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Depressive symptoms in relation to overall survival in people with head and neck cancer: A longitudinal cohort study

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Abstract

Objective: The objective of the study is to investigate the relation between pretreatment depressive symptoms (DS) and the course of DS during the first year after cancer diagnosis, and overall survival among people with head and neck cancer (HNC).

Methods: Data from the Head and Neck 5000 prospective clinical cohort study were used. Depressive symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) pretreatment, at 4 and 12-month follow-up. Also, socio-demographic, clinical, lifestyle, and mortality data were collected. The association between before start of treatment DS (HADS-depression > 7) and course (never DS, recovered from DS, or persistent/recurrent/late DS at 12-month follow-up) and survival was investigated using Cox regression. Unadjusted and adjusted analyses were performed.

Results: In total, 384 of the 2144 persons (18%) reported pretreatment DS. Regarding DS course, 63% never had DS, 16% recovered, and 20% had persistent/recurrent/late DS. People with pretreatment DS had a higher risk of earlier death than people without DS (hazard ratio (HR) = 1.65; 95% confidence interval (CI) 1.33-2.05), but this decreased after correcting for socio-demographic, clinical, and lifestyle-related factors (HR = 1.21; 95% CI 0.97-1.52). Regarding the course of DS, people with persistent/recurrent/late DS had a higher risk of earlier death (HR = 2.04; 95% CI 1.36-3.05), while people who recovered had a comparable risk (HR = 1.12; 95% CI 0.66-1.90) as the reference group who never experienced DS. After correcting for socio-demographic and clinical factors, people with persistent/recurrent/late DS still had a higher risk of earlier death (HR = 1.66; 95% CI 1.09-2.53).

Conclusions: Pretreatment DS and persistent/recurrent/late DS were associated with worse survival among people with HNC.

KEYWORDS

cancer, depression, depressive symptoms, head and neck cancer, mortality, oncology, survival
Clinical depression as well as depressive symptoms (DS) have been reported to increase mortality and reduce survival in different populations.1-3 Among people with different types of cancer, those with a clinical diagnosis of minor or major depression have a 39% higher risk of dying during the follow-up period than people without depression.4 People with increased levels of DS, as measured using validated patient-reported outcome measures, have a 25% higher risk of dying during the follow-up period.1

People diagnosed with head and neck cancer (HNC) are prone to depression or DS.4,5 Previous studies on the association between clinical depression6 or DS7-13 and survival in people with HNC reported mixed results. Some studies reported no association,7,8 while others reported worse survival or higher mortality in people with depression or DS.6,9-13 Half of these studies were, however, limited by small number of events (eg, disease-related or overall deaths),7,9-13 hampering the ability to account for different covariates in the survival analyses. In addition, most studies were limited to a single measurement of clinical depression or DS,7,8,10-13 mostly prior to treatment.7,10-13 As previously reported,14 pretreatment DS may result from the short-term response to cancer diagnosis and may not necessarily reflect a person's long-term course of DS and, therefore, may be a less important associated factor of survival than DS at follow-up.

A previous study reports that, in 40% of people with HNC, DS level indeed changed between the pretreatment and posttreatment measurement.15 Four different courses of DS were identified: people without DS, people who developed DS (33%), people who recovered from DS (7%), and people with persistent DS (4%). A recent study comparing survival outcomes of people with lung cancer reported on 4 comparable courses of DS.16 They found that people who developed or had persistent DS had an increased risk of earlier death, while people who recovered had the same risk as the reference group of people who never reported DS.

A recent large longitudinal study that measured depression more than once in people with HNC in relation to survival found that depression in the 2 years before HNC diagnosis as well as depression in the year after diagnosis was associated with worsened cancer-specific and overall survival.6 In that study, however, no distinction was made between people who recovered from their depression during follow-up and those who did not. In addition, depression was defined as a registered clinical depression diagnosis based on Medicare claims data. The generalizability of these findings to people with DS or undiagnosed depression is unclear.

This study, therefore, aimed to investigate the relation between pretreatment DS as well as the course of DS during the first year after cancer diagnosis and overall survival among people with HNC.

