Simple Predictors of Survival in Head and Neck Squamous Cell Carcinoma

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Objective: To develop a simple prognostic survival rule from easily obtained characteristics of patients undergoing potentially curative resection of head and neck squamous cell carcinoma using classification and regression trees.

Design: Inception cohort.

Setting: Tertiary care center.

Patients: Consecutive patients undergoing resection lasting at least 2 hours, from July 1993 through June 1997.

Main Outcome Measure: Survival, age, TNM tumor stage, functional class, systolic and diastolic blood pressure, body mass index, and serum albumin concentration were evaluated as predictors.

Results: Four hundred six patients were followed up for 5 to 1446 days (median, 391 days), during which time 172 deaths occurred. Median survival was 687 days. Patients with TNM stage I, II, or III squamous cell carcinoma had a mean survival of 1068 days. Patients with TNM stage IV or recurrent disease were further stratified. Those with a serum albumin concentration less than 3.85 g/dL had a median survival of 404 days (95% confidence interval, 286-532 days), and those with an serum albumin concentration of 3.85 g/dL or above had a median survival of 625 days (95% confidence interval, 536-1032 days). A similar survival was found using age younger than 66.5 years as a predictor instead of serum albumin concentration less than 3.85 g/dL.

Conclusions: At our institution, patients with stage I, II, or III squamous cell carcinoma had a mean survival of approximately 3 years. Those with stage IV or recurrent squamous cell carcinoma could be stratified by either serum albumin concentration or by age into 2 groups with a median survival of 1 or 2 years.


PROGNOSIS, including the prognosis of survival, is a fundamental function of physicians, especially physicians who care for patients with cancer. The objective of this study is to develop a simple prognostic survival rule for patients undergoing potentially curative resection of head and neck squamous cell carcinoma (SCC) by using classification and regression trees (CART). Typically, the only patient characteristics considered are age, sex, and performance status. Other characteristics, including blood pressure, body mass index, and serum albumin concentration are easily obtained at the preoperative evaluation and have been shown to predict survival for other conditions. To our knowledge, these factors have not previously been studied in head and neck SCC. Many tumor-related characteristics have been studied, but only disease stage (American Joint Committee on Cancer TNM stage) or T and N Integer Score (TANIS) are prognostically significant and routinely available preoperatively.

Recursive partitioning is an analytic technique that creates increasingly more homogeneous subsets of data with respect to a particular outcome (eg, survival) based on a selected predictor. The method is recursively and independently applied to each subset so that different characteristics may emerge as predictors to further divide the subsets. Schematically, this creates a tree subdividing the original population, with each branch being more homogeneous, enabling more accurate prediction. The tree is then pruned of the smallest branches to avoid overfitting the data. This pruned, simplified tree can then be translated into a prognostic rule. Goldman et al and Lee et al used a recursive partitioning method (CART) to determine probability of myocardial infarction in patients with...
chest pain. Cooper et al.\textsuperscript{14} used recursive partitioning to determine prognostic characteristics in 2105 patients in the Radiation Therapy Oncology Group studies of head and neck SCC. The purpose of the present article is to use CART to determine which routinely available preoperative patient and tumor-related characteristics can predict postsurgical survival in patients undergoing potentially curative resection of head and neck SCC.

METHODS

POPULATION

The study population comprised consecutive patients undergoing potentially curative resection of head and neck SCC by one of us (D.E.S.), lasting at least 2 hours, from July 1993 through June 1997, at the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute of The Ohio State University, Columbus. All patients underwent preoperative evaluation by one of us (H.G.W.), who prospectively collected all data except serum albumin concentration, which was ascertained by retrospective medical record review. Cause of death was ascertained from the hospital electronic record, the clinic chart, or interviews with family members. Only patients with complete data were used.

DEFINITIONS

Age, tumor stage, self-reported functional class, systolic blood pressure, diastolic blood pressure, body mass index, and serum albumin concentration were evaluated as predictors of survival. Survival time was measured from the initial surgery. Vital status was ascertained from the patient, their family, medical center records, and the cancer center’s tumor registry. Age was the age on the surgical date. Blood pressure measurement from the preoperative evaluation was used. Tumor stage was determined by one of us (D.E.S.) according to the TNM classification.\textsuperscript{14} Stage V was defined as recurrent disease. During analysis, the tumor stages were combined into 4 groups: stages I and II were combined owing to the small number of patients in stage I (n=13). Functional classes as determined by the Specific Activity Scale\textsuperscript{16} were combined into 3 groups; classes 3 and 4 were combined owing to the small number of patients in group 4 (n=7).

