Prediction of Survival by Pretreatment Health-Related Quality-of-Life Scores in a Prospective Cohort of Patients With Head and Neck Squamous Cell Carcinoma

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Objective: To evaluate the association between pretreatment health-related quality-of-life (HRQOL) scores and survival in a heterogeneous cohort of patients with newly diagnosed head and neck squamous cell carcinoma (HNSCC).

Design: Prospective cohort study.

Setting: University hospital and referral center in Western Norway.

Patients: A total of 106 patients with intact cognitive functioning who were younger than 78 years, were diagnosed as having HNSCC, and underwent treatment with curative intent from November 1, 2002, through June 30, 2005.

Main Outcome Measures: Overall survival and HRQOL scores obtained at the time of diagnosis.

Results: All dichotomized HRQOL sum scores except the functional score (P = .20) were significantly predictive of survival in univariate analyses. The hazard ratios of the dichotomized general symptom, global quality-of-life, and head and neck sum score were 3.66, 0.31, and 2.28, respectively. All sum scores except the dichotomized functional score remained predictive of survival after sequential adjustment for sociodemographic and clinical characteristics, neuroticism, choice of psychological coping, current smoking and alcohol consumption, and comorbidities. Similar findings were found for specific HRQOL indices of physical functioning, dyspnea, sleep disturbance, appetite loss, swallowing, and social eating from the European Organization for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire, version 3.0, and the Quality of Life–Head and Neck Cancer Module. Moreover, patients in the highest scoring quartiles for the symptom sum scores and/or the lowest scoring quartile for the global score had overall mortality rates of 50% to 64% compared with 23% to 26% among the other patients.

Conclusion: The HRQOL sum scores and specific indices among HNSCC patients predict survival independently of established known prognostic factors.

ORIGINAL ARTICLE

In a worldwide perspective, head and neck (HN) cancer is the sixth most common type of cancer, and squamous cell carcinoma (SCC) constitutes the most common histopathological type.1 In the Western world, patients with HNSCC are relatively young, and curative treatment is achieved in about 60% of the patients.2

Health-related quality of life (HRQOL) has become an important end point in oncology during past decades, and a substantial number of investigations have been published with the aim to assess potential predictors of HRQOL scores.3 Among patients with successfully treated HNSCC, psychological factors (ie, certain personality traits and choices of coping) have been reported to account for approximately one-third of the total HRQOL score variance compared with treatment-related factors that accounted for one-tenth.4 Moreover, HRQOL scores have also been shown to be associated with survival.5

With regard to survival prediction from pretreatment HRQOL data among HNSCC patients, few investigations with some extent of varied findings have been published.5-7 A significant predictive effect of HRQOL scores on survival has been detected, but noteworthy variations with regard to design, sample sizes, and use of HRQOL inventories exist.5 Notably, focus on clarification of the survival predictions (ie, with adjustments for psychological characteristics and comorbidities) shown to be of unique importance in predicting HRQOL scores has been limited.8-10 In light of this lack and the relatively high prevalence of poten-
tially prognostic important comorbidities among HNSCC patients, we need more studies evaluating the survival prediction of pretreatment HRQOL scores.

We obtained HRQOL scores at diagnosis from 2 validated questionnaires, the European Organization for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire, version 3.0 (QLQ-C30) and the Quality of Life–Head and Neck Cancer Module (QLQ-H&N35). The aim of the present study was to examine the extent to which the HRQOL scores, with and without adjustment for sociodemographic, clinical, and psychological characteristics and certain health behaviors and comorbidities, predict survival in a heterogeneous cohort of patients with newly diagnosed HNSCC. In relation to the HRQOL data, we have applied sum scores and individual indices, with the advantage of the sum scores being that they may reduce the risk for coincidental findings and simplify the interpretation of the results.

### METHODS

#### PATIENTS

Patients with adequate cognitive functioning who were younger than 78 years; diagnosed with HNSCC in Western Norway from November 1, 2002, through June 30, 2005; and treated with curative intent were approached at the time of diagnosis for participation in the study. A total of 111 patients were approached, of whom 5 refused to participate, leaving a total of 106 patients and a response rate of 95.5%. At least 80% of all eligible patients were approached. The mean (SD) observation time of the survivors was 63 (9) months. Thirty-four deaths occurred during the observation period. We obtained permission from the regional ethics committee before the study, and all patients signed informed consent forms.