2 | METHODS

2.1 | Design and study population

In this study, data from the Head and Neck 5000 prospective clinical cohort study was used (dataset version 2.1),17,18 including people with HNC from 76 centers in the United Kingdom. People with HNC were asked to participate if they had a new primary HNC diagnosis or were diagnosed with an unknown primary tumor likely to be HNC, and if they were ≥16 years. People were excluded if they did not have the capacity to provide informed consent or were too vulnerable for participation. In total, 5511 persons with HNC consented to participate from April 2011 to December 2014. For this particular study, we limited the population to people diagnosed with cancer of the oral cavity, oropharynx, hypopharynx, or larynx and those treated with curative intent. Besides, participants needed to have a baseline measurement of DS, and have complete socio-demographic, clinical, and lifestyle-related data.

All participants provided written informed consent. The study was approved by the National Research Ethics Committee (South West Frenchay Ethics Committee, reference 10/H0107/57, November 5, 2010), and approved by the research and development departments for participating NHS Trusts.

2.2 | Measures

The English version of the Hospital Anxiety and Depression Scale (HADS) was used to assess psychological distress (HADS-total), level of DS (HADS-D), and level of anxiety symptoms (HADS-A) before the start of treatment, and at 4 and 12-month follow-up.19,20 A HADS-D > 7 was used as a cutoff for identifying persons with DS.21 Internal consistency of the HADS-D in this study was α = .851.

Study-specific questions were used to measure pretreatment tobacco use and alcohol consumption. Tobacco use was categorized as current smoker, former smoker, or never smoked.22 For alcohol consumption, people were categorized as nondrinkers, moderate drinkers (1-14 drinks per week), hazardous drinkers (14-35 drinks/week for women and 14-50 drinks/week for men), or harmful drinkers (>35 drinks/week for women and >50 drinks/week for men).22 In addition, age, gender, marital status, education level, annual household income, and deprivation status were measured. Deprivation status was measured using the Index of Multiple Deprivation (IMD) 2010.23

2.3 | Clinical information

Clinical information was abstracted from the hospital information system and patients’ notes by research nurses. Clinical information included the primary International Classification of Diseases (ICD) 2010 diagnosis, intended and actual received treatment, Adult Comorbidity Evaluation (ACE-27), TNM-stage, and human papilloma virus (HPV) status. Human papilloma virus status was based on serology data, and defined as positive where HPV16E6 was positive (>1000 median fluorescence intensity).24 At the start of the study, participants were flagged with the United Kingdom Health and Social Care Information Centre so that the study team was provided with information on overall mortality (mortality and mortality date).

2.4 | Statistical analyses

All analyses were performed using the IBM Statistical Package for the Social Science (SPSS) version 23 (IBM Corp., Armonk, NY USA). Chi-square tests and independent samples t-test analyses were used to analyze differences between groups.
To assess the association between pretreatment DS and overall survival, a series of Cox regression analyses were performed. At first, minimally adjusted analyses adjusted for age and gender were performed. Analyses were performed in the total population as well as in people with oral cavity, HPV-positive oropharyngeal, and HPV-negative oropharyngeal and laryngeal cancer separately. Survival time was defined as days from date of consent to censoring or date of death. Besides these minimally adjusted analyses, we investigated whether potential associations remained after adjusting for socio-demographic and clinical factors. Also, Cox regression analyses adjusted for lifestyle-related factors were performed. Previous literature hypothesized that lifestyle may mediate the association between depression or DS and survival. However, other studies added lifestyle as a potential confounder to the model. Results can, therefore, be interpreted either as the direct effect after taking the potential mediating role of lifestyle into account or as the association that remains after adjusting for lifestyle as a potential confounder. Finally, post hoc analyses were performed by including each factor 1 by 1 to the minimally adjusted model, to investigate which factors had a strong influence on the association between DS and survival (defined as >10% change in hazard ratio (HR)). All categorical variables adhered to the proportional hazard assumption. Multicollinearity was not found.

Besides analyses on the association between pretreatment DS and survival, unadjusted and adjusted Cox regression analyses were performed using the course of DS in the first year after diagnosis as potential associated factor. For these analyses, people needed to have, besides the previously discussed eligibility criteria, complete HADS-D at 4 and 12-month follow-up, and complete information on actual received treatment. All people were classified according to their course of DS: never DS (below threshold at all measurements), recovered from DS (above threshold at baseline and/or 4-month follow-up, but recovered at 12-month follow-up), or persistent/recurrent/late DS (above threshold at 12-month follow-up, regardless of outcome at baseline and 4-month follow-up). To prevent immortal time bias, landmark analyses with survival time defined as days between 12-month follow-up and date of censoring or death were performed. Immortal time bias is bias resulting from misclassifying immortal time, ie, the time period during which the participants could not have been dead (in this case time between baseline and 12 months follow-up), as survival time.