ANALYSIS

Mean and median survival with 95% confidence intervals (CIs) were estimated with the Kaplan-Meier method.\textsuperscript{15} Recursive partitioning repeatedly separates more and more homogeneous subgroups from the larger population, and the result can be represented schematically as a tree. It has been applied to classification and regression problems. For survival analysis, exponential regression can be used to distinguish the subgroups. To avoid overfitting the data, the complete tree is then pruned using a complexity measure and cross-validation. Cross-validation is usually applied in a “leave-one-out” process to estimate the true predictive error rate. In this process, the population is randomly divided into n subsets. A decision rule is then developed using all but one of the subsets. It is then tested on the “left-out” subset, generating an estimate for the error rate. This is repeated n times, leaving out a different subset each time, and the error estimates are combined to estimate the true predictive error rate. By balancing the cross-validation error estimate and the complexity of the model, a decision rule that reduces overfit can be selected. In the present study, CART\textsuperscript{2} with exponential regression was used to determine predictors of survival. The resulting regression tree was pruned based on the complexity parameter with 10-fold cross-validation. The resulting subsets were evaluated by Kaplan-Meier analysis to determine mean and median survival with 95% CIs. All statistical tests were run with R 1.4 software,\textsuperscript{18} using rpart (recursive partitioning)\textsuperscript{19} for the CART analysis. The Ohio State University institutional review board approved this study.

RESULTS

There were 454 patients in the cohort, 406 (89%) of whom had complete data. Data were missing for serum albumin concentration for 45 patients, follow-up time for 1 patient, tumor stage for 1 patient, and functional class for 1 patient. Patient characteristics are given in the Table. There were no statistically significant differences between patients with complete data and those missing data for age, body index mass, sex, grouped tumor stage, or survival. Between patients with complete data and those missing data there were statistically significant differences for diastolic blood pressure (measurements for blood pressure are mean ± SD mm Hg) (complete data: 88.0±12.62; missing data: 83.3±13.52; t value, 1.9936; P = .05), systolic blood pressure (complete data: 134.0±22.51; missing data: 144.2±23.46; t value, 2.2132; P = .03), and grouped functional class (χ² = 11.8037; P = .008). A cause of death was ascertained in 145 of the 172 deceased patients; 126 patients (87% of patients with a known cause of death) died of their cancer or of a cancer-related cause, and 12 patients (8%) died of a cardiovascular cause.

KAPLAN-MEIER ANALYSIS

Individual patients were followed up between 3 and 1446 days (median, 391 days). There were 172 deaths. The Kaplan-Meier estimate for median survival was 687 days (95% CI, 599-1023 days). Mean survival was 817 days.
CLASSIFICATION AND REGRESSION TREE SURVIVAL ANALYSIS

The model developed using CART to determine survival predictors from among the full set of patient characteristics is shown in Figure 1. After pruning, a model with 3 leaves was selected (Figure 2A). The population was initially split based on TNM stage. Separating out stages I, II, and III, patients selected a group with above-average survival: the mean survival was 1068 days (95% CI, 1023-1100 days). No median survival could be calculated because more than half of the subgroup survived through the follow-up period. Patients with stage IV or recurrent disease were further subdivided into 2 subgroups based on serum albumin concentration. The subgroup with an albumin concentration of 3.85 g/dL or more (ie, the split was between 3.8 and 3.9 g/dL) had a median survival of 625 days (95% CI, 536-1032 days) and a mean survival of 784 days. The remaining subgroup (those with stage IV or recurrent disease and serum albumin concentration <3.85 g/dL) had a median survival of 404 days (95% CI, 286-532 days) and a mean survival of 496 days. The log-rank test revealed a statistically significant difference among the 3 groups (survival rates over time ($p^2=43.9; P<.001$ by the log-rank test). The next best characteristic to serum albumin concentration for the split was age younger than 66.5 years (ie, the split was between 66 and 67 years old) (Figure 3).

