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Pretreatment Depression as a Prognostic Indicator of Survival and Nutritional Status in Patients With Head and Neck Cancer

Patients with head and neck cancer (HNC) often experience negative side effects of treatment such as oral dysfunction (eg, dry mouth, sticky saliva, or oral pain), swallowing and speech problems, insomnia, and fatigue, which are related to distress. A recent meta-analysis demonstrated a pooled estimate of depression among patients with HNC of 11% (95% confidence interval, 3%-34%) as measured by diagnostic interviews and 20% (95% confidence interval, 16%-25%) as measured by screening instruments.¹

We read with great interest the study by Kim et al,² who reported a significant association between pretreatment depression (prevalence of 25% as measured by a screening instrument) and survival in patients with HNC. Among patients with cancer, previous studies also have reported a significant association between depression and survival.^{3,4} In fact, several hundred studies including healthy community samples and disease-specific populations have shown that depression is associated with survival. A recent meta-analysis of 293 studies again demonstrated that there is a significant association between depression and excess mortality, but to our knowledge there are only a few indications that this association is stronger in community or specific patient samples.⁵ This meta-analysis also included 29 studies on cancer, including one regarding HNC. Thus, the study by Kim et al² adds to the large amount of evidence regarding a significant association between depression and survival. However, it is not justified to state that “the results demonstrate a close relation between pretreatment depression and treatment outcome,” and therefore suggest that depression is related to the outcome of treatment. The study by Kim et al² only confirms what has been found in hundreds of earlier observational studies, nothing more.

However, to the best of our knowledge, the mechanisms underlying the association between depression and survival remain unclear and may well be cancer- or tumor-specific.^{6,7} There are several reasons why depression may enhance mortality risk in patients with HNC. Depressed patients with HNC may use ineffective coping strategies,⁸ and they are at risk of suicide.⁹ Unhealthy lifestyle is a risk factor for excess mortality and in patients

with HNC continued alcohol use after diagnosis is reported to have an adverse effect on survival.¹⁰ Empirical evidence has suggested that tumor-related and patient-related biomarkers of endocrine, immune, and autonomic (dys)function also may be associated with depression and survival. There is growing evidence that dysregulation of hypothalamic-pituitary-adrenal axis function is associated with depression and cancer survival. Neuroimmunological explanations include increased immune responses and increased levels of proinflammatory cytokines (eg, interleukin 6), which were found to be associated with depression and survival among patients with HNC.¹¹ Another study has suggested that a common functional promoter polymorphism of the neurotransmitter serotonin transporter gene (serotonin transporter-linked polymorphic region [5-HTTLPR]) may be associated with depression in patients with HNC.¹²

Comprehensive insight into all these factors is necessary to unravel these complex associations. To the best of our knowledge, previous studies investigating the relation between depression and survival in patients with (head and neck) cancer included relatively small cohorts and/or a limited number of possible confounders. Consequently, the association between depression and survival among patients with cancer may have inadequately adjusted for potentially relevant confounders. In the Netherlands, a prospective, multicenter cohort study, the Netherlands Quality of Life and Biomedical Cohort Study in Head and Neck Cancer (NET-QUBIC) (available at: researchers.kubusproject.nl/home), currently is ongoing. The data from this study will allow investigation of the course of depression and the association between changes in depression and survival in patients with HNC, controlling for cancer-related and treatment-related, personal, biological, psychobehavioral, physical, lifestyle-related, and social factors.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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Reply to Pretreatment Depression as a Prognostic Indicator of Survival and Nutritional Status in Patients With Head and Neck Cancer

We thank Verdonck-de Leeuw et al for their considerate comments on our recent article published in *Cancer*.¹ We

are pleased that our study has aroused such attention. Please find our replies below to the issues raised in their review.

The comment that our findings concerning the relation between depression and survival have already been reported in hundreds of earlier observational studies, including those dealing with head and neck cancer (HNC), and especially the mention that our study “only confirms what has been found in hundreds of earlier observational studies, nothing more” are incorrect and diminish the importance of our findings. We believe this comment is based on a recent meta-analysis demonstrating that there is a significant association between depression and excess mortality.² However, the final version of this meta-analysis included only 13 studies reporting different outcomes in men and women out of 293 prospective studies examining mortality in patients with versus those without depression.² Moreover, the final analyses involved samples collected from community or nursing homes that treat mostly patients without cancer. Therefore, we believe that there is a lack of appropriate references to support the comments of Verdonck-de Leeuw et al.

As mentioned previously in our study,¹ many reports have indicated that depression influences survival in patients with cancer.^{3,4} However, to the best of our knowledge, the impact of pretreatment depression on the survival and nutritional outcomes of patients with HNC has been studied only rarely. A retrospective cohort of 35 patients with HNC demonstrated that patients with depression had higher levels of cancer recurrence and cancer-related death compared with patients who were not depressed (50% vs 20%; $P = .03$).⁵ Our study also supports previous findings indicating that depression can negatively influence the nutritional status and quality of life of patients with HNC.^{6,7} However, the most important aspect of our study is that to our knowledge it is the first to demonstrate a close relation between baseline depressive mood and survival outcome in a large cohort of 241 patients with HNC who were enrolled in a well-designed, prospective study.

Verdonck-de Leeuw et al also queried the potential mechanisms underlying the association between depression and survival. As suggested previously, depression among patients with cancer may result in ineffective coping strategies and unhealthy lifestyles, which in turn increase the risk of suicide.^{8,9} In our study, the patients with HNC with depression were more likely to have an advanced initial stage of cancer, poor performance status, and poor nutritional status with hypoalbuminemia.¹ Although the clinical variables were associated with baseline depression, they were not found to be independent variables predicting overall and disease-free survival