General Health Measures and Long-term Survival in Patients With Head and Neck Cancer

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Objective: To determine whether a self-reported, subjective general health assessment tool can provide prognostic information about survival in patients with head and neck cancer.

Design: Prospective observational cohort study.

Setting: Tertiary care center.

Patients: Five hundred seventy-one patients with squamous cell carcinoma of the upper aerodigestive tract who were enrolled in the institution's longitudinal Outcomes Assessment Project between January 1, 1995, and November 30, 2004.

Main Outcome Measures: Actuarial 5-year observed and disease-specific survival.

Results: The physical component summary obtained from the SF-36 (Medical Outcomes Study 36-Item Short-Form Health Survey) was significantly associated with ACE-27 (Adult Comorbidity Evaluation–27) comorbidity ratings. The mental component summary was not associated with ACE-27 scores or survival. Although the comorbidity rating was an independent predictor of observed survival ($P = .002$) only, the physical component summary was independently predictive of both observed ($P < .001$) and disease-specific ($P = .001$) survival. These associations continued to be independently significant when site and stage were included in the analysis ($P = .003$, $P < .001$, and $P = .004$, respectively).

Conclusion: The physical component summary generated by the SF-36, a self-reported, subjective measure of general physical health, is predictive of both observed and disease-specific survival.
The ACE-27 provides a detailed assessment of current illnesses and diseases and generates an overall score that categorizes comorbidity as none (0), mild (1), moderate (2), or severe (3). For this study, a reviewer retrospectively assigned OAP participants a pretreatment comorbidity score based on medical chart information that was available at or before the initiation of therapy. The index cancer, it is to be expected that a recent cancer diagnosis will have a negative effect on patients’ self-assessment of their general physical and mental health. Although the ACE-27 has been shown to correlate with overall survival in patients with head and neck cancer, self-reported measures of general health may also be predictive of head and neck cancer outcomes, particularly response to therapy and disease-specific survival.

The primary goal of the present study was to evaluate pretreatment comorbidity (assessed using the ACE-27) and patient-reported assessments of general physical and mental health (using the SF-36) to determine whether these measures predict observed or disease-specific survival or both in a large group of patients with head and neck cancer.

This prospective observational cohort study included patients enrolled in the Outcomes Assessment Project (OAP) between January 1, 1995, and November 30, 2004. The OAP is a longitudinal study of individuals with upper aerodigestive tract cancers being managed by the Department of Otolaryngology–Head and Neck Surgery at The University of Iowa Hospitals and Clinics. The study collects patient-, disease-, and treatment-related data and asks participants to submit a battery of health-related quality-of-life surveys at pretreatment, then at 3, 6, 9, 12, 24, 36, 48, 60, and 120 months. Survival information (eg, date of last contact and patient and disease status at last contact) is updated periodically. Enrollment was offered to all patients with biopsy-proved squamous cell carcinoma of the upper aerodigestive tract. The primary site was categorized as the oral cavity, oropharynx, hypopharynx, or larynx. Pathological stage was recorded when available; otherwise, clinical stage was used. This study was conducted with the approval of The University of Iowa institutional research review board.

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The SF-36 was included in the battery of surveys administered to OAP participants. It enables respondents to assess their general health and generates 2 composite summary scores representing overall physical health, the PCS and the MCS. These scores are normalized on a scale of 0 to 100, with higher scores representing better functioning. For selected analyses in this study, the PCS and MCS scores were categorized on the basis of quartile ranges established for average SF-36 scores obtained from the general population aged 55 to 64 years (ie, the reference distribution of scores for a similarly aged group of patients).
random age compared with the study group; however, this was the most appropriate age match available. As part of the OAP, the SF-36 is administered at the previously mentioned time points. In this study, only pretreatment SF-36 scores were used.

Statistical analyses were performed using SPSS statistical software (version 13.0 for Windows; SPSS Inc, Chicago, Ill). The actuarial method was used to calculate 5-year observed survival (the end point was death from any cause) and disease-specific survival (the end point was death with cancer present). A Pearson correlation was performed to determine the association between the ACE-27 comorbidity index and SF-36 composite (PCS and MCS) scores. Cox proportional hazards regression analyses were performed to determine whether the comorbidity index, PCS, or MCS was independently predictive of observed or disease-specific survival or both. When disease site and stage were included in the model, a small group of patients with unknown primary or unstageable tumors was excluded from these analyses. Results were considered significant at \( P < .05 \).

