A longitudinal study of depressive symptoms in patients with head and neck cancer undergoing radiotherapy

Authors: Guro Lindviksmoen Astrup, MSc, RN; Tone Rustøen, PhD, RN; Christine Miaskowski, PhD, RN; Steven M. Paul, PhD; Kristin Bjordal, PhD, MD

Author affiliations: Department of Oncology, Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital, Norway (Mrs. Astrup); Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Norway (Dr. Rustøen); Institute of Health and Society, University of Oslo, Norway (Dr. Rustøen); School of Nursing, University of California, San Francisco (Drs. Miaskowski and Paul); Research Support Services, Oslo University Hospital, Norway (Dr. Bjordal); Institute of Clinical Medicine, University of Oslo, Norway (Dr. Bjordal).

Correspondence to: Guro Lindviksmoen Astrup, gurol@ous-hf.no

Oslo University Hospital, Radiumhospitalet

Pb 4953 Nydalen

0424 Oslo

Norway

Conflicts of Interest and Sources of Funding: The study was funded by the Norwegian Cancer Society. The PhD fellowship for G. L Astrup was provided by the Regional Health Authority of South-Eastern Norway, and additional support was provided by The Norwegian Radium Hospital

Foundation. Dr. Miaskowski is supported by grants from the National Cancer Institute and the American Cancer Society. None of the authors have any conflicts of interest.

ABSTRACT

Background: While patients with head and neck cancer are at increased risk for depressive symptoms compared with other cancer patients, few longitudinal studies have evaluated changes in, and predictors of, this symptom over time.

Objective: To determine whether levels of depressive symptoms changed over time, and whether specific demographic, clinical, symptom, or psychosocial characteristics were associated with depressive symptoms.

Methods: In a longitudinal study of patients with head and neck cancer, depressive symptoms were assessed with the Center for Epidemiologic Studies - Depression scale, from the initiation of radiotherapy and for six months following. Hierarchical linear modeling was used to evaluate for changes in, as well as for potential predictors of inter-individual differences in, depressive symptoms.

Results: The severity of depressive symptoms increased during radiotherapy, and then decreased over time. The portion of patients who reported clinically meaningful levels of depressive symptoms at each assessment ranged from 29% to 42%. Several known predictors of pre-treatment severity of depressive symptoms (i.e., physical symptoms, less social support, dissatisfaction with looks) were corroborated. In addition, having surgery prior to radiotherapy was associated with lower levels of depressive symptoms at initiation of radiotherapy.

Conclusion: A moderate proportion of patients with head and neck cancer reported levels of depressive symptoms that indicated the need for clinical evaluation. Several patient characteristics were associated with depressive symptoms.

Implications for practice: Knowledge on prevalence, time course, and predictors of depressive symptoms from this study can be used to identify patients at higher risk for more severe depressive symptoms.

INTRODUCTION

Patients with head and neck cancer (HNC) experience multiple, complex, and concurrent physical, functional, and psychosocial problems as a consequence of their disease and its treatment; the uncertainty of the diagnosis; as well as the impact of the disease on nutritional intake, ventilation, and communication.[1] These negative effects on vital functions, as well as facial disfigurement, may contribute to the high prevalence of depressive symptoms reported by these patients. In fact, depressive symptoms are more common in HNC patients than in other cancer patients,[2] with prevalence rates that range from 22% to 57%.[2] Findings from a systematic review[1] suggest that HNC patients report high levels of depressive symptoms from diagnosis to the first six months following treatment. In addition, depressive symptoms are reported by survivors of this cancer several years after treatment.[3]

In most studies, the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), or the Center for Epidemiologic Studies - Depression (CES-D) scale were used to measure depressive symptoms.[1] However, many studies of psychological distress in HNC patients used general rather than specific measures of depressive symptoms or assessed depressive symptoms as one of many dimensions in a quality of life (QOL) measure. Furthermore, the majority of these studies were cross-sectional and evaluated HNC patients who received a variety of cancer treatments.

When reviewing the literature from the past 15 years, 12 longitudinal studies were found that evaluated depressive symptoms in HNC patients who underwent radiotherapy (RT) specifically, using the CES-D,[4] the HADS,[5-11] the BDI,[10, 12-14] and the Self-Rating-Depression-Scale (SDS).[15] In all of these studies, levels of depressive symptoms increased during RT, peaked at the completion of treatment, and then decreased over time. These studies varied in terms of

length of follow-up, from assessments pre- and post treatment[6, 13] to a total of three years.[5] In addition, sample sizes across these studies ranged from 21[12] to 220.[5]

Several predictors of depressive symptoms in patients with HNC were identified, including younger age,[5, 10] being single or living alone,[10, 16] less education,[15, 16] working,[10] smoking,[10, 16] alcohol usage,[16] specific working conditions,[17] decreased social support,[17] higher stage of disease,[5] tumor site,[17] combined modality treatment,[5] aggressive RT regimens,[15] higher number of comorbidities,[1] lower physical functioning,[18] and increased numbers of physical symptoms and side effects.[7, 11, 12, 17] Findings regarding gender as a predictor of depressive symptoms are inconclusive.[1] In addition, depressive symptoms were associated with malnutrition[19] and changes in body image,[4] as well as with increased anxiety[1] and decrements in various dimensions of QOL.[3, 6, 9, 14, 16] However, none of the aforementioned studies evaluated the combination of demographic, clinical, symptom, and psychosocial characteristics as predictors of depressive symptoms in the same sample of HNC patients who underwent RT.

Based on findings from the review of depressive symptoms in HNC patients,[1] additional research is warranted to evaluate which demographic and clinical characteristics, as well as other symptoms and psychosocial characteristics, are associated with depressive symptoms across the trajectory of these patients' illness. Although a substantial body of literature on depressive symptoms in HNC patients exists, relatively small sample sizes limit one's ability to compare different subgroups and evaluate the effects of multiple predictors. In addition, differences in study designs, choice of measures, and characteristics of the patients evaluated limit one's ability to compare findings across studies.

Newer methods of longitudinal analysis, such as hierarchical linear modeling (HLM), allow for an evaluation of changes in depressive symptoms over time, as well as for the identification of characteristics that predict variability in initial levels (intercept) and trajectories

(slope) of depressive symptoms. This type of analysis may provide insights into which patients experience higher levels of depressive symptoms. Therefore, the purposes of this longitudinal study, in a sample of patients with HNC, were to determine whether levels of depressive symptoms changed from the initiation of RT and for six months following, and to determine whether specific demographic, clinical, symptom, or psychosocial characteristics were associated with initial levels of, or changes in, depressive symptoms.

MATERIALS AND METHODS

Patients and settings - This study is part of a larger, longitudinal study of symptoms and QOL in oncology patients. The patients with HNC were recruited in the RT unit at the Department of Oncology, Norwegian Radium Hospital (NRH), Oslo University Hospital. Patients were eligible to participate if they were ≥18 years of age; were able to read, write and understand Norwegian; and were scheduled to receive RT for HNC. Patients were excluded if they were to receive RT for brain metastases or had a disease that affected their cognitive ability. The study was approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Directorate of Health, the privacy ombudsman at the hospital, and the institutional review board at NRH.