3 RESULTS

The HADS-D score of the total study population (n = 2144) was on average 4.0 (standard deviation = 3.8, range 0-21). Eighteen percent (n = 384) had pretreatment DS (Table 1, Appendices 1 and 2). Median follow-up was 1046 days (range 601-1963). Overall, 439 (20%) people died during the follow-up period, of whom 332 were in the group without (19%) and 107 in the group with DS (28%). Mean survival time was 1509 days (95% confidence interval (CI) 1436-1582) for the group with and 1651 days (95% CI 1620-1682) for the group without DS.

People with pretreatment DS had a higher risk of earlier death compared to people without DS (HR = 1.65; 95% CI 1.33-2.05) (Table 2, Appendix 3). After adjustment for other socio-demographic factors as well as for socio-demographic and clinical factors, the strength of the association decreased (HR = 1.49; 95% CI 1.19-1.86 and HR = 1.29; 95% CI 1.03-1.62, respectively). After additional adjustment for potential mediation or confounding by lifestyle, the direct association further decreased (HR = 1.21; 95% CI 0.97-1.52). Post hoc analyses showed that comorbidity (12% change), income (11% change), and smoking (10% change) had a major influence on the association.

Subgroup analyses were performed for people with oral cavity, HPV-positive oropharyngeal, and HPV-negative oropharyngeal and laryngeal cancer. A higher risk of earlier death was found in people with oral cavity (HR = 1.88; 95% CI 1.30-2.71) and HPV-negative oropharyngeal DS (HR = 1.80; 95% CI 1.05-3.08) and laryngeal cancer (HR = 1.77; 95% CI 1.09-2.88) with DS, compared to people without DS, while no such association was found among people with HPV-positive oropharyngeal cancer (HR = 0.75; 95% CI 0.34-1.66) (Table 2). After additional adjustment, the strength of the associations decreased (Table 2).

3.1 Association between the course of depressive symptoms and overall survival

Of the 2144 people in the original sample, 1217 completed the HADS-D at follow-up (Appendix 1). The other 927 either died before the end of the first year (19%) or had missing follow-up data (81%). Of the 1217 people, 445 (37%) experienced DS during the first year after treatment (13% pretreatment, 29% at 4-month follow-up, and 20% at 12-month follow-up). Regarding their course of DS in the first year after diagnosis: 63% were categorized as never had DS (n = 772), 16% as recovered from DS (n = 198), and 20% as having persistent/recurrent/late DS (respectively 7%, 1%, and 12%) (n = 247) (Appendix 1). The 3 groups differed on all characteristics, except gender (Appendix 4).

Median follow-up from 12 months onwards was 676 days (range 236-1598). In total, 123 (10%) people died during this follow-up period, of whom 66 never had DS (9%), 18 had recovered from DS (9%), and 39 had persistent/recurrent/late DS (16%). Using people who never experienced DS as a reference group, it was found that those with persistent/recurrent/late DS had a HR of 2.04 (95% CI 1.36-3.05), while people who recovered from DS had a comparable hazard as the reference group (HR = 1.12; 95% CI 0.66-1.90) (Table 3 and Appendix 3). After adjustment for other socio-demographic factors as well as for socio-demographic and clinical factors, the HR of the group with persistent/recurrent/late DS compared to the reference group further decreased (HR = 1.88; 95% CI 1.25-2.84 and HR = 1.66; 95% CI 1.09-2.53). For the group who recovered from DS the findings remained stable (HR = 1.10, 95% CI 0.65-1.86 and HR = 1.06; 95% CI 0.62-1.83). Post hoc analyses showed that tumor location (18% change), comorbidity (17% change), and income (10% change) had a major influence on the association.