Figure 1. Complete classification and regression tree of survival of patients undergoing potentially curative resection of head and neck squamous cell carcinoma. The ovals contain the test to apply at each level; a yes answer moves to the left and a no to the right. BP indicates blood pressure; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

Figure 2. Classification and regression tree of survival of patients undergoing potentially curative resection of head and neck squamous cell carcinoma: serum albumin concentration–based decision rule. A, Decision tree; B, Kaplan-Meier survival curves for the decision rule ($p^2=43.9; P<.001$ by the log-rank test). The magenta line represents stage I, II, or III; the cyan line, stage IV or recurrent disease and serum albumin concentration of 3.85 g/dL or greater; and the black line, stage IV or recurrent disease and serum albumin concentration less than 3.85 g/dL.
We evaluated survival in an inception cohort of patients with head and neck SCC undergoing surgery with the intent of cure. Median postsurgical survival was less than 2 years. The strongest predictor of survival was tumor stage. In patients with stage IV or recurrent disease, either a low serum albumin concentration (with a split between 3.8 and 3.9 g/dL) or an advanced age (with a split between 66 and 67 years) indicated an especially poor prognosis. We recommend using age as the prognostic indicator because age is usually easier and less expensive to obtain.

To exemplify the rules, consider the following hypothetical patients. First, consider a 72-year-old man with stage II cancer. For a patient with stage II cancer, the expected mean survival is about 3 years. Because the patient's cancer is stage II, age is irrelevant. Patient sex is always irrelevant in this model. Next, consider a 69-year-old patient with stage IV cancer. For a patient with stage IV cancer, age must also be considered to project survival. For a patient who is 67 years or older, the expected median survival is a little more than 1 year. If this patient were younger than 67 years, then the expected median survival would be about 2 years.

Chiesa et al20 conducted a systematic review of prognostic factors in head and neck SCC for articles published between January 1993 and August 1997. They found that age, sex, and performance status predicted survival in all studies and that family history was also prognostic in some studies. Ildstad et al21 found only age, stage, and tonsillar location of the prime tumor to be prognostic in some studies. Stell,22 using univariate analysis in a series of 4319 patients, found only Eastern Cooperative Oncology Group performance status to be a significant predictor of survival.

In the present study, tumor stage, with either serum albumin concentration or age, best predicted survival. The Specific Activity Scale was not of additional prognostic value. The Specific Activity Scale is a measure of cardiopulmonary exercise capacity and not comparable with performance measures of activities of daily living, such as the Eastern Cooperative Oncology Group performance status. Although up to 10% of patients with head and neck SCC die of cardiac or pulmonary disease unrelated to their cancer within 5 years of cancer surgery (unpublished data, 1995), in this study, a cardiopulmonary functional capacity measure did not predict survival.

The present study differs from that of Cooper et al14 in 3 respects: study subjects, development algorithm, and prediction rule. First, in the study by Cooper et al, the subjects received radiation therapy as primary treatment, whereas our subjects received surgery as primary treatment; second, in Cooper et al’s studies, the development algorithm was recursive partitioning using Kaplan-Meier analysis for the regression, whereas our algorithm was CART, using exponential regression. And third, in Cooper et al’s study, the prediction rule requires N and T stage, primary site, number of primary fractions, Karnofsky performance status, age, and interruptions in treatment, resulting in 6 survival subgroups, whereas our rule requires only tumor stage and patient age, resulting in 3 survival subgroups.

The present study is especially strong because an inception cohort of patients undergoing similar primary treatment was followed prospectively from the time of surgery, data collection was uniform, there was complete data on 89.4% of patients, and survival data on 99.8% of patients. However, external validity (generalizability) of this study’s findings is limited because it was conducted at a single institution and included only patients presenting for potentially curative resection. Furthermore, the entire cohort was used to develop the prognostic rule; the rule was not tested in a validation cohort.

Simple preoperative characteristics can predict survival of patients undergoing potentially curative resection of head and neck SCC. Patients with stage I, II, or III cancer have the best survival, whereas patients with stage IV or recurrent cancer who are older than 66.5 years have the worst survival. Patients with stage IV or recurrent cancer who are younger than 66.5 years have intermediate survival. These findings need to be independently validated.

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