Conceptual framework - The Theory of Symptom Management (TSM) served as the conceptual framework for the original study. The TSM was first introduced by faculty members at the University of California, San Francisco (UCSF) School of Nursing in 1994[20] and has undergone several revisions.[21] The TSM consists of three essential concepts: symptom experience, symptom management strategies, and symptom status outcomes. The concepts are placed within the domains of nursing science, namely the person, health and illness, and the environment. This study focused on the symptom experience, defined as a simultaneous perception, evaluation, and response to a change in one's usual feeling.[21]

Study procedures - During the first appointment in the RT unit, approximately eight days prior to the initiation of RT, patients were provided with information about the study and invited to participate. After obtaining written, informed consent, patients completed self-report questionnaires to obtain information on demographic and clinical characteristics, as well as several instruments that assessed symptoms and QOL. Patients completed mailed questionnaires at approximately 1, 2, 3, and 6 months after enrollment.

Instruments

Demographic characteristics - A demographic questionnaire obtained information on marital status, living situation, level of education, and employment status.

Clinical characteristics - Medical records were reviewed by study personnel for information on specific HNC diagnoses and previous treatments. Based on the patients' tumor, node, and metastases (TNM) classification at the time of diagnosis, stage of disease was classified into 4 stages (I = T1N0M0, II = T2N0M0, III = T1-2N1M0 or T3N0-1M0, and IV = T4, N2-3 or M+) using the Union for International Cancer Control (UICC) guidelines.[22]

Karnofsky Performance Status (KPS) scale - Physical functioning was evaluated by the patients using the KPS scale,[23, 24] where the score ranges from 0 (dead) to 100 (normal; no complaints; no evidence of disease) in 10-point increments. As patients in the current study were outpatients at the time of enrollment, the 40 (disabled; requires special care and assistance) to 100-point range of the KPS scale was used. The KPS scale has well-established validity and reliability with cancer patients.[25]

Self-Administered Comorbidity Questionnaire - 19 (SCQ-19) - Comorbidities were evaluated using the SCQ-19,[26] which includes 16 common and 3 optional conditions. Patients indicated whether they had the condition, and if yes; if they received treatment for it; and if it limited their activities. The SCQ-19 has established validity and reliability with patients with chronic medical

conditions when using the total score (0 to 57).[26] In this study, the total number of comorbidities (0 to 19) was used in the analyses.

Center for Epidemiologic Studies - Depression (CES-D) scale - Depressive symptoms were evaluated using the CES-D,[27] which consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Patients rated how often they experienced symptoms over the past week. The score for each item ranges from 0 to 3 and the total score ranges from 0 to 60. A total CES-D score of ≥16 indicates the need for clinical evaluation of depressive symptoms. While the CES-D was developed for use in the general population, it has been used extensively and has established validity and reliability in patients with cancer in general[28] and in HNC patients.[29] In this study, Cronbach's alpha for the CES-D was .87.

Based on previous literature,[7, 11, 12, 17] three symptoms (i.e., sleep disturbance, fatigue, pain) were evaluated as predictors of initial levels and trajectories of depressive symptoms.

General Sleep Disturbance Scale (GSDS) - Sleep disturbance was evaluated using the GSDS,[30] which consists of 21 items that assess various aspects of sleep disturbance in the past week. The frequency of each item is rated on a 0 (never) to 7 (everyday) numeric rating scale (NRS). The total GSDS score is the sum of the 21 items that can range from 0 (no sleep disturbance) to 147 (extreme sleep disturbance). A total score of ≥43 indicates high levels of sleep disturbance.[30] The GSDS has established validity and reliability with employed women,[30] and was used with cancer patients who underwent RT.[31] In this study, Cronbach's alpha for the GSDS was .86.

Lee Fatigue Scale (LFS) - Fatigue and energy levels were evaluated using the LFS,[32] which consists of 18 items, divided in two subscales (i.e., fatigue and energy). Patients were asked to rate each item based on how they feel "right now" on a 0 to 10 NRS. The subscale scores are calculated as the mean of the subscales items, ranging from 0 to 10, with higher scores indicating

higher levels of fatigue or energy. A score of ≥4.4 indicates high levels of fatigue and a score of ≤4.8 indicates low levels of energy.[31] The LFS has well-established validity and reliability in cancer patients.[33] In this study, Cronbach's alphas for the fatigue and energy subscales were .95 and .91, respectively.

Brief Pain Inventory (BPI) - Pain was evaluated using a single item from the BPI,[34] where patients reported whether or not they had pain. The 15 item BPI has been used extensively and has well-established validity and reliability in cancer patients.[35, 36]

Multidimensional Quality Of Life Scale - Cancer (MQOLS-CA) - The MQOLS-CA[37] measures different dimensions of QOL (i.e., psychological well-being, physical well-being, nutrition, symptom distress, interpersonal well-being) and has well-established validity and reliability.[37-39] Selected subscales and a single item from the MQOLS-CA were used to assess nutrition, social support, and satisfaction with looks, which were associated with depressive symptoms in previous studies of patients with HNC.[4, 17, 19]

MQOLS-CA Nutrition - Nutrition was evaluated using the subscale from the MQOLS-CA.[37] The Nutrition subscale consists of four items that assess appetite, food intake, taste, and weight concerns. Each item is rated on a 0 to 10 NRS. A subscale score was calculated as the mean of the four items, where higher scores indicate better nutritional status. In this study, Cronbach's alpha for the Nutrition subscale was .73.

MQOLS-CA Interpersonal Well-Being - Social support and social role/functioning, shortened to social support, was evaluated using the subscale from the MQOLS-CA.[37] The subscale consists of five items that measure these two constructs, and each item is rated on a 0 to 10 NRS. A subscale score was calculated as the mean of the five items, where higher scores indicate better social support. In this study, Cronbach's alpha for the Interpersonal Well-Being subscale was .65, possibly due to the two different constructs in this subscale.

MQOLS-CA Satisfaction with looks - Satisfaction with looks was evaluated using a single item from the MQOLS-CA.[37] Patients were asked to rate to what degree they were satisfied with their looks on a 0 (very dissatisfied) to 10 (very satisfied) NRS.

Data analysis - Descriptive statistics and frequency distributions for the sample characteristics and symptom severity scores at enrollment were calculated using SPSS version 20 (SPSS Inc., Chicago, Illinois). A mean CES-D score was calculated for each of the five assessments, for use in the subsequent statistical analyses.

HLM, based on full maximum likelihood estimation, was performed using the software developed by Raudenbush and colleagues.[40, 41] Compared with other methods for analyzing change, HLM has two major advantages. First, it can accommodate unbalanced designs and uses all available data by applying the missing at random (MAR) assumption, which allows for analysis of data where the number and spacing of assessments vary across respondents. Second, HLM has the ability to model individual change, which helps to identify more complex patterns of change that often are overlooked by other methods.