4 DISCUSSION

Using data from the Head and Neck 5000 study, it was found that 13% to 18% of people with HNC experience pretreatment DS. During the first year after diagnosis, 63% of people with HNC never had DS, 16% recovered from DS, and 20% had persistent/recurrent/late DS.
| Baseline Characteristics | Population Without Depressive Symptoms (HADS-D ≤ 7) | Population with Depressive Symptoms (HADS-D > 7) | P Value |
|--------------------------|----------------------------------------------------|-------------------------------------------------|---------|
|                          | Frequency | Percentage | Frequency | Percentage |          |
| Socio-demographic        |           |           |           |           |         |
| Age                      |           |           |           |           |         |
| 18-50 years              | 229       | 13.0%     | 53        | 13.8%     | .023    |
| 50-64 years              | 868       | 49.3%     | 218       | 56.8%     |         |
| 65-79 years              | 583       | 33.1%     | 99        | 25.8%     |         |
| 80 and older             | 80        | 4.5%      | 14        | 3.6%      |         |
| Gender                   |           |           |           |           | .267    |
| Men                      | 1353      | 76.9%     | 285       | 74.2%     |         |
| Women                    | 407       | 23.1%     | 99        | 25.8%     |         |
| Marital status           |           |           |           |           | .001    |
| Single/widowed/divorced  | 550       | 31.3%     | 155       | 40.4%     |         |
| Married or living with a partner | 1210 | 68.8% | 229 | 59.6% | |
| Education level          |           |           |           |           | .001    |
| School education         | 777       | 44.1%     | 192       | 50.0%     |         |
| College                  | 615       | 34.9%     | 143       | 37.2%     |         |
| Degree                   | 368       | 20.9%     | 49        | 12.8%     |         |
| Annual household income  |           |           |           |           | <.001   |
| <£18 000                 | 737       | 41.9%     | 233       | 60.7%     |         |
| £18 000-£34 999          | 537       | 30.5%     | 101       | 26.3%     |         |
| >£35 000                 | 486       | 27.6%     | 50        | 13.0%     |         |
| IMD quintiles            |           |           |           |           | <.001   |
| Low deprivation          | 762       | 43.3%     | 119       | 31.0%     |         |
| Moderate deprivation     | 401       | 22.8%     | 82        | 21.4%     |         |
| High deprivation         | 597       | 33.9%     | 183       | 47.7%     |         |
| Clinical                 |           |           |           |           | .442    |
| Tumor location           |           |           |           |           |         |
| Oral cavity              | 503       | 28.6%     | 104       | 27.1%     |         |
| Oropharynx               | 800       | 45.5%     | 173       | 45.1%     |         |
| Hypopharynx              | 69        | 3.9%      | 22        | 5.7%      |         |
| Larynx                   | 388       | 22.0%     | 85        | 22.1%     |         |
| Tumor stage              |           |           |           |           | .028    |
| Stage I                  | 428       | 24.3%     | 66        | 17.2%     |         |
| Stage II                 | 297       | 16.9%     | 69        | 18.0%     |         |
| Stage III                | 216       | 12.3%     | 53        | 13.8%     |         |
| Stage IV                 | 819       | 46.5%     | 196       | 51.0%     |         |
| Intended treatment       |           |           |           |           | .655    |
| Surgery                  | 558       | 31.7%     | 112       | 29.2%     |         |
| Radiotherapy             | 344       | 19.5%     | 73        | 19.0%     |         |
| Chemoradiation           | 595       | 33.8%     | 142       | 37.0%     |         |
| Surgery and adjuvant therapy | 263 | 14.9% | 57 | 14.8% | |
| Comorbidity              |           |           |           |           | <.001   |
| No comorbidity           | 883       | 50.2%     | 136       | 35.4%     |         |
| Mild decompensation      | 560       | 31.8%     | 132       | 34.4%     |         |
| Moderate/severe decompensation | 317 | 18.0% | 116 | 30.2% | |
| HPV status (oropharyngeal cancer only) |           |           |           |           | .025    |
| Positive                 | 508       | 73.3%     | 95        | 64.2%     |         |
| Negative                 | 185       | 26.7%     | 53        | 35.8%     |         |