#### OUTCOMES EXAMINED

##### HRQOL Inventories

We determined the HRQOL by using the validated Norwegian edition of the QLQ-C30 and the QLQ-H&N35. The QLQ-C30 includes 5 functioning scales (physical, role, emotional, cognitive, and social), a global quality-of-life (QOL) scale, symptom indices (fatigue, pain, nausea and vomiting, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea), and perceived financial difficulties. The QLQ-H&N35 consists of 7 multiple-item scales (pain, swallowing, senses, speech, social eating, social contact, and sexuality) and 6 symptom items (teeth problems, opening mouth, dry mouth, sticky saliva, coughing, and feeling ill). The answers were given in a 4-point Likert format except the question regarding global QOL and global health, which was scored in a 7-point Likert format. The functional and the global scales were transformed so that 100 indicates best function and 0, worst, whereas the symptom scales were transformed so that 100 indicates the most and 0 the least symptoms.

In addition, sum scores were defined. A general symptom score and an HR sum score were computed from the symptom indices of the QLQ-C30 and QLQ-H&N35, respectively. A functional sum score based on the functional indices of the QLQ-C30 was calculated similarly. All sum scores had a Cronbach α greater than 0.76, indicating that these scores were internally consistent.

#### Survival

Overall survival data were obtained as of July 1, 2009, from the individual patient journals, which are coupled with the National Population Register of Norway. The patients were classified as dead or alive, and the date of death was registered.

##### COVARIATES EXAMINED

#### Eysenck Personality Inventory

The neuroticism scale of the Eysenck Personality Questionnaire was determined. The neuroticism scale assesses adjustment vs emotional instability and identifies individuals prone to psychological distress and maladaptive coping responses.

#### Coping Inventory

We applied a coping inventory, and 3 of 14 subscales were designated to represent a range of coping approaches. Problem-focused (suppression of competing activity), emotional (seeking social support for emotional reasons), and avoidance-focused (behavioral disengagement) coping were measured. Each index was calculated as the sum of the responses to 4 different questions scored in a 4-point Likert format. For all the coping inventory scales, the Cronbach α was greater than 0.76.

#### Comorbidities

Comorbidities were obtained with the validated medical record-based Adult Comorbidity Evaluation–27 scale (ACE-27). The ACE-27 grades specific conditions into levels of severity as 1 (mild), 2 (moderate), or 3 (severe). Based on the highest-ranked single ailment, an overall comorbidity score (none, mild, moderate, or severe) was assigned. In cases with 2 or more moderate ailments registered in different disease entities, the overall comorbidity score was designated as severe. In addition to the overall comorbidity score, organ system–specific subscores (yes or no) were computed for those diseases with more than 10 positive reports.

#### Tumor Site

The site of the tumor was designated as laryngeal, oral cavity, oropharyngeal, or others. In the analyses, laryngeal cancer was compared with other locations because this site generally is associated with a more favorable prognosis.

#### Smoking and Alcohol Consumption

The estimated weekly consumption of cigarettes was registered and scored as currently smoking (yes or no). Alcohol consumption was determined by selecting 1 of the following choices: never, less than 1 time per week, 1 to 2 times per week, previously more than 2 times per week, and currently more than 2 times per week. In the analyses, previous and current consumption were designated as high and compared with the rest, designated as low.

### STATISTICAL ANALYSIS

Statistical significance was considered as $P < .05$, calculated using 2-sided tests. The associations between the possible prognostic variables with survival were determined using Kaplan-Meier and Cox proportional hazards regression analyses. Sequential multivariate analyses were applied to limit the risk for
unreliable results found when the rate of events per prognostic variable fall to low.\textsuperscript{17} Dichotomized versions of all the enabled HRQOL sum scores were computed,\textsuperscript{12} comparing the upper quartile with the lower 3 quartiles for the symptom scores and the lower quartile with the upper 3 quartiles for the functional and global scores. We used a commercially available statistical program package (PASW for Windows, release 18.0.0; SPSS, Inc).

RESULTS

Sociodemographic and clinical characteristics are presented in Table 1. The mean (SD) age of the patients was 61 (9) years at the time of diagnosis, and 85.8% of the patients were men. Cancer of the oral cavity was the most common tumor site (31.1%), followed by oropharyngeal (25.5%) and laryngeal (24.5%) sites. Levels of comorbidity were moderate or severe in 26.4% of the patients, as evaluated with the ACE-27 inventory. The overall survival at 5 years was 69.1%.

