = Hospital Anxiety and Depression Scale – Depression subscale; ICD-10 = International Classification of Diseases; MILP = Monash Interview for Liaison Psychiatry; RDC = Research Diagnostic Criteria; SADS = Schedule for Affective Disorders and Schizophrenia; SCID = Structured Clinical Interview for DS.

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CHAPTER 3

Screening for psychological distress in follow-up care to identify head and neck cancer patients with untreated distress

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Supportive Care in Cancer 2016; 24(6): 2541-8

ABSTRACT

Purpose. To investigate screening in follow-up care to identify head and neck cancer (HNC) patients with untreated psychological distress.

Methods. From November 2009 until December 2012 we investigated the use of Onco-Quest (a touchscreen computer system to monitor psychological distress (Hospital Anxiety and Depression Scale (HADS)) and quality of life (HRQOL; EORTC QLQ-C30 and H&N35 module) in routine follow-up care. Patients who screened positive for psychological distress (HADS-total > 14, HADS-A > 7, or HADS-D > 7) were telephone-based interviewed by a researcher on receipt of mental treatment.

Results. During the study period of 37 months OncoQuest was used by 720 individual HNC patients, of whom 714 had complete HADS data. Psychological distress was present in 206 patients (29%). Of those patients who fulfilled in- and exclusion criteria (n = 137), 25 received psychological treatment (18%). Receipt of psychological treatment was significantly related to a higher score on the HADS total scale (19.6 versus 16.9; P = .019), a lower (worse) score on the EORTC QLQ-C30 scale emotional functioning (46.0 versus 58.6; P = .023), a higher (worse) score on fatigue (58.2 versus 46.4; P = .032), oral pain (43.8 versus 28.8; P = .011), speech problems (37.0 versus 25.3; P = .042) and less sexuality (57.3 versus 36.5; P = .043).

Conclusions. Screening for psychological distress via OncoQuest is beneficial because 82% of HNC patients identified with an increased level of distress who do not yet receive mental treatment were identified. Untreated psychological distress is associated with better quality of life.

INTRODUCTION

Psychosocial care is increasingly recognized as an integral part of quality cancer treatment[1]. In the Netherlands, government policy statements, various cancer-specific guidelines, reflect broad scientific and societal support for a structured, integrated approach to psychosocial care for cancer patients[2,3]. Although there is evidence that psychosocial care is effective[4-6], referral rates are low[7,8], and many patients have unmet needs, related to e.g., fatigue, sexuality issues and life stress[9-11]. The identification and support of cancer patients with psychological distress is a challenge[10,12], especially in head and neck cancer (HNC) patients, as they do not usually express their emotions spontaneously in front of the oncologists. One of the main barriers to deliver psychosocial cancer care in cancer patients is lack of screening for psychological distress in clinical practice to identify patients[13-16].

Fitch[15] stated that the need for identifying psychological distress is clear and there are suitable patient reported outcome measures (PROMs) available to perform this screening. The Distress Thermometer with the accompanying problem list is often used for assessment of each patient's unique needs[3,17]. Other tools have emerged as well, such as Viewpoint[18], SupportScreen[19], ESRA-C[20], and CHES[21]. At the Department of Otolaryngology-Head and Neck Surgery of VU University Medical Center, efficient screening for distress followed by triage to care has become available in 2006 by a touchscreen computer system (OncoQuest) that was implemented in routine clinical practice[7,22,23]. Via OncoQuest, patients complete quality of life (HRQOL) questionnaires (EORTC QLQ-C30 and condition-specific modules such as the EORTC QLQ-H&N35) and the Hospital Anxiety and Depression Scale (HADS). It takes, on average, 9 minutes to complete the questionnaires[23]. OncoQuest is linked to the hospital patient information system. Data are processed in real-time and a care coordinator (a nurse specialized in HNC) can view the results by clear graphics on a computer in the consulting room and discuss these with the patient. In this prospective surveillance model, HRQOL can be repeatedly monitored and changes can be assessed; physical impairment, functional limitations and psychosocial distress can be identified in an early stage, information and psychoeducation can be provided, and, if necessary, supportive care including rehabilitation, psychosocial care and healthy lifestyle programs can be introduced.

Several studies have shown that using PROMs facilitates communication about patients' symptoms, functioning and distress between doctors, nurses and patients[16]. However, an international debate has emerged concerning screening for psychological

distress in clinical practice with authors with solid arguments in favor of screening[12,16,24-27] and other authors with valid arguments against it[28-30]. For instance, Palmer et al.[29] reported that 36% of recently diagnosed breast cancer patients with elevated distress or a psychiatric disorder already received psychotropic medication. The authors argued that because of this relatively high percentage, screening all breast cancer patients is therefore not very effective. However, information on patients with other types of cancer is scarce, which hampers the discussion on pros and cons of screening for distress in clinical practice.

The aim of this study is to assess the added value of screening in follow-up care to identify HNC patients with untreated psychological distress. Furthermore, socio-demographic and clinical factors and HRQOL outcomes will be investigated that may be associated with untreated psychological distress.

MATERIALS AND METHODS

STUDY POPULATION

All patients who routinely visited our outpatient clinic for follow-up care within a time frame of 37 months (November 2009 – December 2012) were screened for psychological distress as part of standard clinical care. Patients who screened positive for psychological distress (HADS-total > 14, HADS-A > 7, or HADS-D > 7) were assessed for eligibility and, when eligible, asked to participate in a telephone-based interview on receipt of psychiatric or psychological treatment. Eligible patients were those who were treated at least 1 month to 15 years earlier in VU University Medical Center for carcinoma of the lip, oral cavity, oropharynx, hypopharynx, nasopharynx, larynx or salivary glands (all stages), and who were treated with curative intent (all treatment modalities). Exclusion criteria were (i) other (neurological) diseases causing cognitive dysfunction, (ii) end of treatment for a psychiatric disorder < 2 months ago or being under treatment for another psychiatric disorder, (iii) not being reachable, (iv) insufficient knowledge of the Dutch language to fill out the questionnaires, or (v) incomplete HADS data. Sociodemographic (age, gender) and clinical variables (tumor site and stage, treatment modality) were assessed by medical records audit.

The Medical Ethics Committee of the VU University Medical Center in Amsterdam approved this study. All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008, and in accordance with local laws and regulations.

SCREENING FOR DISTRESS

Since 2008, we offer all new HNC patients to use a touchscreen computer system (OncoQuest) to complete the HADS and the EORTC QLQ-C30 and H&N35 HRQOL questionnaires and to consult a specialized nurse, during follow-up visits at (approximately) 3, 6, 9, 12, 18, and 24 months after treatment. If needed, a volunteer supports HNC patients using the computer system. Based on the results of OncoQuest (available in real-time in clear graphics on a computer screen), the nurse can identify and support HNC patients with psychological distress or problems regarding (HNC specific) HRQOL. On average, it takes 9 minutes to complete OncoQuest and the consultations with the nurse are estimated to take 10 minutes[7,22,23].

The HADS is a 14-item self-assessment scale for measuring distress (total HADS score (HADS-total)) with two subscales, anxiety (HADS-A) and depression (HADS-D). The HADS was specifically designed for use in the medically ill[31]. The total HADS score ranges from 0 to 42, the subscales from 0 to 21. A score of > 7 on the anxiety scale, a score of > 7 on the depression scale and/or a total HADS score of > 14 is used as an indicator of a high level of psychological distress[31,32].

The 30-item EORTC QLQ-C30 (version 3.0) includes a global HRQOL scale (2 items) and comprises 5 functional scales: physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items) and social functioning (2 items). There are three symptom scales (nausea and vomiting (2 items), fatigue (3 items) and pain (2 items) and 6 single items relating to dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties. The scores of the QLQ-C30 are linearly transformed to a scale of 0-100, with a higher score indicating a higher (i.e., more positive) level of functioning or global HRQOL, or a higher (i.e., more negative) level of symptoms or problems[33,34].

The EORTC QLQ-H&N35 module covers specific HNC issues and comprises 7 subscales: pain (4 items), swallowing (5 items), senses (2 items), speech (3 items), social eating (4 items), social contact (5 items) and sexuality (2 items). There are 11 single items covering problems with teeth, dry mouth, sticky saliva, cough, feeling ill, opening the mouth wide, weight loss, weight gain, use of nutritional supplements, feeding tubes, and painkillers. The scores of the QLQ-H&N35 are linearly transformed to a scale of 0-100, with a higher score indicating a higher (i.e., more negative) level of symptoms or problems[35]. In the present study the scales and the first 6 single items were used.

THE VALUE OF SCREENING

In the present study, eligible HNC patients in follow-up care with an increased level of psychological distress (HADS-total > 14, HADS-A > 7, or HADS-D > 7) were telephone-based interviewed by a researcher on receipt of psychiatric or psychological treatment. Based on earlier research[7,36] it was expected that in clinical practice 25-30% of HNC patients would present with psychological distress of whom the majority do not receive psychological treatment. Screening for distress in follow-up care was defined to have added value if at least 50% of HNC patients diagnosed with psychological distress did not yet receive psychological or psychiatric treatment.

To provide information on sociodemographic, clinical factors and HRQOL variables possibly associated with untreated psychological distress several univariate analyses were performed. χ^2 tests were used to investigate whether gender (male versus female), tumor location (lip/oral cavity, oropharynx, hypopharynx/larynx, other), tumor stage based on the UICC TNM classification of malignant tumors (I, II, II, IV), treatment modality (single treatment (surgery or radiotherapy) versus combination (surgery and (chemo) radiation)) or time since treatment (1-12 months versus > 12 months) were associated with untreated psychological distress. Independent *t*-tests or, in case of skewness, Mann-Whitney tests were used to investigate whether age, HADS-total, HADS-A, or HADS-D or the EORTC QLQ-C30 and H&N35 subscales were associated with untreated psychological distress. All analyses were performed using the IBM Statistical Package for the Social Science (SPSS) version 20 (IBM Corp., Armonk, NY USA). For all statistical analyses, a *P* value < .05 was considered statistically significant.

RESULTS

PREVALENCE OF DISTRESS AND RECEIPT OF TREATMENT

During the study period of 37 months OncoQuest was used by 720 HNC patients in follow-up care, of whom 714 had complete HADS data. Figure 1 shows the flow diagram of the selection of patients. Among the 714 HNC patients, 206 patients screened positive for psychological distress (29%). Of these 206 patients 69 patients were excluded: 19 could not be reached, 18 were treated less than 1 month earlier, 13 were in the palliative phase of the disease, 5 had insufficient knowledge of the Dutch language, 4 had a cognitive dysfunction, 3 were currently under treatment for a psychiatric disorder other than anxiety or depression, 3 had possible tumor recurrence, 2 had not received

treatment at VU University Medical Center, 1 had received tumor treatment too long ago, and 1 also had another untreated malignancy.

Among the 137 HNC patients who screened positive for psychological distress during the study period and fulfilled the in- and exclusion criteria, 25 (18%) received psychiatric or psychological treatment: 10 received counseling and psychotropic medication, 7 received psychotropic medication, 4 received counseling, and 1 received self-help and psychotropic medication, 3 patients did not provide information about their treatment.

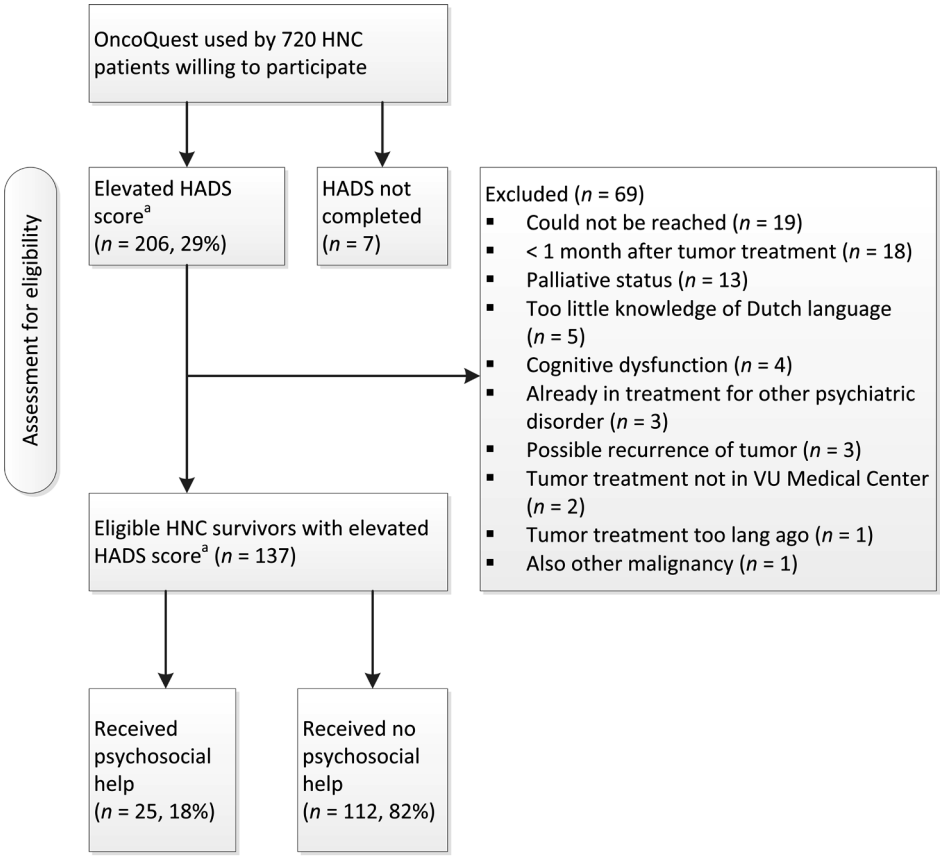

Figure 1. Selection of patients

FACTORS RELATED TO RECEIPT OF PSYCHOLOGICAL OR PSYCHIATRIC TREATMENT

Sociodemographic and clinical characteristics of the study population (*n* = 137) are provided in Table 1, and regarding patient reported outcome measures (HADS, EORTC QLQ-C30 and H&N35) in Table 2.

Table 1. Overview of sociodemographic and clinical characteristics of the study sample

	Total sample (*n* = 137)	Received no psychosocial care (*n* = 112)	Received psychosocial care (*n* = 25)	*P* value
	n	*n* %	*n* %	
Gender				.92
Male	92	75 (81.5%)	17 (18.5%)	
Female	45	37 (82.2%)	8 (17.8%)	
Mean age (SD)	61.7 (10.1)	61.9 (9.8)	61.0 (11.1)	.74
Tumor location				.55
Lip/oral cavity	34	29 (85.3%)	5 (14.7%)	
Oropharynx	36	28 (77.8%)	8 (22.2%)	
Hypopharynx/larynx	46	36 (78.3%)	10 (21.7%)	
Other (e.g., parotis)	21	19 (90.5%)	2 (9.5%)	
Tumor stadium				.31
I	32	29 (90.6%)	3 (9.4%)	
II	28	20 (71.4%)	8 (28.6%)	
III	31	25 (80.6%)	6 (19.4%)	
IV	41	33 (80.5%)	8 (19.5%)	
Unknown	5	5 (100.0%)	0 (0.0%)	
Tumor treatment				.99
Single	82	67 (81.7%)	15 (18.3%)	
- *Surgery*	23	19 (82.6%)	4 (17.4%)	
- *Radiotherapy*	59	48 (81.4%)	11 (18.6%)	
Combination	55	45 (81.8%)	10 (18.2%)	
- *Chemoradiation*	25	21 (84.0%)	4 (16.0%)	
- *Surgery and (chemo)radiation*	30	24 (80.0%)	6 (20.0%)	
Time since treatment				.53
1-12 months	57	48 (84.2%)	9 (15.8%)	
> 12 months	80	64 (80.0%)	16 (20.0%)	

A *P* value < .05 was considered statistically significant.

Receipt of psychological or psychiatric treatment (versus no receipt) was not significantly related to gender, age, tumor location, tumor stage, tumor treatment and time since treatment (Table 1). Receipt of psychological or psychiatric treatment (versus no receipt) was significantly related to a higher score on the HADS total scale (19.6 versus 16.9; *P* = .019), a lower (worse) score on the EORTC QLQ-C30 scale emotional functioning (46.0 versus 58.6; *P* = .023), and a higher (worse) score on fatigue (58.2 versus 46.4;

P = .032), and on the EORTC QLQ-H&N35 scales oral pain (43.8 versus 28.8; *P* = .011), speech problems (37.0 versus 25.3; *P* = .042) and less sexuality (57.3 versus 36.5; *P* = .043).