(Continues)
Two studies in people with different types of HNC pretreatment DS and overall survival have shown inconsistent association was found. Previous studies on the association between while in people with HPV oropharyngeal and laryngeal cancer, DS were associated with worse survival, found that, in people with oral cavity and HPV positive oropharyngeal cancer, no such association was found. Previous studies on the association between pretreatment DS and overall survival have shown inconsistent results. Two studies in people with different types of HNC found no evidence for such an association (after adjustment), while Shinn et al targeting people with oropharyngeal cancer, Zimmaro et al targeting people with mixed HNC treated with chemotherapy, and Chen et al also targeting people with mixed HNC reported an increased risk of earlier death or poorer overall survival among those with pretreatment DS. In contrast to our study, Shinn et al did not stratify for HPV status, as HPV status was only available for a subsample. Nevertheless, they reported no differences in HPV status between those with and without pretreatment DS, while we found such a difference. The inconsistent results of the different studies may be because of the limited statistical power resulting from small sample sizes (130 to 241 persons) in combination with low number of events (18 to 48 persons died during follow-up). In our analyses, data from 2144 people were analyzed, of whom 439 (20%) died during the follow-up period, which provided us with the opportunity to stratify our analyses and to adjust for a wide range of potential confounders. However, for the stratified analyses, additional analyses replicating our findings are warranted.

Besides worse survival in people with pretreatment DS, we also found that those with persistent/recurrent/late DS have higher risk of earlier death compared to the reference group of people who never experienced DS during the first year, while people who recovered from DS had the same risk. This is in line with results of a study among people with lung cancer. The pathways via which DS may influence survival are still unclear. A hypothesized pathway is that DS negatively influences lifestyle, which consequently worsens survival. To provide insight into the potential mediating role of lifestyle, we performed extra analyses in which we adjusted for tobacco and alcohol consumption. We found that after this adjustment, the strength of the association diminished, but remained evident. This suggests that lifestyle may explain part of the pathway between DS and survival, but not all. However, as lifestyle data were limited to pretreatment data, more research is needed on the causal role of lifestyle.

Another pathway may be that untreated depression can cause suicide. Although suicide is, compared to other diseases, relatively common among people with HNC, in absolute terms, it is a rare event. Also, tumor-related and patient-related biomarkers of endocrine, immune, and autonomic (dys)function or other clinical variables may explain the association between depression and survival. This might explain why we found a potential association between pretreatment DS and overall survival in people with HPV-negative oropharyngeal cancer and not in HPV-positive oropharyngeal cancer. However, future research is warranted to replicate these findings and to explore the specific role of HPV status and other biomarkers.

### Study limitations

A limitation of this study was the missing data which may have influenced representativeness of findings and generalizability to the HNC population. Also, people with HNC were dichotomized based on a HADS-D cutoff score of 7, while a score of 1 to 7 may already be indicative of mild DS. Finally, only information on DS and overall survival were available; further studies on clinical depression and disease-specific survival are warranted.

### Clinical implications

People with pretreatment DS as well as persistent/recurrent/late DS are at increased risk of earlier death. Previous studies have hypothesized that lifestyle and suicide may explain (part of) this association. Also, tumor-related or patient-related biomarkers are hypothesized to mediate this association.
TABLE 2  Cox regression analyses on the association between pretreatment depressive symptoms and overall survival

|                | All Head and Neck Cancers | Stratified Oral Cavity Cancer N = 607 | HPV+ Oropharyngeal Cancer N = 603 | HPV− Oropharyngeal Cancer N = 238 | Laryngeal Cancer N = 473 |
|----------------|---------------------------|---------------------------------------|---------------------------------|---------------------------------|------------------------|
|                | HR 95% CI Lower Upper P   | HR 95% CI Lower Upper P               | HR 95% CI Lower Upper P        | HR 95% CI Lower Upper P        | HR 95% CI Lower Upper P |
| Base case analysis<sup>a</sup> |                           |                                       |                                 |                                 |                        |
| No depressive symptoms | Reference <.001         | Reference .001                       | Reference .479                 | Reference .031                 | Reference .021         |
| Depressive symptoms   | 1.65 1.33 2.05           | 1.88 1.30 2.71                       | 0.75 0.34 1.66                 | 1.80 1.05 3.08                 | 1.77 1.09 2.88         |
| Model adjusted for socio-demographic characteristics<sup>b</sup> |                           |                                       |                                 |                                 |                        |
| No depressive symptoms | Reference <.001         | Reference .013                       | Reference .629                 | Reference .108                 | Reference .040         |
| Depressive symptoms   | 1.49 1.19 1.86           | 1.62 1.11 2.36                       | 0.82 0.37 1.82                 | 1.59 0.90 2.79                 | 1.70 1.02 2.81         |
| Model adjusted for socio-demographic and clinical characteristics<sup>c</sup> |                           |                                       |                                 |                                 |                        |
| No depressive symptoms | Reference .025           | Reference .052                       | Reference .322                 | Reference .306                 | Reference .185         |
| Depressive symptoms   | 1.29 1.03 1.62           | 1.46 1.00 2.14                       | 0.66 0.29 1.50                 | 1.35 0.76 2.40                 | 1.43 0.84 2.41         |
| Model adjusted for socio-demographic and clinical characteristics and for confounding/mediation by lifestyle<sup>d</sup> |                           |                                       |                                 |                                 |                        |
| No depressive symptoms | Reference .094           | Reference .067                       | Reference .304                 | Reference .514                 | Reference .247         |
| Depressive symptoms   | 1.21 0.97 1.52           | 1.44 0.98 2.12                       | 0.65 0.28 1.49                 | 1.22 0.67 2.19                 | 1.37 0.80 2.33         |