With HLM, repeated measures of the outcome variable (i.e., depressive symptoms) are conceptualized as being nested within individuals and the analysis of change in depressive symptom scores is at two levels: within persons (level 1) and between persons (level 2). At level 1, the outcome is conceptualized as varying within individuals and is a function of person-specific change parameters plus error. At level 2, the person-specific change parameters are multivariate outcomes that vary across individuals. Level 2 outcomes can be modeled as a function of demographic, clinical, symptom, or psychosocial characteristics that vary between individuals, plus an error associated with the individual. Combining level 1 with level 2 results in a mixed model with fixed and random effects.[40]

During the level 1 analysis, intra-individual variability in ratings of depressive symptoms over time was examined. Four level 1 models were compared to determine whether the patients' depressive symptoms: did not change over time (i.e., no time effect); changed at a constant rate either accelerating or decelerating (i.e., linear time effect, no bends); changed at a rate that accelerated and decelerated over time (i.e., quadratic effect, one bend); or changed at a rate that accelerated, decelerated, and accelerated over time (i.e., cubic effect, two bends). At this point, the level 2 model was constrained to be unconditional (i.e., no predictors) and likelihood ratio tests (i.e., comparison of the deviance values among the models) were used to determine the best model.

During the level 2 analysis, inter-individual differences in the trajectories of depressive symptoms were examined by modeling the individual change parameters (i.e., intercept and slope) as a function of proposed predictors. The first column in Table 1 presents the proposed predictors that were used in the level 2 analysis. This list is based on a review of the literature on depressive symptoms in patients with HNC.[1, 5, 7, 10-12, 15-19] To improve estimation efficiency and construct a parsimonious model, exploratory analyses were done in which each potential predictor was assessed to determine whether it would result in a better fitting model if it alone was added as a level 2 predictor. Predictors with a *t*-value of <2, which indicates a lack of significant effect, were dropped from subsequent model testing.

All significant predictors from the exploratory analyses, indicated with an "x" in Table 1, were entered into the model to predict each individual change parameter. Only predictors that maintained a statistically significant contribution in conjunction with other predictors were retained in the final model. A *p*-value of <.05 indicates statistical significance. The effects of each of these predictors are illustrated in the figures as adjusted change curves for depressive symptoms that were estimated based on differences in dichotomous outcome predictors (yes/no)

or continuous outcome predictors (higher/lower score calculated based on 1 SD above and below the mean score of the predictor).

RESULTS

Patient characteristics - A total of 207 patients were approached and 79% (n=163) consented to participate. Those patients who declined to participate were significantly older (mean 66 years) than those who agreed (mean 61 years; p=.011). While reasons for refusal to participate were not recorded systematically, lack of energy was the most common reason offered by some patients. Five patients were excluded after enrollment due to a non-HNC diagnosis or an altered treatment plan. Of the remaining 158 patients, 84% (n=133) completed the questionnaires prior to initiation of RT. No differences in demographic or clinical characteristics were found between patients who did and did not complete these questionnaires.

The overall attrition rate for this study was 37%. Of the 133 patients who completed the enrollment questionnaire, 59% completed all five assessments. Among those who did not complete all of the assessments, a higher percentage of patients had a primary level of education compared to secondary (p=.009) and received palliative RT (p=.018). A significant difference in mean CES-D scores at enrollment was found between patients who did (10.8, SD 7.8) and did not (14.7, SD 10.9; t=2.261, p=.026) complete the study.

The patients' demographic, clinical, and treatment characteristics are presented in Table 2. Most of the patients were married or partnered; had at least a secondary level of education; and their mean age was 60 years. The most common comorbid conditions assessed on the SCQ-19 were neck/back pain (35%) and hypertension (29%), and 13% of patients indicated that they had a comorbid depression. The majority of patients received a total RT dose of 70 Gray over a period of six weeks.

Individual and mean change in depressive symptoms - The goodness-of-fit tests of the deviance among the models in the first level of the HLM analysis indicated that a cubic model fit the data best ($p<.001$). Table 3 presents the estimates for the unconditional cubic change model. The cubic trajectory of depressive symptoms, illustrated in Figure 1A, changed from 12.6 prior to RT, to just below 16 during and at the completion of RT, followed by a decrease to about the same score of 12.6 at six months. Figure 1B illustrates the individual trajectories for depressive symptoms, which indicates a large amount of inter-individual variability in depressive symptom scores. The mean scores depicted in the figures are estimated or predicted means based on the HLM analyses.

Figure 2 displays the percentage of patients with CES-D scores above the cut-off of ≥16, indicating clinically meaningful levels of depressive symptoms, as well as the observed mean scores at each assessment. A cross-tabulation analysis indicated that among those who completed both the enrollment and the six month assessments, 55% of patients who reported CES-D scores ≥16 at enrollment still had elevated scores at six months.

Inter-individual differences in levels of depressive symptoms - As shown in the final model in Table 3, the five characteristics that predicted inter-individual differences in depressive symptoms at enrollment (i.e., intercept) were: the occurrence of HNC surgery in the six weeks prior to RT, sleep disturbance, fatigue, social support, and satisfaction with looks.

To illustrate the effects of these predictors on patients' initial levels of depressive symptoms, Figure 3 (A-E) display the adjusted change curves for depressive symptoms that were estimated based on differences in the occurrence of HNC surgery in the six weeks prior to RT (yes/no [Figure 3A]); sleep disturbance (higher/lower levels calculated based on ± 1 SD of the mean GSDS total score [Figure 3B]); fatigue (higher/lower levels calculated based on ± 1 SD of

the mean LFS fatigue subscale score [Figure 3C]); social support (higher/lower levels calculated based on ± 1 SD of the mean MQOLS-CA Interpersonal Well-Being subscale score [Figure 3D]); and satisfaction with looks (higher/lower levels calculated based on ± 1 SD of the mean MQOLS-CA item score [Figure 3E]). None of the characteristics identified in the exploratory analyses (i.e., marital status, number of comorbidities, fatigue, energy, nutrition, depressive symptoms at enrollment) predicted inter-individual differences in any of the slope parameters (i.e., trajectories) for depressive symptoms.

DISCUSSION

Consistent with previous reports on depressive symptoms in patients with HNC who underwent RT,[4-15] severity of depressive symptoms increased during RT, peaked around completion, and then decreased to pre-treatment levels in this sample. However, the use of HLM, compared with more traditional statistical approaches (e.g., repeated measures analysis of variance), provided evidence of a large amount of inter-individual variability in levels of depressive symptoms.