Table 2. Overview of outcomes on HADS, EORTC QLQ-C30 and H&N35, and test statistics of between group differences

		Total (*n*)	Mean	SD	No PC (*n*)	Mean	SD	PC (*n*)	Mean	SD	t or Z	df	*P*
HADS	Depression	137	8.77	3.61	112	8.42	3.12	25	10.32	5.06	-1.80	28.19	.082
	Anxiety	135	8.64	3.64	110	8.49	3.64	25	9.28	3.65	-0.98	133.00	.34
	Total score	135	17.39	5.27	110	16.88	4.79	25	19.60	6.70	-2.37	133.00	**.019**
QLQ-C30	Global quality of life	136	58.52	20.37	111	58.93	19.77	25	56.67	23.20	0.50	134.00	.62
	Physical functioning	135	70.86	21.08	110	72.42	20.28	25	64.00	23.49	1.82	133.00	.071
	Role functioning	136	60.66	29.30	111	62.76	28.15	25	51.33	32.96	1.78	134.00	.078
	Emotional functioning	137	56.27	25.08	112	58.56	23.95	25	46.00	27.86	2.299	135.00	**.023**
	Cognitive functioning	137	71.41	22.59	112	72.62	21.90	25	66.00	25.22	1.328	135.00	.19
	Social functioning	135	65.31	25.11	111	66.52	24.77	24	59.72	26.43	1.204	133.00	.23
	Fatigue	137	48.58	24.88	112	46.43	24.56	25	58.22	24.49	-2.172	135.00	**.032**
	Nausea/ vomiting	137	12.53	20.19	112	11.90	20.56	25	15.33	18.58	-1.32	n.a.	.19
	Pain	137	37.47	28.57	112	35.57	28.08	25	46.00	29.77	-1.662	135.00	.099
	Dyspnoea	136	27.94	28.75	112	28.27	27.66	24	26.39	34.02	0.29	134.00	.77
	Insomnia	137	37.71	34.02	112	36.31	34.24	25	44.00	32.94	-1.022	135.00	.31
	Loss of appetite	137	29.93	33.40	112	29.46	33.41	25	32.00	33.99	-0.342	135.00	.73
	Constipation	137	18.49	26.48	112	19.94	27.75	25	12.00	18.95	-1.11	n.a.	.27
	Diarrhoea	137	9.98	21.53	112	10.71	22.47	25	6.67	16.67	-0.74	n.a.	.46
	Financial difficulties	137	20.92	28.87	112	21.73	28.55	25	17.33	30.61	-0.99	n.a.	.32
QLQ-H&N35	Oral pain	136	31.43	26.45	112	28.79	25.16	24	43.75	29.31	-2.565	134.00	**.011**
	Swallowing problems	136	31.62	28.29	112	29.99	28.26	24	39.24	27.75	-1.46	134.00	.15
	Senses problems	136	28.06	27.79	112	28.72	27.51	24	25.00	29.49	0.594	134.00	.55
	Speech problems	136	27.37	25.69	112	25.30	24.61	24	37.04	28.88	-2.055	134.00	**.042**
	Trouble with social eating	134	34.08	30.36	110	31.74	28.86	24	44.79	35.17	-1.927	132.00	.056
	Trouble with social contact	135	17.93	19.77	111	16.04	17.32	24	26.67	27.31	-1.48	n.a.	.14
	Less sexuality	132	40.15	36.89	109	36.54	34.36	23	57.25	44.05	-2.122	27.918	**.043**
	Teeth problems	136	24.75	31.95	112	22.62	30.42	24	34.72	37.40	-1.56	n.a.	.12
	Trouble with opening mouth	136	29.90	33.77	112	27.68	32.23	24	40.28	39.29	-1.67	134	.097
	Dry mouth	136	51.72	36.47	112	53.27	36.20	24	44.44	37.64	1.077	134	.28
	Sticky saliva	136	42.40	34.54	112	43.15	34.26	24	38.89	36.34	0.548	134	.59
	Coughing	136	33.33	29.26	112	33.04	28.47	24	34.72	33.30	-0.255	134	.80
	Feeling ill	136	30.64	30.91	112	28.87	30.18	24	38.89	33.57	-1.447	134	.15

No PC = received no psychosocial care; PC = received psychosocial care; SD = standard deviation.
In some cases the total group was smaller than 137 because of missing values.
A *P* value < 0.05 (presented in bold font) was considered statistically significant.

DISCUSSION

The present study revealed that among HNC patients, screening for distress has added value because of the patients who screened positive for psychological distress (29%), the majority (82%) did not yet receive treatment. This percentage of patients with untreated distress is much higher compared with 64% among newly diagnosed breast cancer patients as reported by Palmer et al.[29]. Therefore and because two-thirds of patients who screen positive may develop a full-blown depression if left untreated[37], we disagree with Palmer et al. and conclude that screening for distress is beneficial among HNC patients. Our conclusion supports the findings of Kotronoulas et al.[38], who reported in their recent review that routine use of PROMs increases communication about patient outcomes during consultations and that PROMs are associated with improved symptom control, increased supportive care, and patient satisfaction.

Receipt of psychological or psychiatric treatment was significantly related to a higher score on the HADS total scale, a lower (worse) score on the EORTC QLQ-C30 scale emotional functioning, a higher (worse) score on fatigue, and on the EORTC QLQ-H&N35 scales oral pain, speech problems and less sexuality. An explanation for these findings might be that patients with more severe problems are more inclined to seek help. But also, these patients might be detected easier by caregivers during follow up consultation and therefore are referred to supportive care earlier. Carlson et al. reported that full screening (online use of PROMs with a personalized printout of results and a list of contact details of services to help with the identified problems) and triage to care (full screening plus the opportunity to speak with a care professional who could refer to services directly) both result in the most benefit for lung cancer patients, compared with screening alone. Fewer patients in the triage group reported a problem with coping (12.9%) compared with patients in the minimal (23.9%) and full (26.9%) screening groups[26]. Mitchell concluded that screening for distress and monitoring HRQOL in clinical practice is likely to benefit communication and referral for psychosocial help, and that it has the potential to influence patient well-being but only if barriers are addressed[16]. However, understanding about the complexities of implementing screening programs is still unfolding[15]. In earlier studies, it was argued that incorporating PROMs in clinical practice should aim at equipping health professionals to use patient PROMs data in managing patients, should employ more condition-specific (rather than generic) PROMs, should improve the interpretability of the PROM data feedback to both medical staff and patients, and should train patients in self-efficacy[39]. Recently, key barriers were

identified as lack of training and support, low acceptability, and failure to link treatment to the screening results[16]. Also, further implementation research is needed to advance knowledge about the most effective strategies in the context of cancer care[27].

A limitation to our study is that we missed information about the receipt of psychosocial care for 10% of the participating HNC patients because they could not be reached. However, these patients had mainly borderline HADS scores and additional information about referral to psychological services was not present in their medical dossiers. Therefore these patients are suspected to not have received any psychosocial treatment. Furthermore, we do not know how many patients who did not receive psychological treatment or psychiatric treatment (82%), had unmet psychological care needs. Based on earlier research (Jansen et al., 2015; Lubberding et al., 2015)[40,41] and clinical practice, our estimation is that many patients with psychological distress do not want to be referred to psychological care. This was the main reason to start a trial on stepped care in which patients are offered low-intensity interventions like self-help first, before being referred to a psychologist or psychiatrist[42]. Although OncoQuest is valued by the coordinating nurse and by patients, not all eligible patients make use of OncoQuest, which may have resulted in selection bias. A mixed method study including qualitative and quantitative research measures is ongoing and will provide detailed insight into possible barriers and facilitators enabling optimization of OncoQuest. In their randomized clinical trial Carlson et al.[43] examining the impact of screening for distress followed by personalised triage versus computerised triage, concluded that the best model of screening may be to incorporate personalised triage for patients indicating high levels of depression and anxiety while providing computerised triage for others. Further research is needed on best-practice approaches for implementing sustainable and acceptable screening for distress and triage programs in clinical settings.

CONCLUSION

Screening for psychological distress among HNC patients is beneficial to identify patients with psychological distress who do not yet receive treatment. Via OncoQuest a broad spectrum of HRQOL is monitored (EORTC QLQ-C30 and QLQ-H&N35 module), enabling identification of not only psychological distress but also of other problems.

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CHAPTER 4

Stepped care targeting psychological distress in head and neck and lung cancer patients: a randomized clinical trial

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ABSTRACT

Background. Psychological distress is common in cancer survivors. Although there is some evidence on effectiveness of psychosocial care in distressed cancer patients, referral rate is low. Lack of adequate screening instruments in oncology settings and insufficient availability of traditional models of psychosocial care are the main barriers. A stepped care approach has the potential to improve the efficiency of psychosocial care. The aim of the study described herein is to evaluate efficacy of a stepped care strategy targeting psychological distress in cancer survivors.

Methods/design. The study is designed as a randomized clinical trial with 2 treatment arms: a stepped care intervention program versus care as usual. Patients treated for head and neck cancer (HNC) or lung cancer (LC) are screened for distress using OncoQuest, a computerized touchscreen system. After stratification for tumor (HNC vs. LC) and stage (stage I/II vs. III/IV), 176 distressed patients are randomly assigned to the intervention or control group. Patients in the intervention group will follow a stepped care model with 4 evidence-based steps: (i) watchful waiting, (ii) guided self-help via Internet or a booklet, (iii) problem-solving therapy administered by a specialized nurse, and (iv) specialized psychological intervention or antidepressant medication. In the control group, patients receive care as usual which most often is a single interview or referral to specialized intervention. Primary outcome is the Hospital Anxiety and Depression Scale (HADS). Secondary outcome measures are a clinical level of depression or anxiety (CIDI), quality of life (EQ-5D, EORTC QLQ-C30, QLQ-H&N35, QLQ-LC13), patient satisfaction with care (EORTC QLQ-PATSAT), and costs (health care utilization and work loss (TIC-P and PRODISQ modules)). Outcomes are evaluated before and after intervention and at 3, 6, 9 and 12 months after intervention.

Discussion. Stepped care is a system of delivering and monitoring treatments, such that effective, yet least resource-intensive, treatment is delivered to patients first. The main aim of a stepped care approach is to simplify the patient pathway, provide access to more patients and to improve patient well-being and cost reduction by directing, where appropriate, patients to low cost (self-)management before high cost specialist services.

Trial registration. NTR1868

BACKGROUND

Every year more than 14,000 patients are diagnosed with lung cancer (LC) (11,470 patients) or head and neck cancer (HNC) (2870 patients) in the Netherlands[1]. Five-year survival rates are estimated on 13% in LC and 50% in HNC. Approximately 80% of the LC patients are male compared with 65% of the HNC patients. Patients often have to deal with devastating side effects of initial treatment (surgery, radiotherapy, and/or chemotherapy), such as pain, fatigue, and respiratory, speech and swallowing problems, negatively affecting health-related quality of life and associated with increased levels of psychological distress. Co-morbid anxiety or depression is present in 20-30% of LC and HNC patients[2-4]. During the first year after treatment there is a gradual improvement of psychological functioning[5,6] but many patients continue to suffer from or develop anxiety or depression[2,7-9].

Because of the overwhelming evidence of psychological distress in LC and HNC patients, intervention is recommended in national guidelines. Some recent reviews have shown evidence on efficacy of psychosocial intervention in cancer patients in general[10,11]. Others question evidence mainly because randomized trials are scarce[12,13] and because most studies included all patients even those without symptoms of depression and anxiety. Furthermore, it appears that most intervention studies are applied in patients with breast cancer. Patients with less prevalent tumors such as HNC or poor survival rates as in LC are often not involved, while LC and HNC patients are among the most distressed patients compared with cancer patients in general[14].

In clinical practice at present, many cancer patients who report high levels of psychological distress are not taking advantage of psychosocial care[14,15]. Barriers to admission to adequate psychosocial care are a lack of adequate screening of anxiety and depression in the often very busy oncology settings, reluctance by patients to be referred because of the already long treatment period, and that traditional models of the delivery of psychosocial care cannot meet current demand. Other forms of delivery, such as brief therapies, group treatments and self-help, and a stepped care approach may provide useful alternatives. Studies regarding cost-effectiveness of psychosocial intervention in cancer patients are scarce[16].

Stepped care algorithms are based on clinically proven, best-practice pathways to care over a series of steps, while taking into account patients' preference[17]. The steps involve watchful waiting, guided self-help and other brief therapies, followed by more intensive psychological interventions or medication. In stepped care, more intensive

treatments are generally reserved for people who do not benefit from simpler first-line treatments, or for those who can be accurately predicted not to benefit from such treatments. The results of treatments and decisions about treatment provision are monitored systematically, and changes are made ('stepping up') if current treatments are not achieving a significant health gain[10]. Stepped care models have been developed for several health problems, including smoking, back pain, alcohol treatment, migraine, anxiety, eating disorders, methadone maintenance, and depression[10].

The main goal of the proposed study is to assess efficacy of a stepped care strategy compared with care as usual in patients with psychological distress after treatment for LC or HNC to improve psychological distress and thereby quality of life.

METHODS / DESIGN

DESIGN

In this prospective randomized controlled trial in two parallel groups, patients are recruited by screening all LC and HNC patients, who visit the Department of Pulmonary Diseases or the Department of Otolaryngology and Head and Neck Surgery of the VU University Medical Center in Amsterdam, the Netherlands, for follow-up consultation at least 1 month after treatment, for distress using a computerized touchscreen data collection system (OncoQuest) or by telephone using the Hospital Anxiety and Depression Scale (HADS). All patients who fulfil the in- and exclusion criteria are asked to participate. After stratification for tumor site (LC vs. HNC) and stage (stage I-II versus III-IV), 176 participating patients are randomly assigned to the intervention or control group. In order to assess efficacy, assessment before and after intervention takes place and at 3, 6, 9, and 12 months follow up.

STUDY SAMPLE

Inclusion criteria are (i) treatment for UICC stage I-IV lung or head and neck carcinoma: ICD-10 C00-C14 (lip, oral cavity and pharynx), C32 (larynx), C33 (trachea), C34 (lung); and (ii) psychological distress or possible or probable cases of depression or anxiety as assessed by the Hospital Anxiety and Depression Scale (HADS; HADS-D > 7 or HADS-A > 7 or HADS-total > 14).

Exclusion criteria are (i) other (neurological) diseases causing cognitive dysfunction, (ii) no motivation to undergo psychological therapy, (iii) current treatment for a depressive

or anxiety disorder, (iv) end of treatment for a psychiatric disorder < 2 months ago, (v) high suicide risk, (vi) psychotic and/or manic signs, or (vii) too little knowledge of the Dutch language to fill out the questionnaires.

RANDOMIZATION

Randomization is conducted centrally by an independent statistician, in blocks of two, stratified for tumor site (LC vs. HNC) and stage (stage I-II vs. III-IV), because these variables have prognostic relevance and need to be distributed evenly across both conditions.

INTERVENTION

Patients in the experimental study arm enter a stepped care program, including (i) watchful waiting, (ii) guided self-help via Internet or a booklet, (iii) face-to-face problem-solving therapy, and (iv) specialized psychological interventions such as cognitive behavioral therapy and/or antidepressant medication.

The basic proposition of stepped care is that all patients are offered the same low intensity (evidence-based) treatment as a first step. Only those patients, who do not recover, step up to a more intensive treatment. The HADS score is used to determine stepped-up levels of care. Stepping up to the next treatment level is indicated when a participant's HADS-A or HADS-D score exceeds 7. The care coordinator controls the process, monitors the symptoms, and makes sure the patient steps up if necessary.

The stepped care program in the present project includes the following four steps.

Step 1: Watchful waiting

In the first step it is agreed on not to start intervention yet, but to wait for further development of symptoms. Because part of the patients recovers spontaneously[18] 'watchful waiting' is included in the multidisciplinary guideline on depression as first treatment step. Duration of the watchful waiting period in the present project including cancer patients is set on 2 weeks.

Step 2: Guided self-help via Internet or a booklet

If there is no spontaneous recovery after 2 weeks, the care coordinator contacts the patient for one counselling session in which the self-help program is introduced. As intervention the existing program "Allesondercontrole" or the web based program "Allesondercontrole" (http://allesondercontrole.psy.vu.nl) is used. "Allesondercontrole" is

a brief intervention for problem solving based on self-examination. "Allesondercontrole" is already available. The website is currently only used for research purposes and both international and national research has shown that this intervention is effective in depression and anxiety[19]. The intervention is based on problem-solving therapy, which has been proven to be effective in several randomized controlled studies[20], also when delivered via the Internet. A recent meta-analysis by our group found that the effects of Internet-based treatments of depression and anxiety disorders are as large as those of face-to-face treatments[21]. The intervention "Allesondercontrole" takes 5 weeks. In that period respondents describe what they think is important in their lives, make a list of their problems and concerns, and divide these into three categories: unimportant problems (problems which are not related to what is important in their life), important and amenable problems (these are solved through a six-step procedure of problem solving), and important but unsolvable problems (such as having a serious disease like cancer); for each of the amenable problems the respondent makes a plan). Trained coaches guide the patients through this process. The coaching consists of brief, weekly contacts by email or by telephone, which takes about 10 to 15 minutes per week. The total coaching time is 1 to 1.5 hours per patient (estimation based on our previous trial). Coaching is not aimed at developing a patient-therapist relation but is only meant to give support in working through the self-help method.

Step 3: Face-to-face problem-solving therapy

When the patient has not recovered from the guided self-help program, a nurse from the department of Psychiatry offers a brief intervention: problem-solving therapy (PST). Earlier studies revealed that PST can be delivered by psychologists as well as nurses[22-24]. PST identifies problems that interfere with everyday functioning and that contribute to depression and anxiety. The treatment provides compensatory strategies that are designed to bypass the person's cognitive limitations and to improve adaptive functioning. PST comprises a short 6-session protocolled intervention. The first session takes 1 hour, the other sessions 45 minutes. PST is an evidence-based intervention for major depression and for psychological distress characterised by symptoms of depression and anxiety[22,23,25-28].

Step 4: Specialized psychological interventions such as cognitive behavioral therapy and/or antidepressant medication

In case all previous steps have not induced recovery, the patient chooses in close cooperation with the care coordinator between medication and psychotherapy. To ease this decision, the patient is offered the patient information letter of the Dutch College of General Practitioners on antidepressant medication. (A) If the patient chooses medication, the care coordinator contacts the patients' physician who prescribes antidepressant medication and monitors outcomes. (B) If the patient chooses psychotherapy, the patient is referred to a psychologist or a psychiatrist. The stepped care program is illustrated in Figure 1.

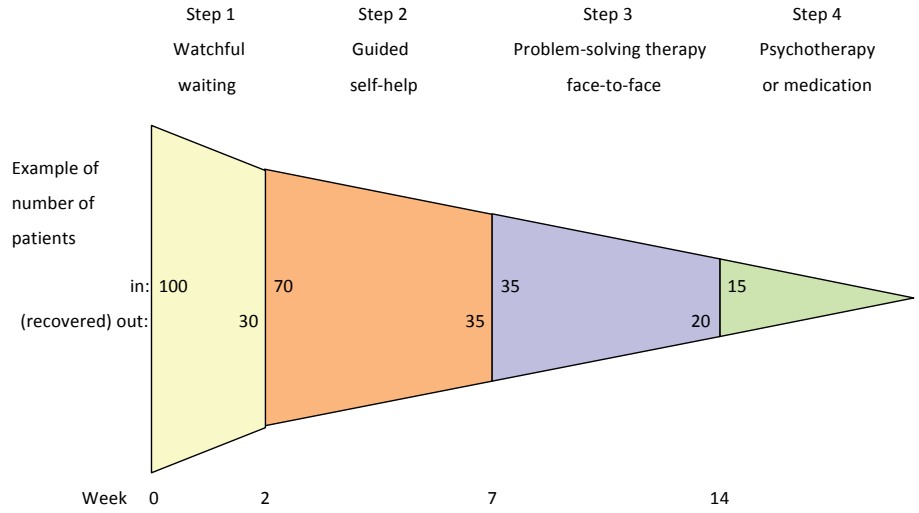

Figure 1. Overview of the stepped care program

CARE AS USUAL

Control group patients receive care as usual, which often means a single interview by a nurse or specialized intervention delivered by a social worker, psychologist or psychiatrist. In the context of the health economic evaluation, health care uptake is closely monitored, thus allowing for detailed post-hoc description of what usual care entailed exactly.