HR, hazard ratio; 95% CI, 95% confidence interval; HADS-D, Hospital Anxiety and Depression Scale-Depression; HPV, human papilloma virus; HPV+, HPV-positive; HPV−, HPV-negative.

<sup>a</sup>The base case analysis is adjusted for age and gender.

<sup>b</sup>Adjusted for age, gender, marital status, education level, income, and IMD deprivation score.

<sup>c</sup>Adjusted for age, gender, marital status, education level, income, IMD deprivation score, tumor location, tumor stage, intended treatment, and comorbidity.

<sup>d</sup>Adjusted for age, gender, marital status, education level, income, IMD deprivation score, tumor location, tumor stage, intended treatment, and comorbidity, and for potential confounding/mediation by tobacco usage and alcohol consumption.
**CONCLUSION**

Results of this study indicate that people with pretreatment DS as well as persistent/recurrent/late DS are at increased risk of earlier death. Further research is needed on potential pathways via which depression or DS may influence survival.

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**CONFLICT OF INTEREST**

None.

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APPENDIX 1. FLOW DIAGRAM

927 HNC persons did not have complete HADS-D data at 4 and 12-month follow-up, because they died before the end of the first year (19%) or dropped out or had missing data (81%).① Never depressive symptoms (n = 772),② Recovered from depressive symptoms before start of treatment or 4 months follow-up (n = 198);③ Persistent/recurrent/late depressive symptoms at 12-months follow-up (n = 247).

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### APPENDIX 2. COMPARISON OF PEOPLE WITH COMPLETE HADS-D, SOCIO-DEMOGRAPHIC, CLINICAL DATA, AND LIFESTYLE DATA (N = 2144), COMPARED TO PEOPLE WITH MISSING DATA (N = 2306)

| Baseline Characteristics | Population with Complete Data | Population with Missing Data | P Value |
|--------------------------|-------------------------------|-------------------------------|---------|
|                          | n = 2144                      | n = 2306                      |         |
|                          | Frequency   | Percentage | Frequency   | Percentage |
| Socio-demographic        |              |            |              |            |
| Mean age (SD)            | 60.9 (10.5) |            | 62.7 (11.0) | <.001      |
| Gender                   |              |            |              | .062       |
| Men                      | 1,638        | 76.4%      | 1,706        | 74.0%      |
| Women                    | 506           | 23.6%      | 600          | 26.0%      |
| Clinical                 |              |            |              | <.001      |
| Tumor location (ICD)     |              |            |              | .622       |
| Oral cavity              | 607           | 28.3%      | 692          | 30.0%      |
| Oropharynx               | 973           | 45.4%      | 905          | 39.2%      |
| Hypopharynx              | 91            | 4.2%       | 125          | 5.4%       |
| Larynx                   | 473           | 22.1%      | 584          | 25.3%      |
| Tumor stage              |              |            |              | .622       |
| Stage I                  | 494           | 23.0%      | 509          | 22.1%      |
| Stage II                 | 366           | 17.1%      | 419          | 18.2%      |
| Stage III                | 269           | 12.5%      | 303          | 13.2%      |
| Stage IV                 | 1,015         | 47.3%      | 1,068        | 46.5%      |
| Missing                  | 0             |            | 7            |            |
| Intended treatment       |              | <.001      |              | <.001      |
| Surgery                  | 670           | 31.3%      | 764          | 33.1%      |
| Radiotherapy             | 417           | 19.4%      | 507          | 22.0%      |
| Chemoradiation           | 737           | 34.4%      | 631          | 27.4%      |
| Surgery and adjuvant therapy | 320       | 14.9%      | 404          | 17.5%      |
| Status                   |              | .008       |              |            |
| Alive                    | 1,705         | 79.5%      | 1,757        | 76.2%      |
| Died                     | 439           | 20.5%      | 549          | 23.8%      |
APPENDIX 3. SURVIVAL CURVES