**RESULTS**

Of the 1334 patients who met the eligibility criteria for the OAP between January 1, 1995, and November 30, 2004, 919 (68.9%) were enrolled and comorbidity data had been collected for 840 of these patients (91.4%) when the present study was initiated. Of the 840 patients with comorbidity data, 571 (68.0%) had also filled out a pretreatment SF-36.

General characteristics of the 571 patients included in this study are given in Table 1. Their mean age was 59.7 years, and approximately two thirds (67.1%) were men. According to the ACE-27 clinical rating, 150 patients (26.3%) had no comorbidities when their cancer was diagnosed (Figure 1). Most patients (229; 40.1%) had mild comorbidities, 125 patients (21.9%) had moderate comorbidities, and 67 patients (11.7%) had severe comorbidities. The distribution of SF-36 scores for the 571 patients studied were ranked on the basis of a comparison with the quartile distribution of a similarly aged, randomly sampled group from the general population (Figure 2). Only 21 patients (3.7%) and 149 patients (26.1%), respectively, had PCS and MCS values in the fourth (best) quartile. The largest proportion of composite scores was in the first (worst) quartile: 43.1% (246 patients) and 41.0% (234 patients) for the PCS and MCS, respectively.

Figure 3 shows the mean pretreatment PCS and MCS scores in patients stratified by each of the 4 pretreatment comorbidity ratings. The mean PCS score decreased (worsened) as the level of comorbidity increased, ranging from 46.6 in patients with no comorbidities to 32.0 in patients with severe comorbidities. A similar trend was not observed for the MCS, which exhibited no significant variation with increasing comorbidity index. The results of a Pearson correlation analysis indicated that the association between the ACE-27 comorbidity rating and the PCS was significant \( (P < .001) \), although the Pearson correlation coefficient of −0.39 indicated a relatively weak correlation, with comorbidity accounting for only 15.3% of the variance in patient-
reported general physical health. The MCS did not correlate with the comorbidity index \((P=.14)\).

**Figure 4** shows 5-year observed and disease-specific survival for each of the ACE-27 comorbidity rating groups. Observed survival demonstrated a consistent downward trend from 67.2% for no comorbidities to 42.0% for severe comorbidities. Five-year disease-specific survival was essentially unchanged across the comorbidity groups, although there was a slight decrease in survival in the severe comorbidity group (63.2% vs 74.8% in the moderate group).

Five-year survival data are shown in **Figure 5**, with the patients grouped by quartiles of the PCS generated from the SF-36. Because of the small number of patients and limited follow-up in the fourth (best) quartile (2 of 21 patients had 5-year follow-up), actuarial survival could not be calculated for this group. (These patients were not eliminated from subsequent multivariate regression analyses because, in that setting, the PCS is treated as a continuous variable.) However, across the third through first quartiles, both observed and disease-specific survival demonstrated a stepwise reduction as the PCS indicated worse general health. Observed survival trended from 77.6% to 44.9%, whereas disease-specific survival decreased from 83.4% to 66.4%. There was no trend in observed or disease-specific survival for patients grouped by quartiles of the MCS (data not shown).

Multivariate regression analyses were performed to determine whether comorbidity rating, self-reported health scores, or both were independently predictive of observed or disease-specific survival or both. Two regression analyses were performed for each type of survival: the first analysis included the 3 general health measures assessed in the current study, and the second analysis additionally incorporated site and stage of disease. The results for observed survival indicated that comorbidity rating \((P=.002)\) and PCS \((P<.001)\) were both independently associated with 5-year observed survival rates (**Table 2**). The results were similar when site and stage were included in the model, with comorbidity rating \((P=.003)\) and PCS \((P<.001)\) remaining independently predictive of 5-year observed survival in addition to disease stage \((P<.001)\).

The hazard coefficients were exponentiated to demonstrate the change in mortality risk for each unit change in the significant parameters in the model. The risk ratio (exponential beta coefficient) values for comorbidity rating, PCS, and stage were 1.25, 0.97, and 1.36, respectively. Thus, a 1-level increase in comorbidity rating (worse comorbid disease) or stage (more extensive disease) results in a 25% or 36% increase in overall mortality risk at 5 years, respectively. A 1-point decrease in the physical health composite score (worse overall health) was associated with a 2.7% increase in overall mortality risk at 5 years.

When similar analyses were performed for disease-specific 5-year survival, the PCS was the only general health measure that exhibited an independent association \((P=.001; \text{Table } 2)\). When site and stage were included in the model, the PCS \((P=.004)\) remained independently associated with 5-year disease-specific survival.