SURVIVAL PREDICTION OF SOCIODEMOGRAPHIC AND CLINICAL VARIABLES

Baseline sociodemographic and clinical variables were examined in univariate Cox proportional hazards regression analyses (Table 2). Increasing levels of comorbidity were associated with worse prognosis (\(P = .03\)), and comorbid disease in the cardiovascular system was the sole prognosticator (\(P = .005\)) at the subcategorized level. We found no prediction of survival by the T or the N stage grouping or tumor site. Previous or current high levels of alcohol consumption were significantly predictive of survival (\(P = .03\)).

SURVIVAL PREDICTION OF THE HRQOL SCORES

The survival predictions of the dichotomized HRQOL sum scores are presented in Table 3. The general symptom sum score (\(P < .001\)), global QOL score (\(P = .001\)), and...
HN sum score ($P = .02$) were all shown to be predictive of survival in univariate analyses, whereas the functional sum score ($P = .20$) was not. The hazard ratios of the general symptom and the HN sum scores were 3.66 and 2.28, respectively, indicating an increased relative mortality risk among the patients reporting the most symptoms. For the global QOL index, higher scores indicate better function, with increased mortality risk among those with lower functioning (hazard ratio, 0.31). Kaplan-Meier plots for the univariate dichotomized HRQOL sum scores found to be predictive of survival (Table 3) are presented in the Figure. The cumulative proportion surviving at 5 years were 78% vs 41% for the general symptom sum score, 75% vs 40% for the global QOL score, and 76% vs 49% for the HN sum score. Moreover, when exploring the overall mortality rates in the highest scoring quartile for the general symptom and HN sum scores and the lowest scoring quartile for the global score, rates of 62%, 50%, and 64% were demonstrated as opposed to 23%, 26%, and 24% among the other patients, respectively.

With the exception of the HN sum score ($P = .054$), all sum scores when adjusted for alcohol consumption, smoking status, and comorbidity remained predictive of survival after sequential adjustment for sex and age, problem- and avoidance-focused coping, levels of neuroticism, TNM stage, tumor site, alcohol consumption, smoking status, and comorbidities (evaluated according to the ACE-27). In a post hoc analysis including all covariates in multivariate regression analyses, the general symptom sum score (hazard ratio, 3.80; $P = .002$) remained significantly predictive of survival.

The mean values and the survival prediction of the continuous QLQ-C30 and QLQ-H&N35 indices are presented in Table 4. Physical functioning, pain, dyspnea, sleep disturbance, appetite loss, head and neck–specific pain, swallowing, social eating, sexuality, teeth problems, coughing, and feeling ill were predictive of survival in univariate analyses. After sequential adjustment for the covariates, physical functioning, dyspnea, sleep disturbance, appetite loss, swallowing, and social eating remained significantly associated with survival.

Among the covariates included in the multivariate HRQOL analyses, age (sleep disturbance), sex (social eating), alcohol consumption (physical functioning and sleep disturbance), comorbidity (swallowing and social eat-
Table 4. Mean Scores and Cox Regression Analyses Evaluating the Survival Prediction of the EORTC QLQ-C30 and QLQ-H&N35 Indices