a) Survival analysis on pretreatment depressive symptoms adjusted for socio-demographic and clinical characteristics and potential mediation or confounding by lifestyle factors

b) Survival analysis on the course of depressive symptoms adjusted for socio-demographic and clinical characteristics
APPENDIX 4. POPULATION CHARACTERISTICS OF THE GROUPS WITH DIFFERENT COURSES OF DEPRESSIVE SYMPTOMS

| Socio-demographic | Never Depressive Symptoms* N = 772 | Recovered from Depressive Symptomsb N = 198 | Persistent/Recurrent/Late Depressive Symptoms 12-month Follow-Upc N = 247 | Frequency | Percentage | Frequency | Percentage | Frequency | Percentage | P Value |
|-------------------|----------------------------------|--------------------------------------------|-------------------------------------------------|----------|-----------|----------|-----------|----------|-----------|---------|
| Age               |                                  |                                            |                                                 |          |           |          |           |          |           | <.001   |
| 18-50 years       | 80                               | 10.4%                                      | 19                                              | 9.6%     | 27        | 10.9%    |           |          |          |         |
| 50-64 years       | 360                              | 46.6%                                      | 120                                             | 60.6%    | 148       | 59.9%    |           |          |          |         |
| 65-79 years       | 292                              | 37.8%                                      | 51                                              | 25.8%    | 67        | 27.1%    |           |          |          |         |
| 80 and older      | 40                               | 5.2%                                       | 8                                               | 4.0%     | 5         | 2.0%     |           |          |          |         |
| Gender            |                                  |                                            |                                                 |          |           |          |           |          |          | .564    |
| Men               | 591                              | 76.6%                                      | 145                                             | 73.2%    | 184       | 74.5%    |           |          |          |         |
| Women             | 181                              | 23.4%                                      | 53                                              | 26.8%    | 63        | 25.5%    |           |          |          |         |
| Marital status    |                                  |                                            |                                                 |          |           |          |           |          |          | .016    |
| Single, widowed or divorced | 205 | 26.6% | 51 | 25.8% | 88 | 35.6% |           |          |          |         |
| Married/living with a partner | 567 | 73.4% | 147 | 74.2% | 159 | 64.4% |           |          |          |         |
| Highest education level |          |                                            |                                                 |          |           |          |           |          |          | .001    |
| School education  | 302                              | 39.1%                                      | 83                                              | 41.9%    | 128       | 51.8%    |           |          |          |         |
| College           | 289                              | 37.4%                                      | 62                                              | 31.3%    | 85        | 34.4%    |           |          |          |         |
| Degree            | 181                              | 23.4%                                      | 53                                              | 26.8%    | 34        | 13.8%    |           |          |          |         |
| Annual household income |                                  |                                            |                                                 |          |           |          |           |          |          | <.001   |
| Less than £18 000 | 280                              | 36.3%                                      | 69                                              | 34.8%    | 137       | 55.5%    |           |          |          |         |
| £18 000-£34 999   | 244                              | 31.6%                                      | 69                                              | 34.8%    | 74        | 30.0%    |           |          |          |         |
| More than £35 000 | 248                              | 32.1%                                      | 60                                              | 30.3%    | 36        | 14.6%    |           |          |          |         |
| IMD quintiles (2010) |                                  |                                            |                                                 |          |           |          |           |          |          | <.001   |
| Low deprivation   | 387                              | 50.1%                                      | 92                                              | 46.5%    | 86        | 34.8%    |           |          |          |         |
| Moderate deprivation | 171                          | 22.2%                                      | 45                                              | 22.7%    | 54        | 21.9%    |           |          |          |         |
| High deprivation  | 214                              | 27.7%                                      | 61                                              | 30.8%    | 107       | 43.3%    |           |          |          |         |
| Clinical          |                                  |                                            |                                                 |          |           |          |           |          |          | <.001   |
| Tumor location (ICD) |                                  |                                            |                                                 |          |           |          |           |          |          |         |
| Oral cavity       | 252                              | 32.6%                                      | 34                                              | 17.2%    | 63        | 25.5%    |           |          |          |         |
| Oropharynx        | 302                              | 39.1%                                      | 138                                             | 69.7%    | 127       | 51.4%    |           |          |          |         |