Both prior to RT and six months after enrollment, the mean CES-D score for this Norwegian sample of HNC patients was 12.6. This score is similar to CES-D scores reported in a Dutch longitudinal study of depressive symptoms in HNC patients receiving surgery and/or RT,[42] where a moderate decrease in mean CES-D scores from 12.2 before treatment to 10.2 at six months was found. However, they did not assess depressive symptoms during treatment. In the current study, the severity of depressive symptoms peaked during treatment. At one month, patients mean CES-D scores were just below the clinically meaningful cut-off score of ≥16. Based on a previous study of breast cancer patients,[43] patients with scores just below this cut-off may be experiencing subsyndromal levels of depressive symptoms that warrant clinical

evaluation. These sub-threshold levels of depressive symptoms may be clinically important, because subsyndromal depression was associated with decreased QOL,[44] as well as an increased risk for clinical depression,[45] in the general population.

While mean CES-D scores were below the clinically meaningful cut-off score throughout our study, a large amount of inter-individual variability was identified (Figure 1B). Furthermore, at each assessment between 29% and 42% of the patients reported CES-D scores of ≥16 (Figure 2). This percentage is higher than that reported in the Dutch study, where the percentage of patients with CES-D scores ≥16 was 28% before treatment and 24% at six months.[42] When compared with other cancer diagnoses, the occurrence rates in our patients are higher than that of patients newly diagnosed with prostate cancer (10%)[46] and gynecological cancer (23%),[47] but lower than those of patients newly diagnosed with breast cancer (39%)[47] and lung cancer (56%).[48] In addition, the occurrence rates are higher than those reported in a study of middle-aged and older people in the general population in Norway, where 21% of the responders had CES-D scores above the cut-off.[49] Given the significant difference in depressive symptom scores at enrollment between patients who did and did not complete the study, there is reason to believe that the levels of depressive symptoms during the study may be underestimated. In the current study, 13% of patients indicated on the SCQ-19 that they had a comorbid depression. Among these patients, only 18% reported that they received treatment for their depression. While studies based on self-report assessments frequently report higher occurrence rates for depressive symptoms compared with structured clinical interviews,[50] there is reason to believe that a high percentage of our patients would benefit from evaluation of clinical depression and subsequent treatment.

Even though previous studies of patients with HNC found that age,[10] marital status,[10] education level,[15] and employment status[10] were associated with depressive symptoms, the current study, as well as several other studies,[5, 7, 10, 15] were not able to find associations between depressive symptoms and demographic characteristics. These inconsistent findings suggest that demographic characteristics are not strong predictors of depressive symptoms in these patients. It should be noted that in the current study, a relatively high percentage of the sample was married, had at least a secondary level of education, and was not working, all of which are associated with lower levels of depressive symptoms. In addition, employment status may influence depressive symptoms to a lesser degree in a Norwegian sample, because all cancer patients are eligible to receive some form of sick leave benefits.

Findings on the associations between depressive symptoms and clinical characteristics were not consistent in previous studies. While some studies found that stage of disease,[5] tumor site,[17] and concurrent CTX,[5] were associated with depressive symptoms, others did not find associations.[10, 11, 15] The finding that patients who had surgery reported lower CES-D scores than those who did not (Figure 3A) is in contrast with one study with opposite results,[5] and with another study that found no such association.[10] However, in both of these previous studies, fewer patients underwent surgery compared to the current study. In addition, in the study by Joseph and colleagues,[5] the tumor site and stage of disease differed from the current study, which may have influenced the results. In the current study, patients who underwent surgery may have reported lower depressive symptom scores because they had started treatment and were less concerned about the outcome of their treatment. An alternative explanation is that patients who received surgery were under the impression that surgery was a more radical approach to treatment compared to primary RT and were more confident about the efficacy of their treatment.

Sleep disturbance (Figure 3B), fatigue (Figure 3C), social support (Figure 3D), and satisfaction with looks (Figure 3E) had an impact on initial levels of depressive symptoms. In the current study, higher levels of sleep disturbance and fatigue were associated with higher levels of depressive symptoms. Although sleep disturbance and fatigue were not reported as predictors of depressive symptoms in previous studies of patients with HNC who underwent RT, our findings are consistent with previous studies that evaluated associations between depressive symptoms and physical symptoms or side effects.[7, 11, 12] In addition, sleep disturbance and fatigue are both symptoms associated with clinical depression.[1]

The fact that patients in the current study reported GSDS scores above the cut-off score of ≥43 and LFS fatigue scores below the cut-off score of ≥4.4 is interesting. The reason for the co-occurrence of a relatively high level of sleep disturbance and a relatively low level of fatigue may be the timing of the assessment (i.e., prior to the initiation of RT). Fatigue generally occurs during RT and increases over time.[51] In contrast, patients may experience sleep disturbance from a variety of causes (e.g., pain, worry, stress).

Consistent with previous studies[17, 42] patients with higher levels of social support reported lower levels of depressive symptoms prior to RT. One study[17] argued that patients with HNC were more likely to come from less privileged social classes because of the risk factors associated with HNC (e.g., smoking, alcohol), which may result in less social support.

The final predictor of initial levels of depressive symptoms in the current study was satisfaction with looks. A recent study among HNC patients who underwent RT[4] found an association between depressive symptoms and body image during and after completion of, but not prior to RT. Patients with HNC experience a significant amount of disfigurement and dysfunction associated with treatment.[4] It is plausible that these changes in body image lead to

decreased satisfaction with looks and interference with self esteem that is associated with higher levels of depressive symptoms.

A few limitations need to be addressed. First, depressive symptoms were evaluated using a self-report questionnaire, while a structured clinical interview is the gold standard. However, self-report measures are resource-efficient in research and appear to be the best approach for identifying individuals who may be at increased risk and who may potentially benefit from an intervention.[50] Second, the sample size was relatively small and the overall attrition rate was 37% for this study. While detailed reasons for withdrawal were not obtained, it is reasonable to hypothesize that HNC disease and its treatment resulted in severe symptoms in some patients decreased their motivation to continue study participation. In addition, the questionnaire was extensive and the follow-up period was relatively long. Finally, the questionnaires were distributed by mail, which may have influenced the response rate.

The lack of significant predictors of the trajectory of depressive symptoms may be partially explained by the sample size because support for predictors of a cubic rate of change in an outcome may require a larger sample and greater variability in the assessed characteristics.[52] In addition, as this study was part of a larger study of oncology patients, an exhaustive list of potential predictors reported in previous studies of patients with HNC (e.g., smoking, alcohol intake) was not evaluated. It should be noted that the inclusion of patients with different treatment intents, tumor sites, and stages of disease results in a more heterogeneous sample. However, as noted in a previous study,[15] most publications on depressive symptoms in patients with HNC did not differentiate among HNC diagnoses. Finally, most of the patients were white, married, and had a secondary level of education or higher, which limits the generalizability of the study findings.

Clinicians can use the knowledge from the current study on prevalence, time course, and predictors of depressive symptoms to identify higher risk patients and educate patients about this symptom. In addition, clinicians may choose to refer patients with higher levels of depressive symptoms for psychological consultation or initiate treatment with antidepressants. Considering the relatively large proportion of patients who reported clinically meaningful levels of depressive symptoms, future studies that test the efficacy of interventions targeted at reducing depressive symptoms are needed. In addition, interventions targeted to mitigate the modifiable risk factors identified in this study (e.g., sleep disturbance, fatigue, social support) need to be tested, as this approach may lessen depressive symptoms.