OUTCOME ASSESSMENT

Main outcome measure

The primary outcome measure is the Hospital Anxiety and Depression Scale (HADS). The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-assessment scale for measuring symptoms of anxiety and depression and has been specifically designed for use in the medical ill. This scale has been proven to have adequate psychometrical properties and the total HADS score has been recommended for routine monitoring of psychological distress in cancer patients[29-32].

Secondary outcomes

Secondary outcome measures are health related quality of life questionnaires (EORTC QLQ-C30), EORTC QLQ-H&N35, EORTC QLQ-LC13), general patient satisfaction (EORTC QLQ-PATSAT), and economic evaluation.

The EORTC QLQ-C30 is a tumor-specific, patient-based questionnaire. The questionnaire includes a global HRQOL scale (2 items) and comprises 5 functional scales: physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items) and social functioning (2 items). There are three symptom scales (fatigue (3 items), nausea, vomiting (2 items) and pain (2 items) and 6 single items relating to dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties[33].

The EORTC QLQ-LC13 module covers specific issues on lung cancer. The questionnaire comprises 12 symptom scales: a 3 item scale on dyspnoea, and 1 item scales on coughing, haemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts[34].

The EORTC QLQ-H&N35 module covers specific issues on head and neck cancer. It has been used previously in studies. The questionnaire comprises 7 subscales: pain (4 items), swallowing (5 items), senses (2 items), speech (3 items), social eating (4 items), social contact (5 items) and sexuality (2 items). There are 10 single items covering problems with teeth, dry mouth, sticky saliva, cough, opening the mouth wide, weight loss, weight gain, use of nutritional supplements, feeding tubes, and painkillers[35].

The EORTC QLQ-PATSAT32 module is a patient satisfaction with care measure. The questionnaire comprises 4 scales on interpersonal skills (3 items), technical skills (3 items), information provision (3 items), and availability (2 items) of doctors, the same 4 scales regarding nurses, 1 scale on other hospital personnel kindness and helpfulness,

and information giving (3 items), 1 scale on waiting time (2 items), 1 scale on access (2 items), and 3 single items on exchange of information, comfort/cleanness, and general satisfaction[36].

The economic evaluation will be conducted as a cost-utility analysis for (changes in) health-related quality of life. Patient outcome analysis: Health-related quality of life is assessed with the EQ-5D[37,38] at baseline and 12 months follow-up. Direct medical and direct non-medical cost data are collected with the TIC-P[39], a widely used health service receipt interview in economic evaluations. Unit resource use (GP visits, hospital days, etc.) will be multiplied by their appropriate integral cost prices[40]. Indirect non-medical cost data related to production losses through work loss days and work cutback days will be sampled with the appropriate PRODISQ modules[41].

SOCIODEMOGRAPHIC AND MEDICAL DATA

Next to the outcome measures, a case record form is developed including sociodemography (age, gender, social economic status), cancer and cancer treatment (TNM and ICD-10 classification, documentation of surgery and (chemo)radiation), and co-morbidity (Adult Comorbidity Evaluation 27 (ACE-27) test). The ACE-27 was designed specifically for cancer patients and classifies patients into 1 of 4 grades of comorbidity (none, mild, moderate, severe)[42].

DIAGNOSTIC EVALUATION

The presence of a major depression or an anxiety disorder is assessed according to the Composite International Diagnostic Interview (CIDI). The CIDI is a comprehensive, fully structured interview designed to be used by trained lay interviewers for the assessment of mental disorders according to the definitions and criteria of ICD-10 and DSM-IV. The diagnostic section of the interview is based on the World Health Organization's Composite International Diagnostic Interview[43,44].

STATISTICAL ANALYSES

Descriptive statistics will be generated for the range of outcome variables, in particular to gauge whether randomization resulted in a balanced distribution of patients' characteristics across the experimental conditions.

Repeated measures ANOVA will be used to determine the efficacy of intervention for continuous outcomes such as changes in HADS depression/anxiety symptom severity.

Longitudinal changes over time in these variables will also be evaluation over all time points simultaneously using generalized estimating equations (GEEs). Analyses will be conducted in agreement with the intention-to-treat principle.

The economic data will be collected at baseline and follow-up and conducted as a cost utility analysis that is with health-related quality of life as the clinical endpoint. For the economic evaluation use will be made of the pertinent guidelines[40,45-47]. In other words, analyses will be conducted in agreement with the intention-to-treat principle; the societal perspective will be taken encompassing intervention costs, direct non-medical costs and indirect costs. Production losses will be economically valuated using the friction cost method[48]. The time horizon will be set at 1 year, and therefore will neither discount costs nor effects. Costs and effects will be analyzed simultaneously, incremental cost-effectiveness ratios (ICERs) will be calculated and placed within 95% confidence intervals, 2500 bootstrap replications of the ICERs will be projected on a cost-effectiveness plane, ICER acceptability curves will be plotted against different willingness-to-pay ceilings[49], and sensitivity analysis will be conducted as a matter of course focussing on uncertainty in the main cost-drivers. This will be done for the costs per QALY gained in a cost utility analysis.

SAMPLE SIZE CALCULATION

To demonstrate an effect size of 0.50 (based on a meta-analysis on psychological treatment in mild depression), 66 patients are needed in each group (power 80%, significance level 5%)[50]. Taking into account a dropout of 25%, in total 176 patients will be included. With an annual intake of 450 LC and HNC patients, 30% having psychological distress, and 50% willing to cooperate, and an inclusion period of 2.5 years, feasibility of the study is guaranteed.

DISCUSSION

There is a rising need towards screening for physical and psychosocial problems and the need for supportive care in routine clinical practice through patient-reported outcomes (PRO's)[51-55]. The use of PRO's has proven to facilitate communication concerning quality of life between patients and health care professionals[56-58]. Evidence that this approach may influence patient outcome or improve quality of life is scarce. Luckett and colleagues[55] recommend additional efforts to strengthen the effects of screening, such as using more

tumor-specific (instead of generic) PRO's, improving the interpretability of feedback for both medical staff and patients, and training patients in self-efficacy. Organizing supportive care according to the chronic care model[59] and providing evidence-based supportive care can also improve disease management in cancer patients.

Disease management refers to a system of coordinated comprehensive care along the continuum of the disease across health care delivery systems, with a specific focus on self-management. Other forms of providing supportive care comprise integrated care, transmural care, collaborative care, case management, and stepped care. In oncological settings, recent projects as "Supporting transmural oncological care"[60] and "Integrated care"[61] revealed that supportive care coordination improves supportive care delivery in cancer patients. A review on professional patient navigation in head and neck cancer patients showed that the presence of a professional care navigator leads to higher patient satisfaction, shorter duration of hospitalization, fewer cancer-related problems, better emotional quality of life, and patient empowerment[62].

At present, in VU University Medical Center in Amsterdam, the Netherlands, efficient structured monitoring of quality of life by a touchscreen computer-based data collection system "OncoQuest" is implemented in routine clinical practice[15,63]. Patients can independently fill in the EORTC QLQ-C30, and tumor-specific modules, and the Hospital Anxiety and Depression Scale (HADS) on a touchscreen. It takes on average 9 minutes to complete the questionnaires. Data are processed in real-time and care providers can watch the results by clear charts (the well-being profile) on a computer in their consulting rooms and, if indicated, set up a custom-made supportive care plan. Nurses are trained as care navigators to arrange the supportive care according to the disease management principles.

From an economic perspective and in an age of increasing numbers of cancer survivors and increasing shortages of health care personnel, it is relevant to integrate cost-effective health care options including eHealth applications into a stepped care approach, as in the presented RCT. This fits right in with the importance that patient organizations, policy makers and researchers currently attach to eHealth self-management tools.

Beside assessing overall efficacy of a stepped care approach targeting psychological distress in cancer patients, also insight will be obtained into possible determinants of the need for psychosocial care and success of a stepped care approach. These possible determinants include sociodemographic and disease and treatment related parameters, comorbidity, and quality of life.

Knowledge transfer of the results of the project on efficacy of stepped care targeting psychological distress in cancer patients into the scientific community includes submitting papers to (inter)national peer-reviewed journals, proceedings, and news letters and presenting papers at national and international conferences, both in early pilot stages and after conclusion of the project.

In case of positive results of this RCT on effectiveness, a second step aims at adaptation and maintenance of the stepped care approach to bring the evidence-based practice regarding improving distress in cancer patients into consistent and appropriate use in all oncological centers in the Netherlands. A sharing mechanism will be designed to facilitate adaptation and maintenance such as informing the Dutch Lung Cancer Study Group, Dutch Society of Pulmonologists (NVALT), Netherlands Society of Otorhinolaryngology and Cervico-Facial Surgery, Dutch Head and Neck Oncology Cooperative Group (NWHHT), Dutch Society of Psychosocial Oncology, oncological and psychiatric nursing societies and patient societies, to structure the results of this project into implementation projects in all oncological centers throughout the Netherlands. Guideline committees will be informed and advised to adapt the Nation-wide Guidelines on Laryngeal (2010, version 3.0), Lung (2004, version 1.0), Oral Cavity and Oropharyngeal (2004, version 1.4) and Hypopharyngeal (2010, version 2.0) Cancer[64-67].

The bottom line of the stepped care approach is healthier patients, more satisfied care providers, and cost savings by empowering both professionals and patients.

ETHICAL CONSIDERATIONS

This study is conducted in accordance with the Declaration of Helsinki and in accordance with local laws and regulations. Eligible patients are fully informed about the study and asked to participate. The patients receive a patient information sheet and have ample opportunity to ask questions and to consider the implications of the study before deciding to participate. Patients consent is noted on an informed consent form compliant with the local and ethical regulations. If during the study the patient for whatever reason no longer wishes to participate, the patient is allowed to withdraw his consent at any time. The study protocol has been approved by the Medical Ethical Committee of VU University Medical Center, Amsterdam, the Netherlands.

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CHAPTER 5

Stepped care targeting psychological distress in head and neck cancer and lung cancer patients: a randomized controlled trial

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Annals of Oncology 2016; 10.1093/annonc/mdw230

ABSTRACT

Background. This study aimed to evaluate the efficacy of stepped care (SC) targeting psychological distress in head and neck cancer (HNC) and lung cancer (LC) patients.

Methods. Patients with untreated distress (Hospital Anxiety and Depression Scale (HADS; HADS-D > 7, HADS-A > 7, or HADS-total > 14)) were randomized to SC (*n* = 75) or care as usual (CAU) (*n* = 81). SC consisted of watchful waiting, guided self-help, problem-solving therapy, and psychotherapy and/or psychotropic medication. The primary outcome measure was the HADS, secondary outcome measures were recovery rate, EORTC QLQ-C30, QLQ-H&N35/QLQ-LC13, and IN-PATSAT32. Measures were assessed at baseline, after completion of care, and at 3, 6, 9, and 12 months follow-up. Linear mixed models, *t*-tests and effect sizes (ES) were used to assess group differences.

Results. Patients with untreated distress were randomized to SC (*n* = 75) or care as usual (CAU) (*n* = 81). The course of psychological distress was better after SC compared with CAU (HADS-total, *P* = .005; HADS-A, *P* = .046; HADS-D, *P* = .007). The SC group scored better post-treatment (HADS-total, ES = 0.56; HADS-A, ES = 0.38; HADS-D, ES = 0.64) and at 9 months follow-up (HADS-total, ES = 0.42 and HADS-A, ES = 0.40). The recovery rate post-treatment was 55% after SC compared with 29% after CAU (*P* = .002), and 46% and 37% at 12 months follow-up (*P* = .35). Within SC, 28% recovered after watchful waiting, 34% after guided self-help, 9% after problem-solving therapy, and 17% after psychotherapy and/or psychotropic medication. The effect of SC was stronger for patients with a depressive or anxiety disorder compared with patients without such a disorder (HADS-total, *P* = .001; HADS-A, *P* = .003; HADS-D, *P* = .041).

Conclusions. SC is effective and speeds up recovery among HNC and LC patients with untreated psychological distress.

Trial registration. Netherlands Trial Register (NTR1868)

INTRODUCTION

Psychosocial intervention in cancer patients is effective[1-4], but many distressed cancer patients are not referred[5,6]. Other forms of care delivery, such as brief therapies, self-help, and collaborative care, may overcome barriers to referral[2,3,5,7,8]. In stepped care (SC), more intensive interventions are reserved for patients who do not benefit from low-intensity interventions[9-11]. We developed an SC program targeting cancer patients with psychological distress[12].

The aim of this study was to assess the efficacy of SC to improve psychological distress compared with care as usual (CAU). Secondary aims were to investigate a possible positively moderating effect of the presence of a depressive or anxiety disorder (versus an increased risk for a disorder), and a possible decay of effect of SC in the long-term. Also, possible positive effects of SC on health-related quality of life and satisfaction with care were explored.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

This study was a monocenter, parallel-group randomized, controlled trial (RCT), and approved by the Medical Ethics Committee of VU University Medical Center and registered in the Netherlands Trial Register (NTR1868)[12].

Eligible participants were treated with curative intent at least 1 month earlier for head and neck cancer (HNC) or lung cancer (LC) and had psychological distress (Hospital Anxiety and Depression Scale (HADS; HADS-D > 7, HADS-A > 7, or HADS-total > 14))[13]. Exclusion criteria were (i) cognitive dysfunction, (ii) lack of motivation to undergo psychological therapy, (iii) currently under treatment for a depressive or anxiety disorder, (iv) treatment for a psychiatric disorder < 2 months ago, (v) high suicide risk, (vi) psychotic and/or manic signs (those patients were referred to the psychiatric service), or (vii) insufficient knowledge of the Dutch language. All HNC and LC patients who visited the outpatient clinic for follow-up consultation between 2009 and 2013 were screened for distress using the HADS via a touchscreen data collection system (OncoQuest) or telephone. All patients with distress received written information and an informed consent form. Patients who returned their signed informed consent had a diagnostic telephone interview (Composite International Diagnostic Interview (CIDI))[14]. After completion of the interview, patients were randomized into the intervention or control group.

INTERVENTION

A description of the SC program can be found elsewhere[12]. In short, it includes (i) watchful waiting, (ii) guided self-help via the Internet or a booklet, (iii) face-to-face problem-solving therapy, and (iv) specialized psychological interventions and/or psychotropic medication. Stepping up to the next treatment was mandated when a patient's HADS-A or HADS-D score remained above 7. All care providers were thoroughly trained using protocol in order to limit differences between care professionals. Therefore, major differences in effect between care providers were not expected. In the control group patients received CAU.

OUTCOMES

Outcome measures were collected at baseline (t0), after the intervention period (time depended upon duration of the SC program) or control period (4 months) (t1), and 3 (t2), 6 (t3), 9 (t4), and 12 months after t1 (t5).

The primary outcome measure was the HADS[13]. The HADS is a 14-item self-assessment scale for measuring distress (total HADS score) with two subscales, anxiety (HADS-A) and depression (HADS-D). The total HADS score ranges from 0 to 42, the subscales from 0 to 21.

Secondary outcomes were health-related quality of life (HRQOL) (EORTC QLQ-C30 (version 3.0), QLQ-H&N35, QLQ-LC13), and patient satisfaction with care (EORTC IN-PATSAT32)[15-18]. Following EORTC guidelines, scores were linearly transformed to 0-100 scores. For the global quality of life scale, functioning scales, and the IN-PATSAT scales, higher scores correspond to better levels of functioning or satisfaction with care, while for symptom scales, higher scores represent higher levels of symptoms/problems. The presence of a depressive or anxiety disorder was assessed according to the CIDI[14].

SAMPLE SIZE

To demonstrate an improvement of five points (based on average scores in earlier studies[19]) on the HADS-total scale after 1 year (power 80%, significance level 5%, standard deviation (SD) 7), 66 patients were needed per group (132 patients in total). A study by Puhan et al.[20], reported that an improvement of about 1.5 on the HADS may already be clinically meaningful for patients.

RANDOMIZATION AND BLINDING

This study was an RCT, with equal randomization [1:1], and stratification for tumor site (LC versus HNC) and stage (I-II versus III-IV) in blocks of two. Randomization was conducted centrally by an independent statistician. Patients and physicians were aware of treatment allocation, whereas statisticians were blinded. Blinding of patients was not possible since they had been given information about SC before inclusion and consequently recognized the applied intervention.

STATISTICAL ANALYSES

Independent samples *t*-tests and χ^2 tests were used to gauge whether randomization resulted in a balanced distribution of patient characteristics across the experimental conditions. Intention-to-treat analyses were carried out. To test differences between conditions regarding the course of distress, HRQOL, and satisfaction with care from baseline to follow-up, linear mixed models were used with fixed effects for group, measurement, and their two-way interaction, and a random intercept for subjects. To assess a potential confounding effect of the time between t0 and t1, an adjusted linear mixed model was analyzed where the time between t0 and t1 was added as (fixed) covariate to the previous model. An increased risk of a depressive or anxiety disorder versus the presence of a depressive or anxiety disorder was taken into account by adding the risk, its two- and three-way interactions with group and measurement to the linear mixed model.

Independent samples *t*-tests were used to measure differences in psychological distress, HRQOL, and satisfaction with care between the conditions at t1 and all follow-up measurements; missing data were excluded analysis-by-analysis instead of list-wise. Effect sizes (ES) were calculated by dividing the difference between the means of the intervention and the control group by the pooled SD. Low, moderate and high ES were defined as ES = 0.10-0.30, ES = 0.30-0.50 and ES > 0.50[21]. An absolute difference in HRQOL ≥ 10% of the instrument range was considered clinically meaningful[22].