<table>
<thead>
<tr>
<th>Index</th>
<th>Mean (SD) Score</th>
<th>Univariate HR (95% CI)</th>
<th>Univariate P Value</th>
<th>All Covariatesb P Value</th>
<th>All Covariatesb P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QLQ-C30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>88 (19)</td>
<td>0.98 (0.96-0.99)</td>
<td>&lt;.001</td>
<td>0.97 (0.95-0.99)</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td>Role functioning</td>
<td>79 (28)</td>
<td>0.99 (0.98-1.00)</td>
<td>.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>77 (19)</td>
<td>0.99 (0.97-1.00)</td>
<td>.07</td>
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<td></td>
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<tr>
<td>Cognitive functioning</td>
<td>84 (21)</td>
<td>1.00 (0.98-1.01)</td>
<td>.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>87 (21)</td>
<td>1.00 (0.98-1.01)</td>
<td>.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (26)</td>
<td>1.01 (1.00-1.02)</td>
<td>.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>6 (18)</td>
<td>1.00 (0.99-1.02)</td>
<td>.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>24 (30)</td>
<td>1.01 (1.00-1.02)</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18 (30)</td>
<td>1.02 (1.01-1.03)</td>
<td>&lt;.001</td>
<td>1.03 (1.02-1.04)</td>
<td>&lt;.001d</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>21 (29)</td>
<td>1.02 (1.01-1.03)</td>
<td>.001</td>
<td>1.02 (1.01-1.03)</td>
<td>.003e</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>18 (32)</td>
<td>1.01 (1.00-1.02)</td>
<td>.009</td>
<td>1.01 (1.00-1.02)</td>
<td>.02</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (25)</td>
<td>1.01 (1.00-1.02)</td>
<td>.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (21)</td>
<td>0.99 (0.97-1.01)</td>
<td>.27</td>
<td></td>
<td></td>
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<tr>
<td>Financial difficulties</td>
<td>9 (23)</td>
<td>1.01 (1.00-1.02)</td>
<td>.08</td>
<td></td>
<td></td>
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<tr>
<td>QLQ-H&amp;N35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>24 (26)</td>
<td>1.02 (1.00-1.03)</td>
<td>.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swallowing</td>
<td>8 (17)</td>
<td>1.02 (1.01-1.04)</td>
<td>.002</td>
<td>1.02 (1.00-1.04)</td>
<td>.02f</td>
</tr>
<tr>
<td>Senses</td>
<td>6 (15)</td>
<td>1.01 (1.00-1.03)</td>
<td>.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speech</td>
<td>16 (22)</td>
<td>1.00 (0.99-1.02)</td>
<td>.67</td>
<td></td>
<td></td>
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<tr>
<td>Social eating</td>
<td>10 (20)</td>
<td>1.02 (1.01-1.03)</td>
<td>.002</td>
<td>1.02 (1.01-1.04)</td>
<td>.007g</td>
</tr>
<tr>
<td>Social contact</td>
<td>4 (9)</td>
<td>1.00 (0.97-1.04)</td>
<td>.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexuality</td>
<td>21 (30)</td>
<td>1.01 (1.00-1.02)</td>
<td>.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teeth problems</td>
<td>11 (27)</td>
<td>1.01 (1.00-1.02)</td>
<td>.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening mouth</td>
<td>11 (24)</td>
<td>1.01 (1.00-1.02)</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>23 (31)</td>
<td>1.00 (0.98-1.01)</td>
<td>.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sticky saliva</td>
<td>22 (30)</td>
<td>1.01 (1.00-1.02)</td>
<td>.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>23 (28)</td>
<td>1.01 (1.00-1.02)</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling ill</td>
<td>12 (24)</td>
<td>1.01 (1.00-1.03)</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; QLQ-C30, 30-Item Core Quality of Life Questionnaire, version 3.0; QLQ-H&N35, Quality of Life–Head and Neck Cancer Module.

aSignificant P values are given in boldface type.
bInclude sex, age, coping by suppression, coping by disengagement, levels of neuroticism, TNM stage, tumor site, alcohol consumption, smoking status, and comorbidity. (Comorbidity was evaluated according to the Adult Comorbidity Evaluation–27 scale.)
cCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.44 [95% CI, 1.08-5.55]; P = .03).
dCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.60 [95% CI, 1.12-6.04]; P = .02).
eCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.44 [95% CI, 1.08-5.55]; P = .03).
fCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.60 [95% CI, 1.12-6.04]; P = .02).
gCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.44 [95% CI, 1.08-5.55]; P = .03).
hCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.60 [95% CI, 1.12-6.04]; P = .02).
iCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.44 [95% CI, 1.08-5.55]; P = .03).
jCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.60 [95% CI, 1.12-6.04]; P = .02).
kCovariate predictive of survival in the multivariate analyses included alcohol consumption (HR, 2.44 [95% CI, 1.08-5.55]; P = .03).

In this prospective investigation conducted among patients with newly diagnosed HNSCC and treated with curative intent, significant survival predictions from all HRQOL sum scores except the functional sum score have been demonstrated. Similar results were shown for the QLQ-C30 and QLQ-H&N35 physical functioning, dyspnea, sleep disturbance, appetite loss, swallowing, and social eating indices. These relations were independent of sequential adjustment for sex, age, problem- and avoidance-focused coping, levels of neuroticism, TNM stage, tumor site, alcohol consumption, present smoking status, and presence of comorbidities (ACE-27).

This study has certain limitations. Owing to the cohort size, the numbers of patients with disease originating from each site are limited, imposing difficulties in the evaluation of site-specific results. Moreover, this difficulty limits the statistical analysis with regard to the number of covariates that may be introduced reasonably in the analyses. Despite these limitations, the general symptom sum score and several QLQ-C30 and QLQ-H&N35 indices remained predictive of survival when all the covariates described in the “Results” section were included in post hoc analyses. The primary end point of this study was death from all causes because we have not defined the accurate cause of death. Overall survival as an end point has the advantage of being simple to measure and straightforward to interpret and convey to the patients. However, among patients with high proportions of potentially lethal comorbidities, inclusion...
of cause of death could provide additional potential mechanisms.