Acknowledgements and conflicts of interest - The authors would like to thank the patients who participated in the study, and the nurses in the RT unit who facilitated the enrollment of patients. The study was funded by the Norwegian Cancer Society. G.L. Astrup received a PhD fellowship from the Regional Health Authority of South-Eastern Norway. Additional support was provided by The Norwegian Radium Hospital Foundation. Dr. Miaskowski is supported by grants from the National Cancer Institute and the American Cancer Society.

The authors have no conflicts of interest to declare.

REFERENCES

1. Haisfield-Wolfe ME, McGuire DB, Soeken K, Geiger-Brown J, De Forge BR. Prevalence and correlates of depression among patients with head and neck cancer: a systematic review of implications for research. *Oncol Nurs Forum.* 2009;36(3):107-125.

2. Archer J, Hutchison I, Korszun A. Mood and malignancy: head and neck cancer and depression. *J Oral Pathol Med.* 2008;37(5):255-270.

3. Bjordal K, Kaasa S. Psychological distress in head and neck cancer patients 7-11 years after curative treatment. *Br J Cancer.* 1995;71(3):592-597.

4. Rhoten BA, Deng J, Dietrich MS, Murphy B, Ridner SH. Body image and depressive symptoms in patients with head and neck cancer: an important relationship. *Support Care Cancer.* 2014;22(11):3053-3060.

5. Joseph LA, Routledge JA, Burns MP, et al. Value of the Hospital Anxiety and Depression Scale in the follow up of head and neck cancer patients. *J Laryngol Otol.* 2013;127(3):285-294.

6. Kelly C, Paleri V, Downs C, Shah R. Deterioration in quality of life and depressive symptoms during radiation therapy for head and neck cancer. *Otolaryngol Head Neck Surg.* 2007;136(1):108-111.

7. Neilson K, Pollard A, Boonzaier A, et al. A longitudinal study of distress (depression and anxiety) up to 18 months after radiotherapy for head and neck cancer. *Psychooncology.* 2013;22(8):1843-1848.

8. Rose P, Yates P. Quality of life experienced by patients receiving radiation treatment for cancers of the head and neck. *Cancer Nurs.* 2001;24(4):255-263.

9. Kohda R, Otsubo T, Kuwakado Y, et al. Prospective studies on mental status and quality of life in patients with head and neck cancer treated by radiation. *Psychooncology.* 2005;14(4):331-336.

10. Chen AM, Jennelle RL, Grady V, et al. Prospective study of psychosocial distress among patients undergoing radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2009;73(1):187-193.

11. Chen SC, Lai YH, Liao CT, Lin CC, Chang JT. Changes of symptoms and depression in oral cavity cancer patients receiving radiation therapy. *Oral Oncol.* 2010;46(7):509-513.

12. Haisfield-Wolfe ME, McGuire DB, Soeken K, Geiger-Brown J, De Forge B, Suntharalingam M. Prevalence and correlates of symptoms and uncertainty in illness among head and neck cancer patients receiving definitive radiation with or without chemotherapy. *Support Care Cancer.* 2012;20(8):1885-1893.

13. de Paula JM, Sonobe HM, Nicolussi AC, Zago MM, Sawada NO. Symptoms of depression in patients with cancer of the head and neck undergoing radiotherapy treatment: a prospective study. *Rev Lat Am Enfermagem.* 2012;20(2):362-368.

14. Chawla S, Mohanti BK, Rakshak M, Saxena S, Rath GK, Bahadur S. Temporal assessment of quality of life of head and neck cancer patients receiving radical radiotherapy. *Qual Life Res.* 1999;8(1-2):73-78.

15. Sehlen S, Lenk M, Herschbach P, et al. Depressive symptoms during and after radiotherapy for head and neck cancer. *Head Neck.* 2003;25(12):1004-1018.

16. Duffy SA, Ronis DL, Valenstein M, et al. Depressive symptoms, smoking, drinking, and quality of life among head and neck cancer patients. *Psychosomatics.* 2007;48(2):142-148.

17. Singer S, Krauss O, Keszte J, et al. Predictors of emotional distress in patients with head and neck cancer. *Head Neck.* 2012;34(2):180-187.

18. Hammerlid E, Ahlner-Elmqvist M, Bjordal K, et al. A prospective multicentre study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. *Br J Cancer.* 1999;80(5-6):766-774.

19. Britton B, Clover K, Bateman L, et al. Baseline depression predicts malnutrition in head and neck cancer patients undergoing radiotherapy. *Support Care Cancer.* 2012;20(2):335-342.

20. Larson PJ, Carrieri-Kohlman V, Dodd MJ, et al. A model for symptom management. *Image J Nurs Scholarsh***.** 1994;26:272-276.

21. Humphreys J, Lee KA, Carrieri-Kohlman V, et al. Theory of Symptom Management. In: Smith MJ, Liehr PR, eds. *Middle Range Theory for Nursing*. 2nd ed. New York: Springer Publishing Company; 2008:145-158.

22. Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumours*. 6th ed. New York: Wiley-Liss; 2002.

23. Karnofsky D, Abelmann WH, Craver LV, Burchenal, JH. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer.* 1948;1:634–656.

24. Karnofsky D. *Performance scale*. New York: Plenum Press; 1977.

25. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol.* 1984;2(3):187-193.

26. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum.* 2003;49(2):156-163.

27. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychology Measurement.* 1977;1:385-401.

28. Hopko DR, Bell JL, Armento ME, et al. The phenomenology and screening of clinical depression in cancer patients. *J Psychosoc Oncol.* 2008;26(1):31-51.

29. Katz MR, Kopek N, Waldron J, Devins GM, Tomlinson G. Screening for depression in head and neck cancer. *Psychooncology.* 2004;13(4):269-280.

30. Lee KA. Self-reported sleep disturbances in employed women. *Sleep.* 1992;15(6):493-498.

31. Miaskowski C, Lee K, Dunn L, et al. Sleep-wake circadian activity rhythm parameters and fatigue in oncology patients before the initiation of radiation therapy. *Cancer Nurs.* 2011;34(4):255-268.

32. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. *Psychiatry Res.* 1991;36(3):291-298.

33. Meek PM, Nail LM, Barsevick A, et al. Psychometric testing of fatigue instruments for use with cancer patients. *Nurs Res.* 2000;49(4):181-190.

34. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994;23(2):129-138.

35. Klepstad P, Loge JH, Borchgrevink PC, Mendoza TR, Cleeland CS, Kaasa S. The Norwegian brief pain inventory questionnaire: translation and validation in cancer pain patients. *J Pain Symptom Manage.* 2002;24(5):517-525.