For all statistical analyses, a *P* value of < .05 was considered statistically significant. Analyses were carried out with SPSS 20.0 (IBM Corp., Armonk, NY USA).

RESULTS

STUDY POPULATION

Patients were screened for distress via the HADS in OncoQuest (2885 times in 920 individual patients) or by telephone (378 patients) (Figure 1). In total, 265 patients met the inclusion and exclusion criteria. Of these patients, 109 patients did not want to participate (n = 102) or could not be contacted (n = 7). In total, 75 were randomized to the intervention and 81 to the control group. The mean time between t0 and t1 of the intervention and control group was comparable (15.0 weeks (SD = 19.5) and 16.3 weeks (SD = 3.6)). At 12 months follow-up (t5), 54 patients in the intervention group and 52 patients in the control group completed the outcome assessment. During the study, 4 patients (5.3%) in the intervention group versus 15 patients (18.5%) in the control group died (P = .012).

The majority was treated for HNC (94%) (Table 1). At baseline, there were no significant differences between the intervention and control group regarding socio-demographic and clinical characteristics. A statistically significant difference was found regarding alcohol dependency: patients in the intervention group were more often alcohol dependent (13.3%) than control patients (3.7%). When comparing the outcome measures at baseline (Table 2, and Table 3), no significant differences between the two groups were observed, except for better scores in the intervention group regarding HADS-D (8.2 versus 9.5; P = .029), the QLQ-C30 scale on social functioning (70.5 versus 59.9; P = .023) and the QLQ-H&N35 scale on social contact (16.4 versus 25.5; P = .014) and sexuality (38.6 versus 53.4; P = .016), and worse scores regarding IN-PATSAT32 on satisfaction with nurses (30.9 versus 40.6; P = .015) and satisfaction with other personnel (33.6 versus 41.3; P = .033).

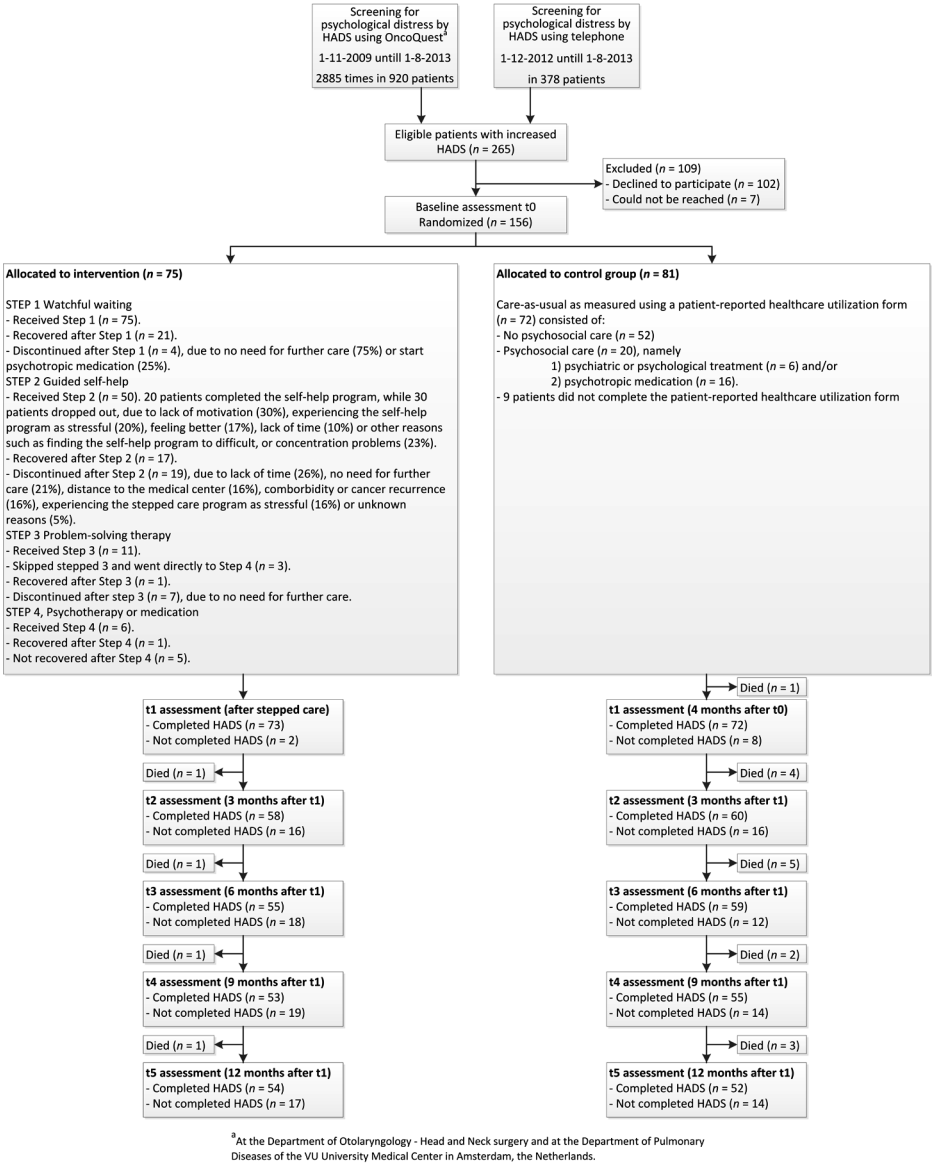

Figure 1. CONSORT flow diagram

Table 1. Overview of patient characteristics

	Total group (*n* = 156)		Intervention (*n* = 75)		Control (*n* = 81)	
	n	%	*n*	%	*n*	%
Age, years						
Mean age (SD)	62.0 (9.4)		62.5 (8.7)		61.6 (10.0)	
Gender						
Male	95	60.9%	47	62.7%	48	59.3%
Female	61	39.1%	28	37.3%	33	40.7%
Marital status						
Married/living with partner	106	67.9%	54	72.0%	52	64.2%
Unmarried/divorced/widowed	50	32.1%	21	28.0%	29	35.8%
Worksituation						
Paid job	48	30.8%	23	30.7%	25	30.9%
No paid job/retired	108	69.2%	52	69.3%	56	69.1%
Tumor location						
Lip/oralcavity/oropharynx	76	48.7%	30	40.0%	46	56.8%
Hypopharynx/larynx	40	25.6%	21	28.0%	19	23.5%
Other head and neck cancers	31	19.9%	19	25.3%	12	14.8%
Lung	9	5.8%	5	6.7%	4	4.9%
Tumor stage						
I	39	25.0%	17	22.7%	22	27.2%
II	25	16.0%	15	20.0%	10	12.3%
III	29	18.6%	12	16.0%	17	21.0%
IV	53	34.0%	22	30.7%	30	37.0%
Unknown	10	6.4%	8	10.7%	2	2.5%
Treatment						
Single treatment	76	48.7%	39	52.0%	37	45.7%
Combination treatment	80	51.3%	36	48.0%	44	54.3%
Time since treatment						
< 7 months	56	35.9%	29	38.7%	27	33.3%
7-12 months	26	16.7%	10	13.3%	16	19.8%
> 12 months	74	47.4%	36	48.0%	38	46.9%
Anxiety or depressive disorder						
Yes	35	22.4%	14	18.7%	21	25.9%
No	121	77.6%	61	81.3%	60	74.1%
Nicotine dependence						
Yes	27	17.3%	12	16.0%	15	18.5%
No	129	82.7%	63	84.0%	66	81.5%
Alcohol dependence*						
Yes	13	8.3%	10	13.3%	3	3.7%
No	143	91.7%	65	86.7%	78	96.3%

* $P < .05$

Table 2. Overview of the course of the HADS scores in the total group, and the course of the HADS scores with respect to presence of a psychiatric disorder (anxiety or depression)

		t0			t1			t2			t3			t4			t5		
TOTAL GROUP		*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*
HADS-A	Intervention	75	9.4	3.6	73	6.8	4.3	58	7.0	3.4	55	6.9	4.1	53	6.8	4.2	55	7.0	4.0
	Control	81	9.6	3.4	72	8.6	5.1	60	8.0	5.1	59	7.4	4.9	55	8.6	4.9	52	7.7	4.4
HADS-D	Intervention	75	8.2	3.7	73	5.6	4.9	58	6.1	4.0	55	6.7	4.7	53	6.5	4.2	55	6.3	4.7
	Control	81	9.5	3.8	72	8.8	5.3	60	7.7	5.2	58	7.3	4.8	55	8.1	4.8	52	7.5	5.0
HADS-T	Intervention	75	17.5	5.2	73	12.4	8.3	58	13.0	6.6	55	13.6	8.1	53	13.3	7.5	55	13.2	7.7
	Control	81	19.1	5.6	72	17.4	9.6	60	15.7	9.6	58	14.5	8.6	55	16.7	8.8	52	15.2	8.6
INCREASED RISK																			
HADS-A	Intervention	61	8.8	3.5	59	6.6	4.2	48	6.7	3.3	45	6.4	3.7	44	6.3	3.8	45	6.4	3.7
	Control	60	9.3	3.1	55	7.5	4.2	48	6.8	4.2	46	6.7	4.2	42	7.3	4.1	40	7.0	4.2
HADS-D	Intervention	61	7.9	3.4	59	5.5	4.5	48	6.1	3.9	45	6.6	4.5	44	6.5	4.0	45	6.2	4.6
	Control	60	8.8	3.5	55	7.5	4.4	48	6.3	4.5	46	6.2	4.4	42	6.5	4.2	40	6.4	4.2
HADS-T	Intervention	61	16.7	4.6	59	12.1	7.8	48	12.8	6.4	45	13.0	7.5	44	12.8	6.6	45	12.6	7.1
	Control	60	18.1	4.9	55	15.1	7.8	48	13.1	8.0	46	12.9	7.9	42	13.8	7.3	40	13.4	7.5
PSYCHIATRIC DISORDER																			
HADS-A	Intervention	14	11.6	2.8	14	7.8	4.8	10	8.4	3.6	10	9.0	5.2	9	9.1	5.7	10	9.2	4.9
	Control	21	10.4	4.1	17	12.0	6.5	12	12.7	5.8	13	10.2	6.2	13	12.7	5.0	12	10.2	4.3
HADS-D	Intervention	14	9.6	4.4	14	6.2	6.3	10	5.7	4.6	10	7.2	5.7	9	6.6	5.4	10	6.8	5.4
	Control	21	11.4	3.9	17	13.1	5.6	12	13.3	4.1	12	11.5	3.9	13	13.1	3.0	12	11.3	5.7
HADS-T	Intervention	14	21.1	5.9	14	14.0	10.5	10	14.1	7.8	10	16.2	10.5	9	15.7	10.7	10	16.0	10.1
	Control	21	21.8	6.6	17	25.1	10.9	12	25.9	9.1	12	20.9	8.8	13	25.8	7.2	12	21.4	9.5
TOTAL GROUP					*ES*	*P value*		*ES*	*P value*		*ES*	*P value*		*ES*	*P value*		*ES*	*P value*	
HADS-A					0.38	**.024**		0.23	.20		0.12	.53		0.40	**.040**		0.19	.33	
HADS-D					0.64	**<.001**		0.35	.062		-0.13	.48		0.35	.076		0.25	.20	
HADS-T					0.56	**.001**		0.32	.086		-0.12	.54		0.42	**.033**		0.24	.21	
INCREASED RISK																			
HADS-A					0.23	.22		0.04	.85		0.06	.78		0.26	.23		0.14	.52	
HADS-D					0.46	**.016**		0.04	.87		0.08	.72		0.01	.98		0.04	.84	
HADS-T					0.39	**.040**		0.04	.84		0.01	.95		0.15	.48		0.10	.64	
PSYCHIATRIC DISORDER																			
HADS-A					0.73	.053		0.86	.057		0.20	.64		0.68	.13		0.21	.63	
HADS-D					1.16	**.003**		1.74	**.001**		0.90	**.048**		1.58	**.002**		0.80	.076	
HADS-T					1.03	**.008**		1.38	**.004**		0.49	.27		1.15	**.015**		0.56	.21	

m = mean; SD = standard deviation; HADS-A = HADS anxiety scale; HADS-D = HADS depression scale; HADS-T = HADS total scale; ES = effect size. Significant differences ($P < .05$) are presented in bold font.

Table 3. Overview of the course of the EORTC QLQ-C30, QLQ-H&N35 and IN-PATSAT32 scales

		t0			t1			t2			t3			t4			t5		
		n	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*
QLQ-C30																			
Global QOL	Intervention	73	59.4	20.2	60	63.6	19.6	58	65.2	20.7	55	61.7	19.1	54	63.3	18.4	55	65.3	17.8
	Control	71	56.2	20.2	71	58.9	20.2	61	60.8	22.3	57	61.8	21.9	54	61.9	22.1	51	67.0	18.3
Physical*	Intervention	73	72.3	21.1	60	77.3	19.6	57	78.6	20.5	55	76.9	19.8	54	79.8	18.7	53	79.6	20.6
	Control	71	69.8	21.1	71	73.5	20.9	61	75.2	21.5	57	75.8	20.9	54	77.2	22.2	51	80.3	19.0
Role*	Intervention	73	63.7	27.5	60	**77.8**	24.3	57	71.6	26.2	55	69.7	28.9	54	73.5	24.3	54	74.4	26.4
	Control	71	57.5	28.7	70	**64.0**	26.9	61	63.9	30.6	57	68.1	30.3	54	66.0	32.4	51	68.3	27.5
Emotional*	Intervention	73	57.6	26.0	60	**69.2**	27.0	58	67.8	21.7	55	66.4	26.2	54	69.6	22.2	55	71.4	22.6
	Control	71	57.5	22.5	71	**58.7**	25.7	61	62.0	26.0	57	65.9	25.0	54	62.8	26.9	51	67.5	24.2
Cognitive*	Intervention	73	71.5	27.0	60	**81.9**	22.4	58	79.6	20.7	55	77.3	25.7	54	**80.9**	21.1	55	79.4	22.9
	Control	71	70.4	24.6	71	**71.1**	22.5	61	72.1	25.4	57	73.7	24.6	54	**68.8**	29.3	51	74.2	22.7
Social*	Intervention	73	**70.5**	26.4	60	**79.2**	24.7	58	**84.2**	20.6	55	78.2	24.2	54	80.6	24.8	55	81.2	23.4
	Control	71	**59.9**	29.4	71	**65.0**	29.2	61	**71.3**	30.3	57	70.5	30.7	54	71.3	30.1	50	73.3	27.8
Fatigue	Intervention	73	48.9	26.4	60	36.2	24.8	57	36.5	23.4	55	39.8	27.4	54	38.2	24.7	54	34.9	23.1
	Control	71	49.1	23.9	71	44.2	26.2	61	41.0	28.1	57	39.0	26.3	54	40.1	28.0	51	38.1	23.9
Nausea	Intervention	73	10.3	16.6	60	5.6	13.3	58	6.0	13.5	55	7.3	12.7	54	11.4	22.9	55	6.7	13.5
	Control	71	11.7	19.0	71	8.2	17.1	61	9.6	20.7	57	7.6	18.4	54	9.0	16.7	51	9.8	17.7
Pain	Intervention	73	33.6	30.4	60	24.7	25.6	58	25.9	24.8	55	27.9	29.2	54	23.8	27.8	55	22.4	22.7
	Control	71	33.8	28.3	71	29.3	31.0	61	24.9	30.7	57	30.1	30.8	54	28.4	31.8	51	25.5	29.3
QLQ-H&N35																			
Oral pain	Intervention	68	29.3	27.7	56	22.5	20.5	52	22.4	21.0	51	24.7	22.4	50	24.0	21.5	51	22.9	20.8
	Control	66	30.9	24.1	67	28.5	23.2	56	23.1	22.4	55	23.9	23.4	51	25.3	25.5	49	26.0	26.3
Swallowing**	Intervention	68	26.8	26.6	56	22.9	23.7	52	21.2	22.4	51	25.3	25.7	50	20.7	22.8	51	22.5	25.7
	Control	65	31.3	29.7	66	30.9	26.6	55	27.1	28.3	54	22.9	25.4	50	24.4	26.5	48	21.4	25.1
Senses**	Intervention	68	26.7	27.2	56	22.3	25.3	52	20.5	25.3	51	20.9	27.0	50	20.7	27.5	51	23.5	30.8
	Control	66	28.3	27.6	66	25.5	27.5	56	23.8	22.0	55	21.2	25.8	50	24.0	28.8	49	21.4	27.0
Speech**	Intervention	68	24.8	24.0	56	21.9	23.7	52	21.2	21.7	51	22.5	22.9	50	20.7	23.1	51	19.0	21.7
	Control	64	28.9	26.6	65	29.1	27.5	55	25.3	28.2	53	23.9	25.0	50	26.8	27.5	48	22.9	25.0
Social eating	Intervention	68	28.1	27.2	56	27.5	28.8	52	**21.2**	25.2	51	27.5	29.1	49	23.6	28.5	50	25.2	29.4
	Control	62	37.9	30.3	64	33.5	30.2	54	**33.1**	32.5	54	26.5	29.2	48	29.1	31.3	45	24.7	29.0
Social contact	Intervention	68	**16.4**	17.2	56	**12.5**	16.9	52	**11.4**	15.9	51	13.8	16.4	49	**10.8**	14.6	51	11.6	14.1
	Control	66	**25.5**	24.4	66	**24.7**	23.3	55	**23.8**	24.9	55	19.9	25.4	51	**21.7**	26.8	49	19.0	23.5
Sexuality**	Intervention	66	**38.6**	34.0	49	**34.7**	35.0	49	39.1	34.6	49	42.5	35.4	47	35.8	34.9	45	33.0	33.0
	Control	59	**53.4**	33.6	58	**54.0**	37.9	49	49.3	39.5	51	49.0	39.2	44	45.8	37.7	42	40.9	35.5