Our group has previously demonstrated significant survival predictions from posttreatment HRQOL sum scores in a cohort of long-term HNSCC survivors.12,18 A limited number of published studies6,19,20 have evaluated the survival prediction from pretreatment HRQOL sum scores, and a single investigation4 found a sum score to be predictive of overall survival in these populations. In the present study, all HRQOL sum scores except the dichotomized functional sum score were found to be predictive of survival. The QLQ-C30 global QOL scale, generally considered an overall score and demonstrated to be uniquely predictive of survival in a general cohort of cancer patients,23 was evaluated and found to be predictive of survival in our study. The present findings are thus in accordance with our previous results of posttreatment HRQOL sum scores because the general symptom sum score and the HN sum score were found to be predictive of survival.12,18 The rationale for the use of HRQOL sum scores thus seems further strengthened.

Several possible explanations for the demonstrated survival prediction from HRQOL scores may exist. An association with the extent of the primary disease could be hypothesized.3 However, TNM stage, stage grouping, and tumor site showed no significant survival prediction; when these characteristics were introduced as covariates in the multivariate analyses, no alteration of the survival prediction from the HRQOL indices was demonstrated. The lack of survival prediction from TNM stage and stage grouping may be due to the limited number of patients in each subgroup or due to the fact that the treatment practice in our department is surgically dominated. The prognostic difference between the tumor burdens may be less pronounced when surgery is the main treatment modality.22 In that aspect, evaluation of the prognostic effects of tumor margins and molecular biology–derived aspects, such as human papillomavirus status,3 presumably of prognostic importance, would be of interest.

Several of the QLQ-C30 and QLQ-HN35 indices found to predict survival are symptom scales (ie, dyspnea, sleep disturbance, appetite loss, and swallowing difficulties) and accordingly could be reflections of important prognostic comorbidities.9 We have therefore applied the validated medical record–based ACE-27.16 The overall score was significantly predictive of survival in the univariate analysis; when our results were analyzed at the level of an organ system, cardiovascular disease was the sole predictor. This finding is interesting because respiratory disease, and not cardiovascular disease, seems to be a predictor of HRQOL sum scores.8 When the level of comorbidity was included as a covariate, however, no alterations in the survival prediction from any of the presented HRQOL indices were demonstrated.

The QLQ-C30 physical functioning index was also shown to be predictive of survival. This finding is in accordance with several previous publications6,7,21; for example, De Boer et al23 proposed that the demonstrated survival prediction could result from superior physical and psychological coping abilities among the patients with good physical functioning. The demonstrated survival prediction from the HRQOL scores may also be due to an association with psychological factors. Several investigations have demonstrated significant and unique relationships between depression and anxiety and HRQOL scores,24 and anxiety and depression have been shown to be predictors of mortality.25 Moreover, anxiety and depression seem to be associated with levels of neuroticism, the personality trait considered the causal element.26 We have applied adjustment for coping mechanisms, and the personality trait neuroticism demonstrated to be of key importance in predicting HRQOL scores among long-term survivors of HNSCC.4 However, no alterations of the survival prediction from HRQOL scores were observed when evaluated in multiple regression analyses.

The present findings should be considered of clinical relevance. We have demonstrated a predictive effect on survival from all HRQOL sum scores except the dichotomized functional sum score. The same holds true for several of the QLQ-C30 and QLQ-HN35 indices. These relationships were demonstrated to be robust and independent of sociodemographic, clinical, and psychological characteristics; health behaviors; and comorbidities. We also showed a substantially elevated overall mortality risk (50%-64%) among the quartiles of patients reporting the highest symptom burden and/or lowest functioning. These findings should be considered of special interest among health care professionals treating and providing surveillance of HNSCC patients because answers to standard questionnaires may provide unique prognostic information beyond what is recognized today. Moreover, the specific indices found to be of importance may provide focus areas for intervention, with potential implications for survival. Based on the present findings, pre-treatment interventions in relation to eating and swallowing status in particular seem warranted because half the demonstrated predictor indices of survival are related to these issues. These issues should constitute the focus of future studies.

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Additional Contributions: Statistical guidance has been provided by Stein Atle Lie, PhD, MSc, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway.

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