36. Wu JS, Beaton D, Smith PM, Hagen NA. Patterns of pain and interference in patients with painful bone metastases: a brief pain inventory validation study. *J Pain Symptom Manage.* 2010;39(2):230-240.

37. Ferrell BR, Wisdom C, Wenzl C. Quality of life as an outcome variable in the management of cancer pain. *Cancer.* 1989;63(11 Suppl):2321-2327.

38. Padilla GV, Ferrell B, Grant MM, Rhiner M. Defining the content domain of quality of life for cancer patients with pain. *Cancer Nurs.* 1990;13(2):108-115.

39. Padilla GV. Validity of health-related quality of life subscales. *Prog Cardiovasc Nurs.* 1992;7(1):13-20.

40. Raudenbush SW, Bryk AS. *Hierarchical Linear Models: Applications and Data Analysis Methods*. 2nd ed. Thousand Oaks, CA: Sage Publications; 2002.

41. Raudenbush SW. Comparing personal trajectories and drawing causal inferences from longitudinal data. *Annu Rev Psychol.* 2001;52:501-525.

42. de Leeuw JR, de Graeff A, Ros WJ, Blijham GH, Hordijk GJ, Winnubst JA. Prediction of depression 6 months to 3 years after treatment of head and neck cancer. *Head Neck.* 2001;23(10):892-898.

43. Dunn LB, Cooper BA, Neuhaus J, et al. Identification of distinct depressive symptom trajectories in women following surgery for breast cancer. *Health Psychol.* 2011;30(6):683-692.

44. Das-Munshi J, Goldberg D, Bebbington PE, et al. Public health significance of mixed anxiety and depression: beyond current classification. *Br J Psychiatry.* 2008;192(3):171-177.

45. Forsell Y. A three-year follow-up of major depression, dysthymia, minor depression and subsyndromal depression: results from a population-based study. *Depress Anxiety.* 2007;24(1):62-65.

46. Jongkamp VG, Roeloffzen EM, Monninkhof EM, de Leeuw JR, Lycklama a Nijeholt AA, van Vulpen M. Brachytherapy for prostate cancer does not influence long-term depression rate. *Brachytherapy.* 2012;11(6):495-501.

47. Stafford L, Judd F, Gibson P, Komiti A, Mann GB, Quinn M. Screening for depression and anxiety in women with breast and gynaecologic cancer: course and prevalence of morbidity over 12 months. *Psychooncology.* 2013;22(9):2071-2078.

48. Aukst Margetic B, Kukulj S, Santic Z, Jaksic N, Jakovljevic M. Predicting depression with temperament and character in lung cancer patients. *Eur J Cancer Care (Engl).* 2013;22(6):807-814.

49. Clausen S. Aldring og depressive studier: En epidemiologisk studie. *Tidsskrift for Norsk Psykologforening.* 2005;42:779-784.

50. Trask PC. Assessment of depression in cancer patients. *J Natl Cancer Inst Monogr.* 2004;(32):80-92.

51. Jereczek-Fossa BA, Santoro L, Alterio D, et al. Fatigue during head-and-neck radiotherapy: prospective study on 117 consecutive patients. *Int J Radiat Oncol Biol Phys.* 2007;68(2):403-415.

52. Raudenbush SW, Xiao-Feng L. Effects of study duration, frequency of observation, and sample size on power in studies of group differences in polynomial change. *Psychol Methods.* 2001;6(4):387-401.

Titles and legends to figures

Figure 1 - Mean (A) and individual (B) trajectories of depressive symptoms from initiation of radiotherapy and for six months following

Figure 2 - Mean score and percentage of patients with scores of ≥16 on the Center for Epidemiologic Studies - Depression Scale (CES-D) at each assessment

Figure 3 - Trajectories of depressive symptoms by occurrence of surgery prior to radiotherapy (A), sleep disturbance (B), fatigue (C), social support (D), and satisfaction with looks (E)

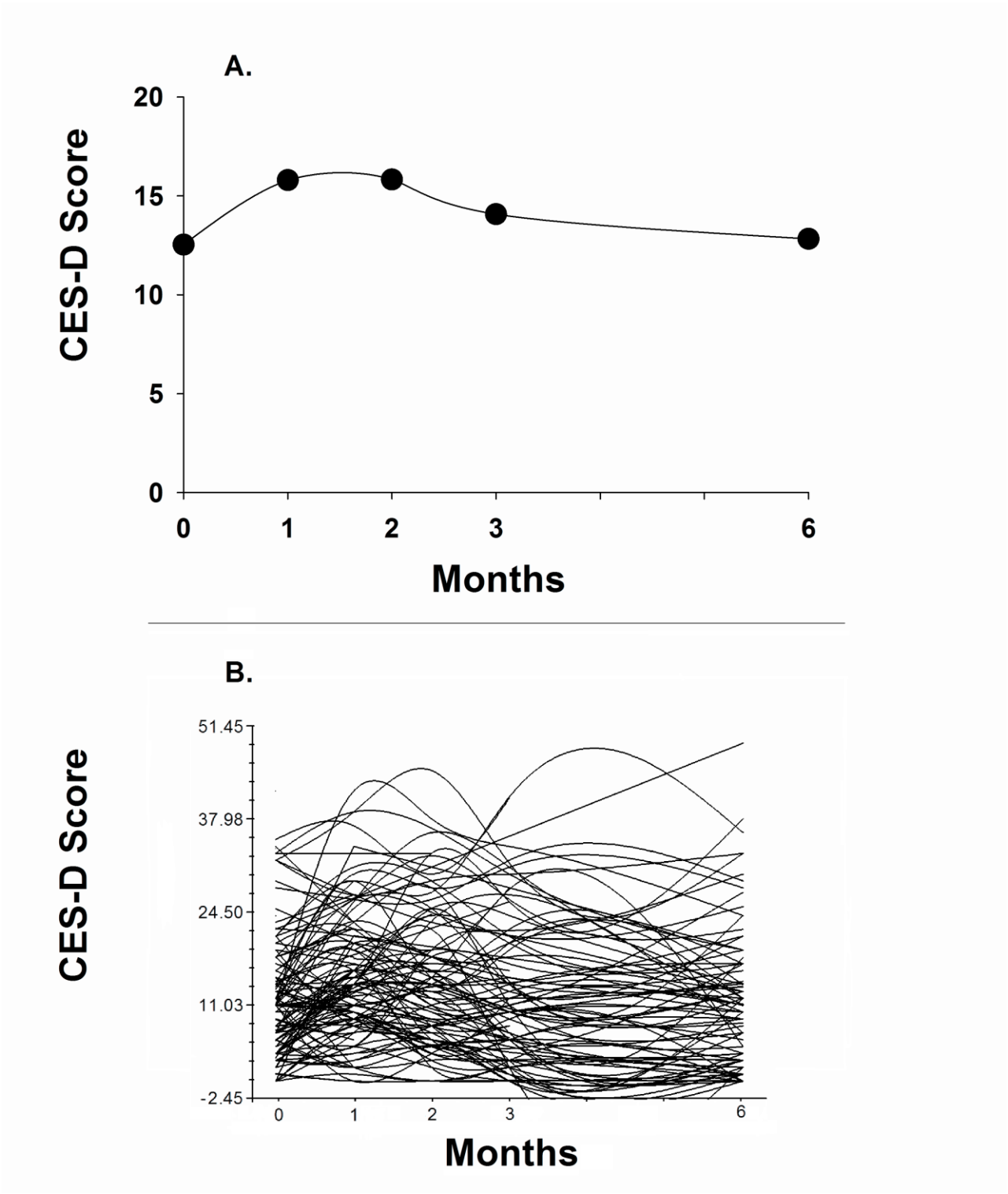
A.
CES-D Score
20
15
10
5
0
0
1
2
3
6
Months
B.
CES-D Score
51.45
37.98
24.50
11.03
-2.45
0
1
2
3
6
Months