Table 3. Overview of the course of the EORTC QLQ-C30, QLQ-H&N35 and IN-PATSAT32 scales *(continued)*

		t0			t1			t2			t3			t4			t5		
		n	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*	*n*	*m*	*SD*
IN-PATSAT32																			
Doctors	Intervention	68	32.1	22.4	57	32.3	23.2	52	28.5	19.9	49	27.8	20.0	46	27.5	23.1	50	27.3	21.0
	Control	65	34.5	22.3	69	37.7	21.8	57	37.6	20.9	51	34.3	27.9	47	27.8	39.9	44	26.5	34.6
Nurses	Intervention	67	**30.9**	21.2	55	34.3	23.1	50	32.3	21.7	46	30.0	20.2	44	26.8	21.9	48	31.6	26.3
	Control	64	**40.6**	24.1	67	38.0	24.0	55	40.1	22.3	48	34.7	29.6	45	31.3	43.4	42	31.0	37.3
Other pers.	Intervention	66	**33.6**	19.9	54	35.0	23.3	49	33.7	21.1	47	32.6	21.3	44	27.7	21.6	47	33.0	25.6
	Control	63	**41.3**	20.5	67	39.9	20.7	55	41.4	21.8	48	36.6	28.3	45	27.2	40.9	42	29.4	36.5
Waiting time	Intervention	65	34.0	21.6	55	38.9	21.9	50	35.0	23.8	47	34.3	22.0	45	30.3	23.2	49	31.9	27.3
	Control	64	39.1	22.8	67	39.0	22.0	55	42.0	23.7	48	35.9	29.9	45	29.2	42.7	42	29.5	37.5
Access	Intervention	66	50.4	22.2	55	51.8	22.5	50	48.0	23.9	47	45.7	26.1	45	41.9	28.3	49	39.5	29.2
	Control	64	52.5	24.5	68	50.9	22.6	56	52.0	22.5	48	47.4	32.5	45	41.1	45.2	42	42.9	40.1
Information	Intervention	63	59.9	23.1	53	56.6	22.5	49	60.7	25.0	45	62.2	23.0	45	60.6	23.5	48	58.3	25.4
	Control	60	53.3	28.9	66	53.0	26.5	52	53.4	25.3	48	60.4	31.7	44	63.1	45.9	42	64.3	40.6
General sf.	Intervention	66	58.3	23.8	54	54.6	22.8	50	57.0	25.8	46	57.6	22.3	45	60.0	27.4	49	57.7	28.5
	Control	62	48.8	25.8	66	50.0	24.8	55	51.8	25.8	48	55.2	33.4	45	57.8	48.2	42	57.1	41.4

m = mean; SD = standard deviation; * = .. functioning; ** = problems with .. ; general sf. = general satisfaction; other pers. = other personnel. Significant differences ($P < .05$) are underlined and clinically relevant differences (>10 points difference) are presented in bold font.

EFFICACY OF THE SC PROGRAM

The course of distress over time (Table 2) was significantly better for the intervention compared with the control group regarding HADS-total (assessment * group: $P = .005$), HADS-A (assessment * group: $P = .046$), and HADS-D (assessment * group: $P = .007$). After correcting for time between t0 and t1, the course of distress over time was still significantly better regarding HADS-total (assessment * group: $P = .006$), HADS-A (assessment * group: $P = .0496$), and HADS-D (assessment * group: $P = .008$). When adjusting for baseline HADS, the course of distress over time was still significantly better (HADS-total (assessment * group: $P = .002$ and HADS-D (assessment * group: $P < .001$), except for HADS-A (assessment * group: $P = .061$). At t1, the intervention group scored significantly better regarding HADS-total ($P = .001$; ES = 0.56), HADS-A ($P = .024$; ES = 0.38), and HADS-D ($P < .001$; ES = 0.64). At t2, t3, and t5 (3, 6, and 12 months follow-up), there were no significant differences between the two groups. At t4 (9 months follow-up), the intervention group scored significantly better on HADS-total ($P = .033$; ES = 0.42) and HADS-A ($P = .04$; ES = 0.40).

The SC program had more influence on the course of distress among patients with a depressive or anxiety disorder compared with patients without a psychiatric disorder, regarding HADS-total ($P = .001$), HADS-A ($P = .003$), and HADS-D ($P = .041$) (Table 2).

The recovery rate of distress (HADS-A ≤ 7 and HADS-D ≤ 7) at t1 was 54.8% in the intervention group versus 29.2% in the control group ($\chi^2 = 9.769$; $P = .002$), and at t5 this was 45.5% in the intervention versus 36.5% in the control group ($\chi^2 = 0.878$; $P = .349$). In total, 28% recovered after watchful waiting, 34% after guided self-help, 9% after problem-solving therapy, and 17% after psychotherapy and/or psychotropic medication).

For patients in the control group, CAU mostly consisted of no additional care (72.2%), while in some cases psychiatric or psychological treatment (8.3%) and/or psychotropic medication (22.2%) was provided.

Results on HRQOL and satisfaction with care are presented in Table 3. Results of the QLQ-LC13 are not presented because of the small number of LC patients. The course of the QLQ-C30 emotional functioning scale was significantly different for the intervention compared with the control group (assessment * group: $P = .033$). Post-treatment (t1), patients in the intervention group scored clinically and statistically significantly better on role, emotional, cognitive, and social functioning (QLQ-C30), and social contacts and sexual functioning (QLQ-H&N35). At 3 months follow-up (t2), this positive effect remained

regarding social functioning and social contacts. Also, at t2, patients in the intervention group reported less trouble with social eating. At 9 months follow-up (t4), patients in the intervention group had statistically and clinically better scores regarding cognitive functioning and social contacts. At 6 (t3) and 12 (t5) months follow-up, there were no significant differences between the two groups.

DISCUSSION

SC is effective to reduce distress and improve HRQOL among HNC and possibly LC patients. The course of distress from baseline to 12 months follow-up was significantly better for the intervention group compared with the control group. ES at separate time points revealed moderate to strong effects of SC on distress and several HRQOL aspects post-treatment and at short-term follow-up, but no longer at 12 months follow-up (decay effect). Also, the recovery rate was significantly higher post-treatment (55% in the intervention group versus 29% in the control group) but not at 12 months follow-up (46% versus 37%, respectively). Thus, SC seems to speed up recovery of distress and improvement of HRQOL.

A meta-analysis on RCTs (n = 14) on SC for depression in a mixed population also showed that SC has a moderate effect on depression (pooled ES of 0.34 (95% confidence interval 0.20-0.48))[23]. The SC interventions varied greatly in number of treatment steps, treatments offered, professionals involved, and criteria to step up, which makes it difficult to compare study outcomes. A study among breast cancer patients[7] reported on an SC program with two steps (stress management education (all patients), followed by a stress management intervention (patients with distress)), which is clearly different from our approach with four steps. It was striking that in our study almost 30% of distressed cancer patients recovered after 2 weeks of watchful waiting. This percentage is much higher compared with the 5% after 4 weeks of watchful waiting among primary care patients with a depressive or anxiety disorder[24]. The percentage of recovered cancer patients after step 2 of the SC program (guided self-help) was also much higher: 34% versus 9% in the previous study. An explanation might be that cancer patients were screened for distress and entered the SC program at the time of their medical follow-up consultation, which is often very stressful. After reassurance that malignancy has not recurred, distress may resolve spontaneously.

The SC program was especially beneficial for cancer patients suffering from a depressive or anxiety disorder. Patients with psychological distress (but not a psychiatric disorder) did benefit from CAU as much as from SC.

The research findings should be held against some limitations of this study. We included 156 cancer patients, but only 106 had complete data at 12 months follow-up. Significantly fewer patients died in the intervention compared with the control group (5.3% versus 18.5%). Depression and HRQOL are related to survival and a debate is ongoing on the effect of psychosocial interventions on survival[25,26]. However, it seems unlikely that higher survival was an effect of SC, since the effect of SC on distress was no longer present at 12 months follow-up. Another limitation is that some small differences between the two groups were observed at baseline. Some differences where in favor of the intervention group (i.e. better scores for depression, social functioning, social contact, and sexuality), while others were at the expense of the intervention group (i.e. worse scores for patient satisfaction and alcohol dependency). These differences were considered to be coincidental: additional analyses adjusting for baseline depression did not influence the findings. Furthermore, only a small number of LC patients participated. The prevalence of distress among LC patients was much lower than anticipated[27]. Further research is needed to obtain more insight into these unexpected findings.

The influence of the level of psychological distress on the efficacy of SC and the fact that almost one third of cancer patients who screen positive for distress recover after a period of watchful waiting sheds a new light on the ongoing debate on the benefit of screening for distress in clinical practice[5,28,29]. In our opinion, it is important that decisions about treatment provision are monitored systematically, and changes are made if current treatments do not achieve a significant health gain. Further research is needed to predict whether a patient needs the entire SC model or can skip a step, based on which SC can be further improved towards a personalized SC approach.

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CHAPTER 6

A guided self-help intervention targeting psychological distress among head and neck cancer and lung cancer patients: motivation to start, experiences and perceived outcomes

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Supportive Care in Cancer 2016; 10.1007/s00520-016-3393-x

ABSTRACT

Background. Recent results of a randomized clinical trial showed that a guided self-help intervention (based on problem-solving therapy) targeting psychological distress among head and neck cancer and lung cancer patients is effective. This study qualitatively explored motivation to start, experiences with and perceived outcomes of this intervention.

Methods. Data were collected from semi-structured interviews of 16 patients. All interviews were audio-recorded and transcribed verbatim. Data were analyzed individually by two coders and coded into key issues and themes.

Results. Patients participated in the intervention for intrinsic (e.g., to help oneself) and for extrinsic reasons (e.g., being asked by a care professional or to help improve health care). Participants indicated positive and negative experiences with the intervention. Several participants appreciated participating as being a pleasant way to work on oneself, while others described participating as too confrontational. Some expressed their disappointment as they felt the intervention had brought them nothing or indicated that they felt worse temporarily, but most participants perceived positive outcomes of the intervention (e.g., feeling less distressed and having learned what matters in life).

Conclusions. Cancer patients have various reasons to start a guided self-help intervention. Participants appreciated the guided self-help as intervention to address psychological distress, but there were also concerns. Most participants reported the intervention to be beneficial. The results suggest the need to identify patients who might benefit most from guided self-help targeting psychological distress, and that interventions should be further tailored to individual cancer patients' requirements.

INTRODUCTION

Head and neck cancer (HNC) and lung cancer (LC) patients are often confronted with functional impairments. Many HNC patients have oral dysfunction, and speech and swallowing problems. LC patients often have to cope with dyspnea and coughing. Functional impairments can result in psychological distress[1-3] and symptoms of anxiety or depression are highly prevalent in these patients[4,5]. Previous studies concluded that psychosocial interventions in cancer patients are effective[6,7]. However, many HNC and LC patients do not use psychosocial interventions[8,9] due to barriers such as a lack of knowledge about the availability of psychosocial facilities, and high costs[6,9,10].

Self-help interventions are brief, easily accessible and low-cost forms of psychosocial support[11],[12]. In primary care, cognitive behavioral therapy (CBT) for depression and anxiety provided as guided self-help can be as effective as face-to-face treatment[12-16].

Results of a recent randomized controlled trial (RCT) showed that a guided self-help intervention based on the principles of problem-solving therapy (PST) for HNC and LC patients with psychological distress is effective as part of a stepped care (SC) approach compared with usual care[17,18]. The SC model consisted of: Watchful waiting (2 weeks), Guided self-help (5 weeks) via the Internet or a booklet, face-to-face PST delivered by a nurse, and psychotherapy or medication.

The aims of the present study were to examine cancer patients' motivation to start a guided self-help intervention, their experiences with the intervention, and the perceived outcomes.

METHODS

CONTEXT

The present study was conducted in the context of the RCT evaluating the efficacy of two guided self-help interventions via the Internet or a booklet: "Headlines" and "Living with lung cancer" as part of SC[17,18]. In this RCT, 81 patients were randomized into the SC study arm; 54 patients had not recovered after step 1 (watchful waiting) and were offered the guided self-help intervention (step 2). The majority (n = 50, 93%) wanted to start the intervention, of which 40% (n = 20) completed the intervention. Participants in the present study were recruited from these 50 patients.

"Headlines" and "Living with lung cancer" are modified versions of an effective brief intervention based on PST[11,19-22]. The intervention helps participants to regain

control over their problems and lives by (i) determining what really matters, (ii) focusing only on problems related to what matters, (iii) thinking less negatively about problems not related to what is important in life, and (iv) accepting important but unsolvable problems. The core of the intervention focuses on solving manageable problems[11,19,22]. Information about HNC or LC, cancer treatment and the potential impact on quality of life is included. The intervention consists of 5 lessons and takes 5 weeks. Each lesson contains stories from other HNC or LC patients (matching the experience of a patient treated for HNC or LC). Patients are asked to complete assignments focusing on regaining control over their problems and lives. Trained coaches guide the patients. The coaching consists of brief (10 to 15 minutes) weekly contacts by email or by telephone and was aimed at providing support in working through the self-help method.

STUDY PARTICIPANT SELECTION

Participants were eligible for the study if they had started the guided self-help intervention within the previous 18 months. In total, 22 patients were eligible of whom 16 were willing to participate. The remaining patients did not want to participate (n = 1) or could not be reached (n = 5). All participants provided written informed consent. See Table 1 for the participants' characteristics.

PROCEDURE AND INTERVIEW STRUCTURE

Interviews were performed by one interviewer (HM), and scheduled at the participant's preferred location. The semi-structured interview schedule consisted of three main topics (motivation, experiences, and perceived outcomes) with corresponding questions (Table 2). The interview topics and questions were derived from our clinical experience and the literature[19,22]. The interviews lasted between 35 and 99 minutes (median 63.5 minutes), and were digitally recorded and transcribed verbatim.

Table 1. Overview of participant characteristics

	Total group (*n* = 16)
Sex (*n*, %)	
Female	8 (50)
Male	8 (50)
Age in years	
Mean (SD)	61.8 (9.0)
Marital status (*n*, %)	
Married/living with partner	15 (93.8)
Unmarried/divorced/widowed	1 (6.3)
Work situation (*n*, %)	
Paid job	7 (43.8)
No paid job/retired	9 (56.3)
Tumor location	
Lip/oral cavity/oropharynx	6
Hypopharynx/larynx	1
Other head and neck cancers	6
Lung	3
Tumor stage	
I	4
II	2
III	4
IV	2
Unknown	4
Time since last treatment	
< 7 months	5
7-12 months	1
> 12 months	10
Treatment	
Surgery	2
Radiotherapy	6
Chemoradiation	1
Surgery + radiotherapy	5
Surgery + chemotherapy	1
Surgery + chemoradiation	1
Adherence	
Completed the intervention	7
Did not complete the intervention	9

Table 2. Interview topics

Topics	Questions
Motivation for participation	- Why did you decide to participate in the intervention? - Did you have considerations against participating in the intervention? If yes, which considerations?
Experiences with the intervention	- Can you tell something about your experiences with the intervention? - Can you tell something about your experiences with 1) assignments, 2) coaching, 3) stories of other participants, 4) the focus of the intervention on cancer patients instead of a general approach to depressive symptoms, and 5) time investment?
Perceived outcomes from participation	- In what way did the intervention influence your thoughts and behavior? - Did the intervention help you to cope with cancer?

DATA ANALYSIS

Data were analyzed independently by two coders (AK and HM) using thematic analysis[23]. Both coders read all transcripts separately several times to familiarize themselves with the data. Quotes relating to the 3 main topics were independently selected and coded into key issues and themes. Findings were discussed after every three coded transcripts, and differences resolved until consensus was reached. The coders created a coding framework, which was revised if necessary following consensus meetings. In case of disagreement, a third coder (CvU) was consulted.

One coder (AK) examined the raw data again to ensure the robustness of the analytical process and to confirm that all data were reflected in the coding. Quotes provided in this article were translated from Dutch into English. To ensure anonymity all identifying information was removed.

RESULTS

MOTIVATION TO START

Participants had both intrinsic and extrinsic reasons to start the intervention (Table 3). One intrinsic reason was self-help. Participants assumed that participating would make them feel happier. Furthermore, participants expected to regain a grip on their lives after partaking:

"Cancer is kind of a life sentence, but I do not want it to rule my entire life; it has done enough of that, and I am being offered the chance of a bit of life and I want to have a grip on it myself."

Several participants mentioned that they decided to start out of curiosity: the intervention seemed interesting and they expected to learn something. Also, some anticipated that they could save time and money compared with regular care. Others started for less clear reasons, such as "It can't hurt to try".

Most reported reasons to start were extrinsic: being asked to participate by a care professional or to help others. Practically all wanted to participate to help science or to improve healthcare. Giving something in return for being treated well was also mentioned.

Not all participants were immediately convinced, and some considered not taking part initially. Nevertheless, they decided to start, mainly for extrinsic reasons.