**Table 2. Multivariate Analyses of Association Between Pretreatment Health Scores and 5-Year Survival**

<table>
<thead>
<tr>
<th>Survival Models and Variables</th>
<th>Association With 5-Year Survival</th>
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<tbody>
<tr>
<td></td>
<td>Observed Survival</td>
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<tr>
<td>Health measures and disease factors§</td>
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<td>Mental component summary</td>
<td>...†</td>
</tr>
<tr>
<td>Site of cancer</td>
<td>...‡</td>
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<tr>
<td>Cancer stage</td>
<td>1.36</td>
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</tbody>
</table>

*The risk ratio \((\exp(B))\) indicates relative mortality risk for a single unit increase in each tested variable; that is, 1 level from 0 to 3 for comorbidity index, a single point from 0 to 100 for the physical or mental component summary, and 1 level from I to IV for cancer stage.

†Model did not include disease factors, and analysis was performed in 571 patients with head and neck cancer.

‡Risk ratios only provided for significant associations.

§Model included disease factors, and analysis was performed in 487 patients with cancers of the oral cavity, oropharynx, hypopharynx, and larynx.
in addition to disease stage ($P<.001$). The risk ratios (exponentiated hazard coefficients) indicated that a 1-level increase in stage and a 1-point decrease in the PCS were associated with a $54\%$ and $2.5\%$ increase in 5-year disease-specific mortality risk, respectively.

### COMMENT

The distribution of ACE-27 comorbidity ratings in these patients with head and neck cancer is similar to that observed in other studies.\(^1\)\(^-\)\(^9\)\(^-\)\(^10\) Clearly, the selection criteria for the study group will affect this distribution. In the present study, the largest group of patients had mild comorbidities, followed by no and moderate comorbidities. This distribution is not unexpected given the age of the patients studied.

In the current study's patient sample, the SF-36 instrument is predictive of both overall and disease-specific survival. This finding suggests that this tool captures prognostic information related to the cancer state. The use of comorbidity evaluation in conjunction with stage improves the ability to predict overall survival prognosis in patients with head and neck cancer. This study demonstrates that the use of self-reported health status, in conjunction with cancer stage, adds to the prediction of both observed and disease-specific survival.

There was a discrepancy between comorbidity indices and self-reported PCS and MCS scores using the SF-36. When distributed on the basis of quartile cutoffs of normative reference values from a similarly aged sample of the US population, less than $4\%$ of patients scored in the fourth (best) quartile on the PCS, representing a negative self-assessment. This percentage increases consistently across quartiles, with more than $40\%$ of patients scoring in the first (worst) quartile. By comparison, only $11.7\%$ of patients objectively scored in the most severe comorbidity category. A similar trend exists for the MCS, except that a larger proportion of patients ($26.1\%$) scored in the fourth quartile. However, more than $40\%$ of patients placed themselves in the worst category for general mental health.

This discrepancy may arise largely because the ACE-27 does not take into account the index tumor. At the initial SF-36 assessment, patients would have been experiencing the physical and psychological stressors of a new cancer diagnosis, which likely altered their self-perception about both physical and mental health. As shown in Figure 3, patients with significantly more severe comorbidities had essentially the same MCS scores as patients with no or mild comorbidities, which suggests that the variation in the PCS score is primarily related to the patient's perceptions of physical health deficits. This concept is in agreement with previous findings by Funk et al\(^11\) in a similar population. After treatment, many of these patients’ SF-36 scores may improve; however, it is unlikely that their comorbidity index scores will change significantly.

In the present study, both pretreatment ACE-27 comorbidity rating and SF-36 PCS scores were independent predictors of observed survival (Table 2). Comorbidity rating was not, however, a predictor of disease-specific survival. The pretreatment PCS score was an independent predictor of disease-specific survival, which suggests that this measure is influenced significantly by the severity of the head and neck cancer.