Figure 1

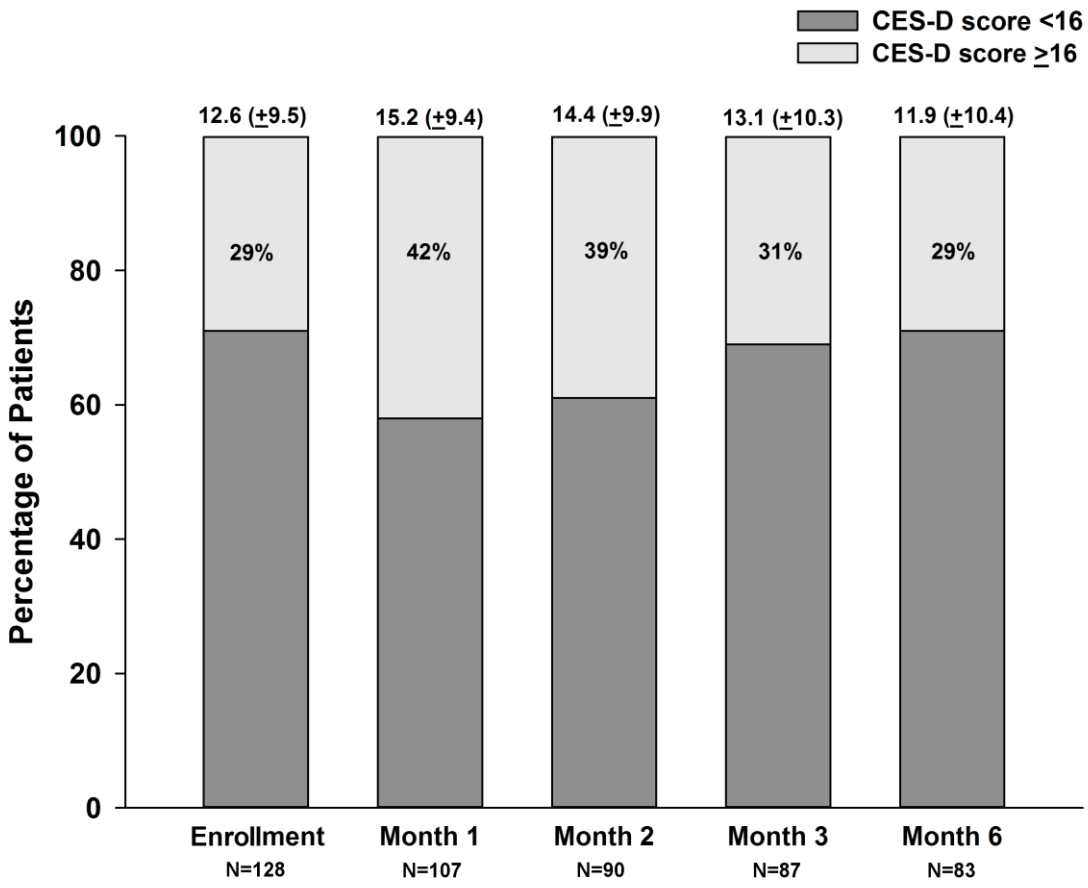
CES-D score <16
CES-D score ≥16
12.6 (±9.5)
15.2 (±9.4)
14.4 (±9.9)
13.1 (±10.3)
11.9 (±10.4)
100
80
60
40
20
0
Percentage of Patients
29%
42%
39%
31%
29%
Enrollment
N=128
Month 1
N=107
Month 2
N=90
Month 3
N=87
Month 6
N=83

Figure 2

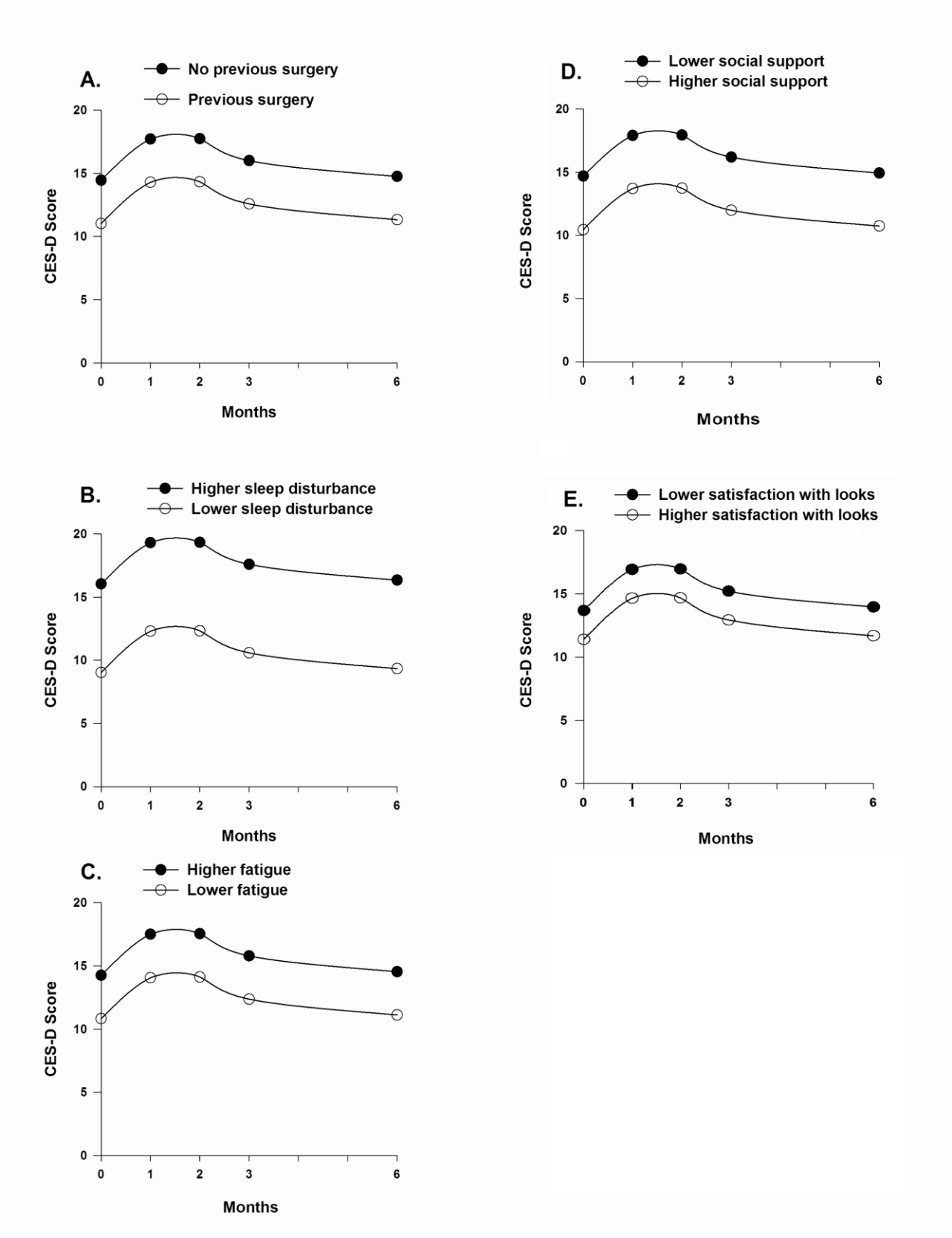
A.
No previous surgery
Previous surgery
CES-D Score
Months
B.
Higher sleep disturbance
Lower sleep disturbance
CES-D Score
Months
C.
Higher fatigue
Lower fatigue
CES-D Score
Months
D.
Lower social support
Higher social support
CES-D Score
Months
E.
Lower satisfaction with looks
Higher satisfaction with looks
CES-D Score
Months