Table 3. Overview of participants' motivation to start

	Key issues	Themes
Motivation	**Intrinsic reasons to start**	
	To help one-self	- Not feeling happy - Ability to tell one's story to someone - Expectation to regain grip on own life - Expectation to improve troubled home situation
	Curiosity	- Intervention seemed to be interesting - Expectation to learn something
	Save time and money compared with traditional psychosocial help	- No need to travel to visit a psychologist
	Extrinsic reasons to start	
	Asked to participate	- Asked to participate by care professional in hospital
	To help others	- Help science/improve health care - Give something in return for good cancer treatment
	Considerations to not start	
	Did not feel the need	- Dealing with problems already sufficiently - Feeling happy - Sufficient self-knowledge
	Too much effort	- Rather do something fun
	Did not expect a positive outcome	- Distress not related to cancer - Intervention does not cure cancer

Table 4. Overview of participants' experiences with participation

	Key issues	Themes
Experiences with…	Assignments	*Positive experiences assignments* + Pleasant way to work on self + Ability to re-read assignments *Negative experiences assignments* - Writing down feelings and thoughts is confronting, upsetting - Assignments were unclear - Not able or no discipline to complete assignments - Too little room to share own story - Too many forms to fill out and too much repetition - Not rewarding
	Coaching	*Positive experiences coaching* + Coach is professional (e.g., calm and understanding attitude) + Coach has listening ear (safe to share thoughts and experiences, attention) + Coach is crucial, indispensable and source of motivation + Feedback is short but powerful + Feedback is educational *Negative experiences coaching* - Feedback has shallow draft - Feedback not helpful, only proof that homework has been read - Feedback is patronizing - Feedback does not provide advice or judgement
	Cancer-specific format	*Positive experiences cancer-specific format* + Stories other patients recognizable and realistic + Stories put own situation in perspective + Feeling less unfortunate through downward social comparison + Information about cancer included is informative + Distress related to cancer is incomparable to other matters *Negative experiences cancer-specific format* - Stories are not recognizable (e.g., too severe, frightening, depressing) - Distracts from own situation - Being confronted with negative sides of the disease - Distress not related to cancer and therefore no need to take a closer look on cancer
	Homesetting	*Positive experiences* + Familiar surroundings + Less time investment compared with seeing a therapist
	Time investment	Positive experiences time investment + Able to do course in own pace, no pressure + Forms were filled out quickly *Negative experiences time investment* - Takes too much time daily - Duration of intervention too short; achieving change requires months
	Adherence	*Completed the intervention* + You have to finish what you have started *Did not complete the intervention* - Preference to manage problems by oneself - Feeling adequately supported by someone else (spouse, physiotherapist) - Not perceiving any benefit or added value of the intervention - Perceiving the intervention as too confronting or distressing - Feeling too worried to focus on the intervention - Preference for talking with a professional

EXPERIENCES

In general, both positive experiences -"pleasant", "clarifying", and "supportive"- and negative experiences -"exhausting" or "confronting"- were expressed in terms of the intervention (Table 4).

Experiences with assignments. Several participants indicated that writing down their thoughts on what matters in life as well as their problems was a pleasant way to work on oneself. They especially appreciated the fact that the assignments could be re-read later in time:

"Yes, and I can also read it again. It helps you along quite a bit (…) You can then log on again and read back what you said before. Slowly I could start to make my own lists of what is important (…) This is what you thought at that time, here's what you think now: it is good, leave it. Here is the focus, here is what you should think about."

In contrast, just as many participants indicated that writing this down was confronting and upsetting:

"And then you are also faced with this block, you know, I sit there with that pen hovering over that piece of paper and (…) then I throw in the towel. It's like me not wanting to know the type of cancer. I think: I simply can't handle it – because then I would, you know, become aware of certain cases where they end. (…) And if you get something similar, you have to open up, open all the boxes, which I don't want to do."

Some mentioned that the intervention was too complicated: assignments were unclear, and finding the right words was difficult. Participants experienced the assignments as containing too much repetition, too many forms, or too little room to share their own story. Others found they lacked the self-discipline to complete the assignments or that completing was considered as not rewarding.

Experiences with coaching. Most participants valued the coach and indicated that the coach was understanding and monitored their well-being. Participants also felt safe to share shameful thoughts and experiences. Participants stated that the personal contact was crucial and indispensable. The coach encouraged them to complete the intervention and served as a source of motivation:

"Well, yes, because you talk to someone on the phone. They ring you. So that is, of course, even more motivation to do it – to do those worksheets and to, to properly think about things and try to change them. I mean, you are supposed to be able to tell something when someone calls, aren't you? So, to me it was an incentive to do my very best, so to speak."

All participants indicated that the feedback provided was short. Some found the feedback powerful and educational. Others evaluated it as being shallow, not helpful, serving only as proof that the assignments had been read, or described the feedback as patronizing:

"Oh, she says: Yes, you have answered the assignments correctly, you are making a good effort. And I thought: come on, you must be joking, I am not a toddler."

Several participants remarked that the coach did not give any advice despite their need:

"(…) yes, I do think so, and I thought, like: yes, he is only calling to discuss it. You don't get, ehm, like: you had better do this or better do that… No. I somehow missed that."

Experiences with the cancer-specific format. Some participants experienced the cancer-related stories of others as recognizable and realistic. Others mentioned that the stories made them put their own situation into perspective. A couple said that they found it interesting to read about a more severe case than their own:

"No, I liked to read all of those. I wasn't necessarily looking for people with the same experience I had. But it was also nice to see, to say: oh, I don't have that (…) That is one up for me."

Several participants appreciated the cancer-specific format, because they believed that psychological distress caused by cancer is different:

"Because this fear of death is completely different from other stress in life. That is what it is all about, the fear of death – and not just death, but a long, nasty and painful death from cancer."

However, others stated that the stories were too severe or distracted them from their own situation. Some noted that it was difficult to be confronted with the negative sides of the disease in the cancer-related stories.

Experiences with the home setting and time investment. The ability to follow the course at home was viewed as a positive experience by almost all:

"At home you are in your familiar surroundings. Perhaps that makes you talk more freely, because everything around you is familiar. If you have to go to a psychiatrist, you might be nervous – and don't really know what to say exactly."

The home setting could also lead to less time investment compared with seeing a therapist. In addition, several expressed that they could follow the course at their own pace, and that the homework forms were filled out quickly. Others felt that the intervention took up too much time. Finally, a couple of participants remarked that they had experienced the intervention as too short to be able to achieve a significant psychological change:

"You can say to people, like, you have to think this or that. But really, it is just like walking: It takes months for people to be brainwashed."

Adherence. All 7 participants who adhered to the intervention indicated they finished the intervention because of their attitude that you should finish something you have started.

The 9 participants who did not adhere mentioned several reasons. Some preferred to manage their problems by themselves or felt adequately supported by someone else (spouse, physiotherapist). Others mentioned that they did not perceive any benefit or evaluated the intervention as too confrontational or distressing:

"By the time of the next class you can do the same, really, and then you have to indicate whatever has changed. Well, nothing had changed for me. It is… I felt the same from the start, really, so it only reinforced my feeling of, well, this is useless."

Several participants indicated that they felt too worried to be able to focus on the intervention or preferred talking with a professional.

PERCEIVED OUTCOMES

Participants perceived various outcomes (Table 5).

Positive psychological changes. Several participants indicated to have learned to structure their feelings and thoughts through participating:

"I was made wiser, how important it was to focus on my thoughts in a structured way. I have also changed that, I am still trying to do so."

Others explained that they learned how to put things into perspective. Several mentioned that they now realized that what happens in daily life could be viewed from other perspectives:

"Well, if someone is for instance (…) rude to you. Then I always thought, like: oh, I knew it, she doesn't like me. But then, you can also look at it in another way, like: oh, she must be busy."

A couple indicated that participation helped to stop ruminating. They explained that specifically the ability to re-read the completed assignments supported them in doing so.

In addition, they learned that looking for distraction helps to stop worrying:

"If I feel very down about something, so last week too, then I also had it (…). I then called the hairdresser's and made an appointment with the hairdresser."

Participants also learned to point out what is most important in their lives by setting priorities: focus on what is important in life ("spouse", "kids", "having fun") and drop what is less important ("doing chores", "being liked by others").

Some indicated that they had learned to accept unchangeable problems. Some mentioned that their self-knowledge and self-reflection had improved:

"Well, better insight in myself, think about myself, and yet see things in a different perspective."

Others stated that partaking in the intervention led to a "confirmation of self-insight".

Several indicated that their openness or attitude towards other people had improved:

"That you do not keep everything to yourself after all, become a bit more open towards your family, but that you do not burden anyone with it, just try to find a golden mean."

Finally participants indicated they managed to take up the threads of life after cancer.

Less psychological distress. Most participants stated that they had more peace of mind:

"Here is the focus, this is what you must think about. That also helped me, because I just do so once in a while and then leave it. Not always fret, fret, fret. That is really exhausting."

No positive psychological changes. Others did not perceive any positive outcomes. A few participants declared that they already had sufficient coping strategies. They explained for example that the intervention did not bring them anything or that they perceived partaking as a disappointment because the intervention only led to a "confirmation of self-insight":

"I know myself in that respect extremely well, that this doesn't help me, because I already am such a reflective person; because I already write down everything I feel and think, of pain and gloom. I am a bit of therapeutic myself (…) Plus I have considerable self-knowledge."

Some participants expressed that they did not learn how to deal with unchangeable problems, e.g., fear of recurrence of cancer:

"No, not really, for things that do not tally and are not changeable, I worry about those."

In addition several declared they appreciated they could express negative feelings during the intervention, but that these feelings were not removed:

"Well, I did enjoy participating, for at that moment you can share your feelings for a few moments. But, well, see, you can't make it disappear."

(Increased) psychological distress. Several participants expressed that they still felt helpless or (temporarily) felt worse as an outcome of participation. For those participants who indicated to feel worse this was often a reason to end participation:

"Yes, for I am haunted by it. Ehm, yes, it stayed with me for a while, a few days (…) that was worse for me and then I thought, I have to quit."

Table 5. Overview of participants' perceived outcomes of participation

	Key issues	Themes
Perceived outcomes	Positive psychological changes	+ Structuring of feelings and thoughts + Putting things in perspective + Stop ruminating + Stop worrying (e.g., by looking for distraction) + Learned what is most important in life + Improved acceptance of unchangeable problems + Improved self-knowledge and self-reflection + Confirmation of self-insight + Being more open to close circle + Taken up threads of life
	Less psychological distress	+ More peace of mind
	No positive psychological changes	- Already had sufficient coping strategies - Confirmation of self-insight - Bad feelings are expressed, but not taken away - Did not learn to deal with unchangeable problems (e.g., fear (for recurrence) of cancer)
	(Increased) psychological distress	- Still feeling helpless - Temporarily feeling worse

DISCUSSION

This study investigated the experiences and outcomes of a guided self-help intervention targeting psychological distress among HNC and LC patients and their motivation to start the intervention.

Understanding the motivation to participate is important, as it may influence outcomes[24,25]. This study showed that many HNC and LC survivors started the intervention for extrinsic reasons. Altruism is common among cancer patients who participate in research[26-28]. However, there were also patients who started the intervention for intrinsic reasons.

In our trial on stepped care, only 7% of patients who had not recovered after a period of watchful waiting declined the guided self-help intervention. This percentage is much better compared with the 71% that declined help in a study by Clover et al.[29], exploring reasons for declining help among cancer patients with significant emotional distress. The most common reason for declining help in that study was "I prefer to manage myself". This underscores that guided self-help is welcomed by cancer patients.

Participants recalled positive and negative experiences. Writing down thoughts and what matters in life, and being able to re-read the assignments was experienced as

pleasant by several participants. This is in line with results from Beattie et al.[30], regarding experiences with online CBT for depression in primary care. They concluded that online CBT was more attractive to patients who felt comfortable communicating their feelings in writing, and enjoyed to review what was written down.

The cancer-related stories were experienced as either recognizable and pleasurable, or as distressing. Previous studies have shown that individual differences in self-reported health status, sensitivity to social comparison information, and neuroticism determine how cancer patients react to stories of other cancer patients and whether they benefit from it or not[31-33]. These findings are important to take into account to tailor the cancer-specific format of the guided self-help intervention in the future.

Ly et al.[34] found that coaching was depicted as an essential component of a smartphone-based treatment for depression in primary care. Also Gerhards et al.[35] found that participants believed guidance would improve adherence. These perceived advantages of guidance have been confirmed in several reviews and meta-analyses, revealing that internet-based interventions with guidance are more effective and lead to greater adherence[15,16,36,37,38,39].

Similar to our findings, Donkin et al.[40] found in their study examining motivators to persist with online interventions, that completers indicated they had finished the intervention because of their sense of duty and commitment. Furthermore the perception of receiving a benefit from the program was a reason to persist, as well as feeling in control by e.g., being able to set the pace. A motivational interview prior to start of the intervention, individual tailoring[35], and increasing dialogue support through reminders are suggested to improve adherence[38,41,42].

By exploring participants' perceived outcomes, we gained insight in how they believed they were affected by partaking. Some perceived positive outcomes, while others perceived no positive psychological changes or remained distressed. Several participants stated to have learned what matters in life, to be able to put things in perspective, and indicated that they had taken up the threads of life. These perceived outcomes can be summarized as achieving an "enhanced internal locus of control". The achievement of feeling in control is aimed for by "Headlines" and "Living with lung cancer", since this is one of the protective factors against the development of symptoms of anxiety or depression[19]. Additionally, participants noticed to be more open to friends and family and to have more self-knowledge.

Negative outcomes were also identified in this study. The negatively perceived outcomes imply that a guided self-help intervention may have harmful consequences for some participants. Future research should disentangle which patients benefit from guided self-help interventions.

A limitation of the study was that interviews were conducted after participants had completed the intervention and follow-up measures had been conducted. Consequently, the elapsed time since starting the intervention varied. Participants who had more recently started the intervention may have had a more detailed recollection of their experience. Also, the experiences and outcomes obtained were linked to the current intervention and may not be applicable to other self-help interventions for cancer patients.

From a clinical point of view, it can be concluded that the guided self-help intervention is perceived as beneficial but may be improved by incorporating a motivational interview prior to start, and by tailoring the intervention to patients' individual needs.

CONCLUSION

Cancer patients had various reasons to start a guided self-help intervention. They appreciated the intervention in terms of recovering from psychological distress, yet there were also concerns in the way participants experienced the intervention. Although most reported the intervention as beneficial, not all participants perceived improved outcomes. These results suggest the need to identify patients who might benefit most from guided self-help targeting psychological distress.

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CHAPTER 7

General discussion

The goal of this thesis was to investigate innovative psychosocial care for HNC and LC patients with symptoms of anxiety and depression. Studied topics were prevalence of depression, screening for distress, stepped care, and self-management and eHealth. In this final chapter, the main findings are summarized. Subsequently, the main findings are discussed in relation to prior research. Clinical implications are addressed and suggestions for future research are provided. This chapter is completed with a general conclusion.

SUMMARY OF THE MAIN FINDINGS

Prevalence of depression in cancer survivors during or after treatment ranged between 8% and 24% and depended on the instruments used, type of cancer and treatment phase (Chapter 2). Among HNC patients, screening for distress appeared to have added value because of the patients who screened positive for psychological distress (29%), the majority (82%) did not yet receive treatment (Chapter 3). Stepped care consisting of (i) watchful waiting (2 weeks), (ii) guided self-help (5 weeks) via the Internet or a booklet, (iii) problem-solving therapy delivered by a nurse, and (iv) psychotherapy or psychotropic medication, was found to be effective to reduce distress and improve HRQOL among HNC and possibly LC patients with untreated psychological distress (Chapter 5).

With respect to step 2 of the stepped care program, reasons to start a guided self-help intervention were intrinsic (e.g., to help oneself) and extrinsic (e.g., being asked by a care professional or to help improve health care). Although some patients felt the intervention had brought them nothing or indicated that they felt worse temporarily, most participants perceived positive outcomes of the intervention such as feeling less distressed and having learned what matters in life (Chapter 6).

DISCUSSION OF THE MAIN FINDINGS

SCREENING FOR PSYCHOLOGICAL DISTRESS

Nowadays, both national and international cancer institutions widely recommend the assessment and treatment of psychosocial distress in routine cancer care as a quality care standard[1-4]. In the study on the added value of screening for psychological distress among HNC patients it was concluded that screening for psychological distress was beneficial because nearly one third of patients who screened positive for psychological distress did not yet receive treatment (Chapter 3). Interestingly enough, the stepped care

trial showed that 28% of patients in the intervention group had recovered after two weeks of watchful waiting, that is two weeks after screening (step 1) (Chapter 5). It may be that the distress of these patients resolved spontaneously after reassurance in the medical follow-up consultation that malignancy had not recurred, which consultation occurred at the same day as screening for distress. Another explanation might be that offering distressed cancer patients the chance to discuss their distress after screening plus the prospect of getting psychosocial help makes a substantial contribution to their well-being. In a large clinical trial on the efficacy of screening for psychological distress by Carlson et al.[5], 585 patients with breast cancer and 549 patients with lung cancer were randomized to one of three conditions, including (i) minimal screening, in which only the Distress Thermometer was administered without feedback to the patient or clinician; (ii) full screening with multiple questionnaires, followed by a printed personalized feedback report and a summary report that that was included in the patient's medical file; and (iii) full screening as described above plus an optional personalized phone triage with referral to resources. Similar to the finding in the RCT as presented in this thesis, the authors reported that the patients who were offered a chance to discuss their psychosocial issues with a staff member followed by triage to appropriate resources demonstrated a larger decrease in distress at 3 months follow up than those patients who received screening only. However, whether the decrease in distress was induced by the offered psychosocial care, or by the referral itself was not investigated.

Although screening for psychological distress via OncoQuest is valued by the coordinating staff and by patients, not all eligible patients made use of OncoQuest. A mixed method study including qualitative and quantitative research measures is ongoing and will provide detailed insight into possible barriers and facilitators among patients as well as care providers. The results of this study will also enable further optimization of OncoQuest in clinical practice. OncoQuest is a tool to facilitate communication between patient and care provider (in the RCT as presented in this thesis: a nurse) and can be seen as a quick scan of health related quality of life. Obviously, OncoQuest does not comprise all possible health related quality of life issues that patients may encounter, because it consists of only three patient-reported outcome measures (the EORTC QLQ-C30, the EORTC tumor-specific module, and the HADS). Also, the program does not include an open question on the need for supportive care such as "What kind of supportive care would you like?". Therefore, it is crucial to combine OncoQuest with a consultation with a nurse who can discuss the results of OncoQuest more in-depth with the patient. For

example, many patients who do not reach screening criteria for psychological distress do want psychological help[6-8], and vice versa patients who do reach screening criteria may need explanation on the benefit of psychosocial care to help them to decide. Another example refers to Salander et al.[9] who found that a substantial part of cancer patients want help for interpersonal or existential issues that might not be identified by the HADS or EORTC questionnaires embedded in OncoQuest. Perhaps exchanging the diagnostic framework for screening, in which health need is indicated by the presence of a psychological disorder, for a framework in which health need is identified from multiple perspectives, is recommendable[10]. Further research is needed to advance knowledge about the most effective implementation strategies in the context of cancer care[11].