| Hypopharynx       | 18                               | 2.3%                                       | 5                                               | 2.5%     | 9         | 3.6%     |           |          |          |         |
| Larynx            | 200                              | 25.9%                                      | 21                                              | 10.6%    | 48        | 19.4%    |           |          |          |         |
| Tumor stage       |                                  |                                            |                                                 |          |           |          |           |          |          | <.001   |
| Stage I           | 249                              | 32.3%                                      | 18                                              | 9.1%     | 47        | 19.0%    |           |          |          |         |
| Stage II          | 143                              | 18.5%                                      | 22                                              | 11.1%    | 49        | 19.8%    |           |          |          |         |
| Stage III         | 94                               | 12.2%                                      | 24                                              | 12.1%    | 33        | 13.4%    |           |          |          |         |
| Stage IV          | 286                              | 37.0%                                      | 134                                             | 67.7%    | 118       | 47.8%    |           |          |          |         |
| Actual received treatment |                                  |                                            |                                                 |          |           |          |           |          |          | <.001   |
| Surgery           | 221                              | 28.6%                                      | 20                                              | 10.1%    | 51        | 20.6%    |           |          |          |         |
| Radiotherapy      | 162                              | 21.0%                                      | 22                                              | 11.1%    | 43        | 17.4%    |           |          |          |         |
| Chemoradiation    | 221                              | 28.6%                                      | 118                                             | 59.6%    | 100       | 40.5%    |           |          |          |         |
| Surgery and adjuvant therapy |      |                                            |                                                 |          |           |          |           |          |          |         |
| Comorbidity index |                                  |                                            |                                                 |          |           |          |           |          |          | <.001   |
| No comorbidity    | 407                              | 52.7%                                      | 106                                             | 53.5%    | 94        | 38.1%    |           |          |          |         |
| Mild decompensation | 250                         | 32.4%                                      | 62                                              | 31.3%    | 84        | 34.0%    |           |          |          |         |
| Moderate/severe decompensation | 115 | 14.9% | 30 | 15.2% | 69 | 27.9% |           |          |          |         |
| Lifestyle                        | Never Depressive Symptoms<sup>a</sup> N = 772 | Recovered from Depressive Symptoms<sup>b</sup> N = 198 | Persistent/Recurrent/Late Depressive Symptoms 12-month Follow-Up<sup>c</sup> N = 247 | Frequency | Percentage | Frequency | Percentage | Frequency | Percentage | P Value |
|---------------------------------|-----------------------------------------------|--------------------------------------------------------|-------------------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|----------|---------|
| Tobacco usage                   |                                               |                                                        |                                                 |           |           |           |           |           |           |         |
| Current smoker                  | 94                                             | 25                                                     | 62                                               | 12.2%     |           | 12.6%     |           | 25.1%     |           | <.001    |
| Former smoker                   | 467                                            | 110                                                    | 137                                              | 60.5%     |           | 55.6%     |           | 55.5%     |           |         |
| Never smoked                    | 211                                            | 63                                                     | 48                                               | 27.3%     |           | 31.8%     |           | 19.4%     |           |         |
| Alcohol consumption             |                                               |                                                        |                                                 |           |           |           |           |           |           | .001     |
| Nondrinker                      | 168                                            | 45                                                     | 76                                               | 21.8%     |           | 22.7%     |           | 30.8%     |           |         |
| Moderate drinker                | 207                                            | 46                                                     | 37                                               | 26.8%     |           | 23.2%     |           | 15.0%     |           |         |
| Hazardous drinker               | 301                                            | 72                                                     | 92                                               | 39.0%     |           | 36.4%     |           | 37.2%     |           |         |
| Harmful drinker                 | 96                                             | 35                                                     | 42                                               | 12.4%     |           | 17.7%     |           | 17.0%     |           |         |

<sup>a</sup>HADS-D below threshold at all measurements.

<sup>b</sup>HADS-D above threshold at baseline and/or 4-month follow-up, but recovered at 12-month follow-up.

<sup>c</sup>HADS-D above threshold at 12-month follow-up, regardless of outcome at baseline and 4-month follow-up.