Figure 3

Table 1 Exploratory Analysis of Potential Predictors of Depressive Symptoms in Patients with Head and Neck Cancer

Characteristics	I	LC	QC	CC
Demographic				
Age				
Gender				
Marital status	x		x	x
Education level				
Employment status				
Children living at home				
Clinical				
Time since diagnosis				
Karnofsky Performance Status score	x			
Number of comorbidities	x	x	x	x
Tumor site				
Stage of disease at enrollment				
Current treatment intent				
Surgery prior to radiotherapy	x			
Chemotherapy concomitant with				
Symptom				
Pain	x			
Sleep disturbance	x			
Fatigue	x		x	x
Energy	x	x	x	x
Psychosocial				
Nutrition	x		x	x
Social support	x			
Satisfaction with looks	x			
Depressive symptoms at enrollment (for		x	x	x

Note: Potential predictors that had a *t*-value of 2 or higher in the exploratory analysis are indicated with an "x"

Abbreviations: CC=Cubic Component; I=Intercept; LC=Linear Component; QC=Quadratic Component

Table 2 Demographic, Clinical, Symptom, and Psychosocial Characteristics of Patients with Head and Neck Cancer (N=133)

Characteristic		**Mean (SD)**	**Min/max**
Age, *years*		60 (11)	24/87
Time since diagnosis, *weeks*	Primary disease	5 (9)	0/90
	Residual/recurrent disease	159 (159)	10/581
Clinical characteristic scores at enrollment	KPS score (40-100)	86 (13)	40/100
	Number of comorbidities (0-19)	2 (2)	0/16
Symptom and psychosocial characteristic scores at enrollment	Sleep disturbance (0-147)	46.1 (22.0)	8.4/108.2
	Fatigue (0-10)	2.5 (2.0)	0.0/8.0
	Energy (0-10)	5.4 (2.2)	0.0/10.0
	Nutrition (0-10)	7.9 (2.2)	0.5/10.0
	Social support (0-10)	8.0 (1.5)	1.8/10.0
	Satisfaction with looks (0-10)	7.7 (2.4)	0.0/10.0
		N	**%**
	Pain (yes)	68	51
Gender	Male	94	71
	Female	39	29
Ethnicity	White	132	99
	Asian	1	1
Marital status	Married/Partnered	91	68
	Unmarried/Divorced/Widowed	42	32
Education level	Primary	29	22
	Secondary	66	50
	College/University	38	29
Employment status	Full/Part time work	14	11
	Sick leave/Disability benefit	85	64
	Retired/Other	34	26
Children living at home	Yes	30	23
	No	103	77
Tumor site	Oral cavity	36	27
	Pharynx	61	46
	Larynx	15	11
	Other	21	16
Stage of disease at enrollment	I	10	8
	II	12	9
	III	11	8
	IV	81	61
	Residual/recurrent	19	14
Previous treatment	Surgery	18	14
	Radiotherapy (RT)	15	11
	Chemotherapy (CTX)	6	5
Current treatment intent	Curative [a]	120	90
	Palliative [b]	13	10
Current treatment	Surgery prior to RT [c]	65	49
	RT	25	19
	RT and concomitant CTX	35	26
	Post-operative RT	46	35
	Post-operative RT and concomitant CTX	11	8

	Hyperfractioned/palliative RT	16	12
	Post-RT surgery primary tumor/lymph node	28	21
	Post-RT symptomatic/palliative surgery	15	11
Status after 6 months	Disease free	113	85
	Alive with disease	9	7
	Death by index tumor	7	5
	Death by other disease	4	3

Abbreviations: KPS=Karnofsky Performance Status
[a] Including 9 patients with recurrent disease
[b] Including 3 patients with primary disease
[c] Including 5 patients who underwent primary RT, and 3 patients who underwent hyperfractioned/palliative RT

Table 3 Hierarchical Linear Modeling of Depressive Symptoms in Patients with Head and Neck Cancer

	Coefficient (SE)					
Variable	Unconditional model			Final model		
Depressive symptoms						
Fixed effects						
Intercept	12.584	(0.832)	[d]	12.536	(0.577)	[d]
Time [a] (linear rate of change)	5.299	(1.129)	[d]	5.364	(1.131)	[d]
$Time^2$ (quadratic rate of change)	-2.319	(0.525)	[d]	-2.346	(0.527)	[d]
$Time^3$ (cubic rate of change)	0.240	(0.059)	[d]	0.243	(0.059)	[d]
Time invariant covariates						
Intercept:						
Surgery prior to				-3.422	(0.927)	[d]
Sleep disturbance				0.160	(0.031)	[d]
Fatigue				0.861	(0.347)	[b]
Social support				-1.371	(0.343)	[d]
Satisfaction with looks				-0.484	(0.218)	[b]
Variance component						
In intercept	74.568		[d]	27.733		[d]
In linear rate	70.082		[d]	76.426		[d]
In quadratic rate	11.788		[c]	13.066		[c]
In cubic rate	0.131		[c]	0.145		[c]
Goodness-of-fit deviance (df)	3321.274 (15)			3191.319 (20)		
Model comparison ($\chi 2$)				129.955 (5)		[d]

[a] Time was coded as zero at the visit prior to radiotherapy; [b] $p<.05$; [c] $p<.01$; [d] $p<.001$