ORGANIZATION OF CARE

The Institute of Medicine (IOM) Report entitled Cancer Care for the Whole Patient published in 2008[12] recommended that cancer care includes the provision of appropriate integrated psychosocial care. Integrated care refers to a system of care in which all the services needed to treat the patient are combined in a way that makes them accessible for the patient who needs these services. It should include identification of psychosocial care needs, a plan to address these needs, routes to connect patients with psychosocial care services, support of self-management, and follow-up on provided care[12]. In their adaptation of the Pan-Canadian Practice Guideline on Screening, Assessment, and Care of Psychosocial Distress (Depression, Anxiety) in Adults With Cancer[13], Andersen et al.[3] recommended in 2014 that all patients with cancer should be evaluated for symptoms of depression and anxiety at periodic times across the trajectory of care, using validated, published measures (such as the HADS) and procedures. An integrated care model has shown to be (cost-)effective to treat depression in an oncologic setting is collaborative care[14-16]. The collaborative care model was originally developed to improve management of depression in primary care: a psychiatrist and a care manager collaborate with the patient's primary care physician to provide systematic, hands-on treatment and follow-up[17]. The model emphasizes three core concepts: population-based care (improving the quality of care and outcomes of defined populations with chronic illness), measurement-based care (including tracking systems and timely measurements of disease control), and stepped care[18]. In stepped care, the primary focus is on psychological interventions of increasing intensity and expense. In a recent meta-analysis and review of all randomized trials on stepped care for depression, van Straten et al.[19] discussed that there is only

limited evidence to recommend stepped care above alternative systems. They could not draw firm conclusions, because they found considerable variety in the implementation of the stepped care programs. For instance, the majority of included trials did not provide a program with progressive increase in treatment intensity. The RCT as reported on in this thesis showed that, a 'true' stepped care program, including increasing treatment intensity, was effective in reducing distress and improving health related QOL among HNC and possibly LC patients with untreated psychological distress compared with care as usual. One could argue that the care as usual in the trial as presented in this thesis was no 'true' care as usual, because an active approach was used to recruit and select patients. Before being asked to participate, patients were screened for distress, eligible patients were made aware of their HADS score by a researcher, and psychosocial issues were discussed. The awareness, insight and attention given by the researcher may have positively influenced feelings, thoughts and behavior among patients in both intervention group and care as usual group. Nevertheless, the stepped care program proved to be effective.

It would be interesting to compare the stepped care program with a similar care program, such as "Depression Care for People with Cancer" (DCPC). DCPC is an integrated collaborative care program targeting major depression in patients with cancer, which has been found to be (cost-)effective in the SMaRT Oncology trials[14,16]. The main difference between DCPC and the stepped care program as presented in this thesis is that the latter starts with watchful waiting and a self-help course, as where DCPC directly starts with face-to-face sessions with a specialized nurse.

To make matters clear, the findings of this thesis fortify the current opinion that decisions about psychosocial treatment provision should be followed up systematically in cancer care, and that changes should be made if current treatments do not achieve a substantial health improvement.

SELF-MANAGEMENT AND EHEALTH

Self-management support has been identified as an opportunity to improve health outcomes in cancer care[20]. Health care interventions, including self-management support, are increasingly being delivered through the Internet[21]. The Internet is a practical, cost-effective, widely accessible medium with the ability to provide customized information and support[22-27]. Internet interventions have the potential to fill an important gap in quality cancer care by augmenting limited available mental health services[28]. Also, Internet

interventions create greater privacy and confidentiality. Patients can seek treatment at home at their convenience, an important aspect for patients reluctant to frequent medical appointments and the stigma associated with the receipt of psychological therapy. Though web-based (eHealth) self-management interventions can reduce symptoms of depression and anxiety, and improve overall quality of life among cancer patients, evidence-based (eHealth) self-management interventions targeting psychological distress in HNC and LC patients are scarce[29-32]. The results of the RCT as presented in this thesis showed that a guided self-help intervention via the Internet or a booklet for HNC and possibly LC patients with psychological distress as part of the stepped care program is effective compared with care as usual, and seems to be welcomed by cancer patients. The qualitative analysis in this thesis of the self-help intervention showed that, though most, but not all, reported the intervention to be beneficial. Incorporating a motivational interview prior to start of the intervention and tailoring the intervention and coaching sessions to patients' individual needs might improve the beneficial effects of the self-help intervention. Patients who are actively engaged in their treatment may be more likely to retain, and use newly learned techniques - effects possibly mediated through greater self-efficacy[33].

CLINICAL IMPLICATIONS

With the increasing number of cancer patients in the coming decades, the demand for psychosocial support will rise equally. The Dutch Society for Psychosocial Oncology (Nederlandse Vereniging voor Psychosociale Oncologie, NVPO), Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland, IKNL) and the Dutch Cancer Society (KWF Kankerbestrijding) have together developed a multidisciplinary, evidence-based guideline called 'Screening for psychosocial distress'[2]. The guideline should support care providers in providing integrated psychosocial care to the patient with cancer. Identifying psychological distress, discussing it with the patient and referral to specialized psychosocial care, if necessary, form part of this integrated care. The findings from the present thesis strengthen the recommendations presented in the Dutch guideline. Routine screening for psychological distress in patients with cancer is crucial (via the Distress Thermometer as recommended in the Dutch guideline or, for instance, via the HADS in OncoQuest) at key points in the disease journey. When psychological distress is identified, ideally an (specialized) oncology nurse of the treating team should

take responsibility for coordinating proper assessment, referral and follow-up. A stepped care model is proposed, starting with the least (cost-)intensive intervention available that is still likely to provide a significant health gain. The results of treatment are monitored systematically, and changes are made ('stepping up') if the current intervention is insufficient in improving health. Each cancer facility should identify their own referral system based on the current care structure and local health resources, as well as patients' preference. Feedback of the content and results of the provided supportive care to the cancer care provider and the primary care provider is a vital element of multidisciplinary integrated care.

RECOMMENDATIONS FOR FUTURE RESEARCH

As currently routine screening for psychosocial distress in cancer care is recommended as a quality care standard, screening through the Internet may be a way to increase access and convenience, save time and space, and reduce costs in the often busy oncological clinics. The Internet provides the ability to make OncoQuest (or the Distress Thermometer) available for patients at home and share their results with all involved care providers. OncoQuest is considered as a quick assessment of quality of life, which facilitates communication between patient and care provider on quality of life issues. Another approach is the development of a self-management application called Oncokompas2.0, an integrated eHealth application to monitor health related quality of life, to provide personalized information on quality of life and supportive care, and to support cancer survivors by finding and obtaining optimal supportive care, adjusted to their personal health status and preferences. OncoKompas2.0 comprises a generic module for all cancer survivors, targeting healthy lifestyle (smoking, alcohol use, exercising, nutrition, weight, stress), physical functioning (pain, sexuality, sleep, fatigue, body image, diarrhoea, constipation, hearing, loss of appetite, nausea/vomiting, neuropathy, lymph edema, functioning in daily living), psychological functioning (anxiety, depression, fear of recurrence, cognitive functioning), social functioning (social life/loneliness, relationships, relation with children, financial issues, return to work, communication with care providers), and existential issues (meaning, religion, future perspectives). Furthermore tumor-specific modules will be available, for example for head and neck cancer patients (swallowing, speech, oral function, neck and shoulder function, tube feeding, loss of smell and taste). All patients receive tailored information

on their lifestyle, their physical, psychological, and social functioning, and existential issues; patients with minor problems are informed on self-help interventions, and on professional care in case of major problems. Further research is needed (and ongoing) on the (cost-)effectiveness of Oncokompas2.0, including the stepped care approach build into this self-management application.

Treating numerous patients with inappropriate low-intensity interventions that are not beneficial for part of them is a waste of money, time, and impacts the quality of life of patients. Therefore, taking the stepped care program from an experimental phase to routine cancer care practice, further research is needed to predict whether a patient can follow the entire stepped care model or needs to skip a step, based on which stepped care can be further tailored towards a personalized stepped care approach. Also, more studies should be carried out to demonstrate the cost-effectiveness of stepped care in oncological settings. Future research can create an evidence-based blueprint for implementation of stepped care in clinical practice, including crucial determinants of effectiveness. Meta-regression and qualitative analyses may be useful in dismantling active ingredients in complex intervention models like stepped care[34].

Further, though web-based (eHealth) self-management interventions can reduce symptoms of depression and anxiety, and improve overall quality of life among cancer patients, not all patients perceived positive experiences and outcomes. Future research should identify patients who might benefit most from (web-based) self-management targeting psychological distress.

In multicultural countries like the Netherlands, (web-based) self-help interventions have the advantage that they can easily be translated into different languages, further increasing access to supportive cancer care also among ethnic minorities[35]. And, as the Internet evolves, in the future, interaction between coach and participant as part of web-based guided self-help interventions can be improved through synchronous (real-time) audio-video communication (e.g., video chat programs such as Skype or Facetime)[36]. This type of communication closely resembles face-to-face contact and gives access to essential face-to-face signals such as intonation, facial expressions, and body language. Through live guidance, the coach may be able to offer more personalized feedback. In addition, this type of contact may facilitate feelings of accountability and social support, higher engagement, an improvement of the therapeutic bond, and reduce the risk of misinterpretations, compared with e-mails and text messages[37,38].

CONCLUSION

The prevalence and impact of depression and anxiety in cancer patients demand optimization of access to mental health interventions, urging the health care system to develop and employ (cost-)effective programs. A stepped care program proved to be effective in reducing psychological distress and improving HRQOL among HNC and possibly LC patients. Furthermore, screening for distress is important and should be part of clinical cancer care. It is indispensable that the results of treatment and the decisions about treatment provision are monitored systematically, and that changes are made ('stepping up') if current treatments do not achieve a significant health gain.

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SUMMARY

Chapter 1 comprised the general introduction of this thesis. The focus in this thesis was on head and neck cancer (HNC) and lung cancer (LC) patients. A description of these cancer types and their treatment options is given and the impact on quality of life. Symptoms of depression and anxiety (psychological distress) are highly prevalent in cancer patients. Though psychological interventions have proven to be effective in cancer patients, many distressed cancer patients do not make use of psychosocial care and as a result psychological comorbidity is often undertreated in cancer patients. Barriers to referral to psychosocial care are insufficient screening for anxiety and depression at the often busy clinics, costs, and a lack of knowledge about available psychosocial services on the part of both care providers and patients. A comprehensive and integrated organization of psychosocial care, such as stepped care, might be an effective method to tackle undertreatment of distress in cancer patients.

Stepped care is a care program based on clinically proven, best-practice pathways to care over a series of steps. The steps targeting psychological distress usually involve watchful waiting, guided self-help and other brief therapies, followed by more intensive psychological interventions or medication. In stepped care, more intensive treatments are generally reserved for people who do not benefit from simpler first-line treatments, or for those who can be accurately predicted not to benefit from such treatments. The results of treatments are monitored systematically, and changes are made ('stepping up') if current treatments are not achieving a significant health gain.

The goal of this thesis was to investigate innovative psychosocial care for HNC and LC patients with symptoms of anxiety and depression. Studied topics were prevalence of depression, screening for distress, efficacy of stepped care, and self-management and eHealth.

Chapter 2 described a meta-analysis on the prevalence of depression and depressive symptoms in cancer patients during or after treatment. Pooled mean prevalence of (symptoms of) depression in cancer patients in non-palliative care settings during or after treatment ranged between 8% and 24% and depended on the instruments used, type of cancer and treatment phase. Structured diagnostic interviews were used to assess depression in 49 studies. Cut-off scores of the Hospital Anxiety and Depression Scale-depression subscale (HADS-D $\geq$ 8 or HADS-D $\geq$ 11), and of the Center for Epidemiologic Studies (CES-D $\geq$ 16) were used to assess depressive symptoms in 66, 53 and 35 studies, respectively. Mean prevalence of depression was 13%. Mean prevalence of depressive symptoms was 17%, 8%, 24%, respectively.

Prevalence of (symptoms of) depression ranged from 3% in patients with lung cancer to 31% in patients with cancer of the digestive tract. Prevalence of (symptoms of) depression was highest during treatment: 14%, measured by diagnostic interviews, and 27%, measured by self-report instruments. In the first year after diagnosis, prevalence of (symptoms of) depression measured with diagnostic interviews and self-report instruments was 9% and 21%, respectively, and 8% and 15% longer than 1 year after diagnosis.

In *Chapter 3*, the added value of screening in follow-up care to identify HNC patients with untreated psychological distress was examined. Screening for distress has added value because of the patients who screened positively for psychological distress (29%), the majority (82%) did not yet receive treatment. Patients who received psychological or psychiatric treatment had a significantly higher score on the HADS total scale, a lower (worse) score on the EORTC QLQ-C30 scale emotional functioning, a higher (worse) score on fatigue, and on the EORTC QLQ-H&N35 scales oral pain, speech problems and less sexuality.

Chapter 4 described the study protocol of a randomized clinical trial by means of which the efficacy of a stepped care strategy targeting psychological distress in HNC and LC patients was examined. The stepped care model included watchful waiting, guided self-help via Internet or a booklet, brief face-to-face problem-solving therapy, and specialized interventions such as cognitive behavioral therapy and/or antidepressant medication. Stepping up to the next treatment was mandated when a patient's score on the HADS total scale remained above 7. In the control group patients received care as usual.

Chapter 5 presented the results of this randomized controlled trial. The main finding of this study was that SC is effective to reduce distress and improve HRQOL among HNC and possibly LC patients with untreated psychological distress. The course of psychological distress from baseline to 12 months follow-up was significantly better for the intervention group compared with the control group. Effect sizes at separate time points revealed moderate to strong effects of SC on psychological distress and several HRQOL aspects post-treatment and at short-term follow-up, but no longer at 12 months follow-up (decay effect). Also, the recovery rate was significantly higher post-treatment (55% in the intervention group vs. 29% in the control group) but not at 12 months

follow-up (46% vs. 37%, respectively). The stepped care model was especially effective for patients with depression as assessed with the CIDI psychiatric interview, compared with patients with depressive symptoms only. It is concluded that SC speeds up recovery of distress and improvement of HRQOL.

In *Chapter 6*, HNC and LC patients' motivation to start a guided self-help intervention (based on problem-solving therapy, step 2 in the stepped care model) targeting psychological distress, experiences with the intervention, and the perceived outcomes were qualitatively explored. Patients participated in the intervention for intrinsic (e.g., to help oneself) and for extrinsic reasons (e.g., being asked by a care professional or to help improve health care). Participants indicated positive and negative experiences with the intervention. Several participants appreciated participating as being a pleasant way to work on oneself, while others described participating as too confrontational. Some expressed their disappointment as they felt the intervention had brought them nothing or indicated that they felt worse temporarily, but most participants perceived positive outcomes of the intervention (e.g., feeling less distressed and having learned what really matters in life for them).

Finally, in *Chapter 7*, the main findings of this thesis were discussed, clinical implications were addressed, and recommendations for future research were given. It is concluded that the prevalence and impact of depression and anxiety in cancer patients demand optimization of access to mental health interventions, urging the health care system to develop and employ (cost-)effective programs. A stepped care program proved to be effective in reducing psychological distress and improving HRQOL among HNC and possibly LC patients. Furthermore, screening for distress is important and should be part of clinical cancer care. It is indispensable that the results of treatment and the decisions about treatment provision are monitored systematically, and that changes are made ('stepping up') if current treatments do not achieve a significant health gain.

SAMENVATTING

(SUMMARY IN DUTCH)

In *hoofdstuk 1* wordt de algemene introductie van dit proefschrift beschreven. De nadruk in dit proefschrift lag op patiënten met hoofd-halskanker (HHK) en longkanker (LK). Een omschrijving van deze vormen van kanker en de behandelmogelijkheden werd gegeven, alsook de invloed op de kwaliteit van leven. Een aanzienlijk deel van patiënten met HHK of LK leidt aan symptomen van angst of depressie (psychische *distress*). Hoewel studies hebben aangetoond dat psychosociale hulp aan patiënten met kanker effectief is, maken veel patiënten geen gebruik van deze hulp. In de oncologische praktijk wordt verwijzing naar psychosociale zorg onder andere belemmerd door onvoldoende adequate screening op psychische *distress*, kosten en een gebrek aan kennis over beschikbare psychosociale zorg bij zowel zorgverleners als patiënten. Een geïntegreerde organisatie van psychosociale zorg, zoals een *stepped care* benadering, heeft potentie om de doeltreffendheid van psychosociale zorg in de oncologische setting te verbeteren.

Stepped care is een zorgprogramma waarin verschillende behandelmethoden voor bijvoorbeeld psychische *distress* worden aangeboden, waarvan is bewezen dat ze werkzaam zijn en die in de praktijk worden toegepast. Het verschil met andere zorg-programma's is dat deze methoden op een andere manier worden georganiseerd, namelijk stapsgewijs. *Stepped care* bestaat doorgaans uit waakzaam afwachten, een (begeleide) zelfhulpcursus, kortdurende gesprekstherapie en gespecialiseerde interventies. Binnen het *stepped care* programma krijgen alle patiënten in eerste instantie de minst intensieve behandeling aangeboden. De klachten van de patiënten worden zorgvuldig gemonitord en wanneer de patiënt onvoldoende opknapt, wordt overgegaan op een meer intensieve behandeling.

Het doel van dit proefschrift was om innovatieve psychosociale zorg voor patiënten met HHK en LK met psychische *distress* te onderzoeken. Bestudeerde onderwerpen waren prevalentie van depressie, screenen op psychische *distress*, effectiviteit van *stepped care*, zelfmanagement en eHealth.