Many studies support the value of comorbidity in predicting mortality; a variety of comorbidity indexes have been studied in the context of multiple different cancers, and it has now become generally accepted that, in most cases, worsening comorbidities result in decreased overall survival. The recent literature contains several studies that demonstrate a relationship between ACE-27 comorbidity rating and observed survival in head and neck cancer. However, there are conflicting data on the relationship between comorbidity and disease-specific survival. In 2000, Piccirillo\(^7\) used a modified version of the KFCI, which would ultimately become the ACE-27,\(^8\) to demonstrate a correlation with 2-year overall survival rates in patients with head and neck cancer. Chen et al\(^8\) studied 182 patients with advanced laryngeal cancer and found that the modified KFCI to be predictive of overall survival but not disease-specific survival. When stratified into 2 groups by the modified KFCI, there was no difference between the groups in time to first recurrence. Similarly, Borggreven et al\(^9\) found that an ACE-27 rating of 3 predicted worse overall survival compared with a rating of 2 or lower; the disease-free interval and tumor-specific survival were not significantly different between the 2 groups. On the other hand, Paleri et al\(^9\) found the ACE-27 score to be predictive of both 5-year overall and disease-specific interval.

Other authors have studied comorbidity in relation to treatment-related complications. Singh et al\(^9\) noted an increase in severity of complications in patients with a KFCI score of 2 or 3, although the number of complications did not increase. The ACE-27 comorbidity rating was noted by Ferrier et al\(^9\) to predict an increase in major complications in patients with surgically treated head and neck cancer. In a study of 100 consecutive patients with advanced oral cavity or oropharyngeal squamous cell carcinoma who underwent excision and microvascular reconstruction, an ACE-27 rating of 2 or higher was a strong predictor of moderate to major postsurgical complications.\(^6\)

As with all prospective outcomes studies, there is a selection bias toward patients who are willing to participate in a study and those who will accurately and completely fill out the questionnaires. The general assumption is that these patients are healthier and do better than patients who refuse to participate or drop out. In addition, our study numbers are reported on the basis of our intent to enroll. Unfortunately, we can gather and report no information about the patients who declined to participate. Comparison between OAP-enrolled patients with and without complete data allowing participation in this study did not reveal any significant differences in mean age, cancer stage, or comorbidity, indicating that our results are representative of the patients enrolled in the OAP. Our study included 571 patients with a mean age of 59.7 years; mean comorbidity grade was 1.2. Cancer was in the early stage in 33.8% and the advanced stage in 61.3%, and was not staged in 4.9%. In 269 OAP-enrolled patients not included in our study be-
cause of incomplete data, mean age was 60.5 years and the mean comorbidity grade was 1.2. For these patients, cancer was in the early stage in 34.6% and the advanced stage in 55%, and was not staged in 10.4%. However, in this project and other prospective outcome studies, enrolled patients with complete data should, in general, be considered globally performing at a higher level than those who refused to participate or dropped out.

This study focused on a limited number of pretreatment independent variables. We chose comorbidity and self-assessment of general health on the presumption that these measures capture a great deal of prognostic information contained in a number of other individual variables (eg, tobacco use, alcohol use, and history of cardiovascular disease). For some purposes, a more detailed evaluation of pretreatment factors influencing outcome would be useful. In addition, we did not evaluate any treatment variables because we wanted to confine our focus to information available before treatment. This study demonstrates that self-assessed general health is an independent predictor of both observed and disease-specific death in patients with head and neck cancer. Although this is an interesting observation and seems to add to the information obtained from an analysis of comorbidity alone, the clinical relevance and utility of this relationship remain to be explored.

Given the current findings, further study is warranted to determine whether the predictive value of the SF-36 instrument can be integrated usefully into clinical staging. Piccirillo and others have strongly advocated for and demonstrated the utility of a composite staging system that includes both disease-specific factors captured by the TNM system and patient-specific factors such as comorbidity. It remains to be seen whether a composite of the TNM system with an overall health assessment tool such as the SF-36 can potentially have captured by the TNM system and patient-specific factors such as comorbidity. A composite staging system may potentially be more useful in patients with head and neck cancer. Although this is an interesting observation and seems to add to the information obtained from an analysis of comorbidity alone, the clinical relevance and utility of this relationship remain to be explored.

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Author Contributions: Drs Jameson, Karnell, Christensen, and Funk had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jameson, Karnell, and Funk. Acquisition of data: Grignon, Karnell, and Funk. Analysis and interpretation of data: Jameson, Karnell, Christensen, and Funk. Drafting of the manuscript: Grignon, Jameson, Karnell, Christensen, and Funk. Critical revision of the manuscript for important intellectual content: Jameson, Karnell, Christensen, and Funk. Statistical analysis: Karnell and Funk. Obtained funding: Karnell and Funk. Administrative, technical, and material support: Grignon, Jameson, and Karnell. Study supervision: Karnell and Funk.

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