Hoofdstuk 2 beschrijft een meta-analyse naar de prevalentie van depressie en symptomen van depressie bij patiënten met kanker gedurende of na behandeling voor kanker. De gemiddelde prevalentie van (symptomen van) depressie bij patiënten in niet-palliatieve settings tijdens of na behandeling voor kanker varieerde tussen 8% en 24% en was afhankelijk van de gebruikte meetinstrumenten, kankertype en behandelfase. Gestructureerde diagnostische interviews werden gebruikt om een depressie te meten in 49 studies. Afkapwaarden van de Hospital Anxiety and Depression Scale-depressie

subschaal (HADS-D ≥ 8, en HADS-D ≥ 11), en van de Center for Epidemiologic Studies (CES-D ≥ 16) werden gebruikt om symptomen van depressie te meten in respectievelijk 66, 53 en 35 studies. De gemiddelde prevalentie van depressie was 13%. De gemiddelde prevalentie van symptomen van depressie was respectievelijk 17%, 8%, 24%. De prevalentie van (symptomen van) depressie varieerde van 3% bij patiënten met longkanker tot 31% bij patiënten met kanker van het spijsverteringskanaal. De prevalentie van (symptomen van) depressie was het hoogste tijdens de behandeling: 14%, gemeten middels diagnostische interviews en 27%, gemeten door zelfrapportage instrumenten. In het eerste jaar na de diagnose bedroeg de prevalentie van (symptomen van) depressie, gemeten met diagnostische interviews en zelfrapportage instrumenten, respectievelijk 9% en 21%, en langer dan 1 jaar na de diagnose was dat respectievelijk 8% en 15%.

In *hoofdstuk 3* wordt de toegevoegde waarde van screenen op psychische distress bij patiënten met HHK gedurende de follow-up zorg behandeld. Screenen op psychische *distress* heeft toegevoegde waarde, omdat van de patiënten die positief screenden op psychische klachten (29%), de meerderheid (82%) nog geen behandeling kreeg. Patiënten die psychische of psychiatrische behandeling kregen, hadden een significant hogere score op de HADS totaal schaal, een lagere (slechtere) score op de EORTC QLQ-C30 schaal emotioneel functioneren, een hogere (slechtere) score op vermoeidheid, en een hogere (slechtere) score op de EORTC QLQ-H&N35 schalen pijn in de mond, spraakproblemen en problemen met seksualiteit.

Hoofdstuk 4 beschrijft het studieprotocol van een gerandomiseerde studie waarmee de effectiviteit van het *stepped care* programma bij patiënten met HHK en LK met klachten van psychische *distress* onderzocht werd. Het *stepped care* programma bestond uit 4 stappen: (i) waakzaam afwachten, (ii) een begeleide zelfhulpcursus via Internet of via een boekje, (iii) kortdurende gesprekstherapie (*problem-solving therapy*), en (iv) intensievere psychotherapie en/of medicatie. Binnen het *stepped care* programma kregen patiënten eerst de minst intensieve behandeling aangeboden. De klachten van de patiënten werden zorgvuldig gemonitord en wanneer de HADS totaal score boven de 7 bleef, werd overgegaan op een meer intensieve behandeling. Patiënten in de controlegroep kregen de gebruikelijke psychosociale zorg aangeboden.

In *hoofdstuk 5* worden de resultaten van de gerandomiseerde studie gepresenteerd. De belangrijkste bevinding van deze studie was dat *stepped care* effectief is om psychische *distress* te verminderen en de kwaliteit van leven te verbeteren bij patiënten met HHK en mogelijk ook met LK met depressieve en/of angstklachten. Het beloop van de psychische *distress* van baseline tot 12 maanden follow-up was significant beter voor de interventiegroep vergeleken met de controlegroep. De effectgroottes op verschillende tijdstippen toonde een matig tot groot effect van *stepped care* op psychische *distress* en op een aantal kwaliteit van leven domeinen na behandeling voor kanker en op de korte termijn follow-up, maar niet meer op 12 maanden follow-up (uitdoofeffect). Ook de mate van herstel van psychische *distress* was significant beter na de behandeling (55% in de interventiegroep versus 29% in de controlegroep), maar niet meer op 12 maanden follow-up (respectievelijk 46% versus 37%). Het *stepped care* model was vooral effectief bij patiënten met een depressieve stoornis zoals gemeten met het Composite International Diagnostic Interview (CIDI), vergeleken met patiënten met alleen symptomen van depressie. Geconcludeerd werd dat *stepped care* psychisch herstel en verbetering van kwaliteit van leven versnelt.

Hoofdstuk 6 beschrijft een kwalitatief onderzoek naar de motivatie om een begeleide zelfhulpcursus (gebaseerd op *problem-solving therapy*, stap 2 in het *stepped care* model) te starten en de ervaringen met deze interventie van patiënten met HHK en LK. Patiënten namen deel aan de interventie om intrinsieke (bijvoorbeeld om zichzelf te helpen) en extrinsieke redenen (bijvoorbeeld omdat ze uitgenodigd waren om mee te doen door een zorgprofessional of om de gezondheidszorg mee te helpen verbeteren). Verschillende deelnemers ervoeren deelname als een aangename manier om aan zichzelf te werken, terwijl anderen deelname als te confronterend beschouwden. Hoewel sommigen vonden dat de interventie hen niets had opgeleverd of dat ze zich tijdelijk slechter voelden, hadden de meeste deelnemers positieve ervaringen met de interventie (bijvoorbeeld minder *distress* voelen en geleerd hebben wat echt belangrijk is in het leven).

Tenslotte worden in *hoofdstuk 7* de belangrijkste bevindingen van dit proefschrift en de klinische relevantie besproken, en aanbevelingen voor toekomstig onderzoek worden gegeven. Geconcludeerd werd dat de prevalentie en de impact van depressie en angst bij patiënten met kanker optimalisatie van de toegang tot de geestelijke gezondheidszorg vereisen, en dat de ontwikkeling en toepassing van (kosten)effectieve zorgprogramma's

noodzakelijk zijn. Het *stepped care* programma bleek effectief in het verminderen van depressieve en/of angstklachten en in het verbeteren van de kwaliteit van leven bij patiënten met HHK en mogelijk ook LK. Verder is screenen naar *distress* belangrijk en zou standaard deel uit moeten maken van de oncologische zorg. Het is noodzakelijk dat de resultaten van psychosociale behandeling en de beslissingen omtrent deze behandeling systematisch worden gemonitord, en dat wijzigingen worden aangebracht ('intensivering') als de huidige psychosociale behandeling geen significante gezondheidswinst oplevert.

ABOUT THE AUTHOR

Anne-Marie Krebber was born on March 12, 1982 in Maastricht, the Netherlands. In 2000, she completed General Secondary Education (ASO, direction Latin-Math) at the Heilig Graf Institute in Bilzen, Belgium. Subsequently, she studied biology for 1 year at Utrecht University, and thereafter, she studied medicine at VU University Amsterdam. After graduation in January 2009, she started working as a PhD student at VU University Medical Center Amsterdam, department of Otolaryngology/Head and Neck Surgery, in close collaboration with the department of Pulmonary Diseases, the department of Psychiatry, EMGO+ Institute for Health and Care Research, VUmc Cancer Center, and the department of Clinical Psychology of VU University Amsterdam. She examined a stepped care approach targeting psychological distress in head and neck cancer and lung cancer patients, which resulted in this thesis. In her free time, in 2011, she completed the bodywork instructor course at VU Sports Center Amstelveen, and thereafter, in 2012, the Official Zumba® Fitness Instructor training at Health Club Gold's Gym Nieuwegein. She has been giving Zumba® and aerobics classes throughout Amsterdam and Amstelveen ever since. On June 6, 2013, Anne-Marie and her team of colleagues climbed the Alpe d'Huez by bike four times to raise money for the Alpe d'HuZes Foundation/Dutch Cancer Society. In 2014, she moved to Aruba to gain clinical experience as a ward physician at the Dr. Horacio E. Oduber Hospital in Oranjestad. Currently, Anne-Marie is working as a physician at the Psychiatric Emergency Service in Amsterdam. As of April 2017, she will start her residency in Psychiatry at GGZ inGeest Amsterdam.

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DANKWOORD

(ACKNOWLEDGEMENTS)

Het is zover: mi buki ta cla! Sinds 2009 heb ik dit mooie onderzoeksproject mogen coördineren en samen met een groot aantal mensen bergen werk verzet. Het beklimmen van de Alpe d'Huez was er een eitje bij. Ik wil iedereen bedanken die een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift. Het zou nooit voltooid zijn zonder jullie hulp, ideeën en ondersteuning. Mijn dank is groot! Graag wil ik een aantal personen (en dieren) in het bijzonder bedanken.

Allereerst alle mensen met hoofd-halskanker of longkanker die mee hebben gewerkt aan de studies die beschreven zijn in dit proefschrift. Ik heb het samenwerken met jullie en jullie verhalen als bijzonder inspirerend ervaren. Bedankt voor jullie bereidwilligheid om deel te nemen aan dit project in een periode die voor velen niet makkelijk was. Zonder jullie inbreng zou dit proefschrift er nooit zijn geweest.

Daarnaast wil ik ZonMw en Fonds NutsOhra bedanken voor de financiering van het onderzoeksproject.

Mijn promotor, prof. dr. I.M. Verdonck-de Leeuw, beste Irma. Onder jouw begeleiding ben ik in 2009 het *stepped care* avontuur aan mogen gaan. Ik heb je ervaren al een zeer betrokken, goedlachse, positieve, altijd in oplossingen denkende powervrouw met een ongekende helicopterview en werkethos. Een betere promotor had ik me niet kunnen wensen. Bedankt voor je vertrouwen in mij, je geduld en steun in de rug, de fijne samenwerking en de pret buiten kantooruren. Ik heb veel van je geleerd, zowel op wetenschappelijk als persoonlijk vlak.

Mijn promotor, prof. dr. C.R. Leemans, beste René. Heel graag wil ik u bedanken voor de kans die u mij geboden heeft om dit promotieonderzoek uit te voeren binnen de afdeling Keel-, Neus- en Oorheelkunde/Hoofd-halschirurgie van het VU Medisch Centrum te Amsterdam. Bedankt dat u in mij bent blijven geloven toen ik in 2012 besloot om mijn loopbaan na mijn promotietraject elders voort te zetten en toen ik in 2014 naar Aruba emigreerde om te gaan werken als zaalarts in het Dr. Horacio E. Oduber Hospitaal.

De leden van de leescommissie en de promotiecommissie, prof. dr. N.K. Aaronson, prof. dr. R.J. Baatenburg de Jong, prof. dr. A.T.F. Beekman, prof. dr. J.B. Prins, prof. dr. H. Riper, dr. M.R. Vergeer en prof. dr. H.C.P.M. van Weert wil ik hartelijk danken voor de bereidheid om zitting te nemen in de commissie en voor het kritisch beoordelen van dit proefschrift.

Heel graag wil ik alle co-auteurs bedanken voor jullie aandeel in het tot stand komen van dit onderzoeksproject, jullie waardevolle commentaar op de verschillende manuscripten en het prettige samenwerken. Drie co-auteurs wil ik in het bijzonder bedanken. Dr. L.M. Buffart, beste Laurien. Hartelijk dank voor je betrokken, enthousiaste begeleiding tijdens het uitvoeren van de meta-analyse. Mijn hemel, wat hebben we veel artikelen beoordeeld voor deze studie!! Dr. B.I. Witte, beste Birgit. Veel dank voor de vruchtbare samenwerking, je statistiekexpertise, het meermaals verwerken van datasets en je heldere uitleg en feedback. Je werk is net zo hoogwaardig als je sportprestaties! Dr. C.F. van Uden-Kraan, beste Nelly. Heel veel dank voor je intensieve en fijne ondersteuning bij het ontrafelen van de kwalitatieve puzzel.

Alle artsen, verpleegkundigen, assistenten en vrijwilligers van de poliklinieken Keel-, Neus- en Oorheelkunde/Hoofd-halschirurgie en Longziekten van het VU Medisch Centrum te Amsterdam, in het bijzonder Yvonne Cruijff-Bijl, Petra van Kooperen, Janneke Lantink, Claudia Meuris en Irmgard de Jong. Bedankt voor jullie tomeloze inzet om het gebruik van OncoQuest en de inclusie ten behoeve van dit onderzoeksproject succesvol te laten verlopen.

Psychiatrisch verpleegkundigen Marga Jaspers, Rob Groenendaal, Hans Baeten en Els Dozeman, en psychiater Guus Eeckhout, van de afdeling Psychiatrie van het VU Medisch Centrum en van Prezens GGZ inGeest te Amsterdam, hartelijk dank voor het aanbieden van de verschillende interventies als onderdeel van het *stepped care* programma. Jullie toewijding heeft mij zeer geraakt.

Systeembeheerder Ton Houffelaar, de man achter de techniek, veel dank voor de ontwikkeling van OncoQuest, het aanleveren van datasets en je welwillendheid. Ik ben de tel kwijtgeraakt van hoe vaak ik bij je op de deur heb geklopt met een verzoek.

Hanneke Tielens, Maarten Regtuit, Jacqueline Geskus en Patty Veenvliet, heel erg bedankt voor jullie inspanningen ten behoeve van dit promotieonderzoek.

Op deze plek wil ik mijn directe onderzoekscollega's bedanken. Kamergenootjes Marieke de Bruijn, Ingrid Cnossen, Annette Wehman-van Nieuwenhuizen, Femke Jansen en Sanne Duman-Lubberding, bedankt voor al jullie hulp, ideeën, de verrassende gesprekken en vooral de lol die we met elkaar hebben gehad! "Holla hee holla hee holla hopsaseee!" (het begeleidende dansje moeten jullie er maar bij denken). Ik mis onze muzikale intermezzo's en jouw "dikke bonus!", Annette. Sanne, Alhamdulillah! Labratten Géke Flach en Derrek Heuveling, veel dank voor de gezellige kletspraatjes, jullie vriendschap en de vieze koffie! Lieve Géke, we did it!! We moeten echt nog eens een rondje over de Zuid-Limburgse heuvels gaan fietsen. Sandra Biemans, rots in de branding, hartelijk dank voor al je logistieke ondersteuning, gemoedelijkheid en warme betrokkenheid. Gitta Kleijn, bedankt voor je vrolijke energie, de fijne samenwerking aan de meta-analyse en je hulp bij de inclusie ten behoeve van dit onderzoeksproject. Heleen Melissant, heel veel dank voor het afnemen van de interviews ten behoeve van de kwalitatieve studie, en voor het vervolgens plezierige (deels trans-Atlantische) samenwerken aan de analyse van de verkregen data. Inge Braspenning, bedankt voor het uittypen van een aantal interviews ten behoeve van de kwalitatieve studie. Een tijdrovende klus was dat!

Mijn teamleden en de supporters van het Alpe d'HuZes fietsteam 'Samen leven met kanker'. Ik heb ontzettend genoten van het met jullie houden van de fantastische benefietacties (zoals de Zumba® marathon en het verkopen van de 'Rubbertjes van Oranje' en de 'Willem de Glijers' op Kroningsdag op de Wallen), de gezellige trainingen en natuurlijk de onvergetelijke koersweek met als hoogtepunt de beklimmingen van de Alpe d'Huez. Opgeven was geen optie! Dank voor deze gouden tijd!

Mijn paranimfen Ingrid Cnossen en Femke Jansen. Lieve Ingrid, samen met Marieke stonden wij aan de wieg van de onderzoeksgroep 'Samen leven met kanker'. We waren 'Irma's Angels'. Wat hebben we veel (verhuizingen) meegemaakt samen! Heerlijk hoe jij van elke publicatie een feest maakt en hoe jij tranen met tuiten kunt lachen. Lieve Femke, het *stepped care* project is ook een beetje jouw kind geworden. Ik bewonder je scherpe blik, snelheid en mentaliteit. Bijzonder veel dank voor al jullie inzet, support en vriendschap!

Lieve vrienden en vriendinnen, lieve (oud-)huisgenoten, lieve (oud-)collega's van het Dr. Horacio E. Oduber Hospitaal, van VUmc School of Medical Sciences en van GGZ inGeest. Bedankt voor de fijne vriendschap, jullie humor en begrip, en de welkome afleiding tijdens mijn promotietraject (zoals de crazy Zumba® fun, de vaartochtjes op de *terrace boat*, NYC ontdekken met 'de grootste mens van Manhattan', de na de zangles borrels, het rauwe maar gezellige Rotterdam en de hilarische tripjes naar Parijs! Broche Diarée!). Lieve Jacqueline Houting, Jawina Weisz, Kimberly Margarita, Karlijn de Vries en Floyd Douglas Grobbe, ik bewonder jullie intelligentie en levensinstelling! Jullie inspireren mij als geen ander om buiten mijn referentiekader te denken en mijn hart te volgen. Jacqueline, sinds ons eerste co-schap zijn we vriendinnen. Heel veel dank voor je fijne gezelschap, wijze raad, energie en voor het tekenen van de prachtige, alleszeggende prent voor op de omslag van dit proefschrift.

Mijn lieve familie. Papa, mama, aan jullie heb ik dit alles te danken. Papa, niemand begrijpt mij zo goed als jij. En niemand kan haar kinderen zo goed in de watten leggen als jij, mama. Grote broer Willem, gelukkig hoef jij voorlopig even niet meer op missie. Dorine, jij bent de beste Schwess (en nagellakker) van de wereld, en mijn liefste vriendin. Zwager Lars Kienhuis, koning, snel weer samen fietsen in 't Gooi en langs de plassen! Schoonschwess Sandra Krebber-den Teuling, Lotte, Pien, en petekids Gijs en kleine Liz. Met jullie is het altijd genieten! Bedankt voor jullie eindeloze steun, het meedenken en de gezelligheid!

En last, but zeker not least: mijn kleine maatjes. Lieve Roeltje en Toof, de vele uren waarin ik me thuis heb afgezonderd om dit proefschrift te voltooien, waren jullie bij me. Half op het toetsenbord van mijn laptop snurkend, jezelf poetsend, met mijn papieren of pen spelend, om knuffels vragend, winden latend, als een geit door de kamer springend, aan mijn bril neuzend, ongemerkt de stekker uit de router trekkend, elkaar achterna zittend, op de uitkijk liggend, in mijn gezicht gapend. Geen moment heb ik mij alleen gevoeld! Jullie zijn het einde!

Milou, lieve, ouwe dibbes, dank voor het waken over de poezen toen ik op Aruba zat; je optreden tegen Sam de buurkat was heldhaftig!

Lieve Rover, jij blijft voor altijd in mijn gedachten. Dit proefschrift draag ik op aan jou.