An Oral Cavity Carcinoma Nomogram to Predict Benefit of Adjuvant Radiotherapy

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Importance: After surgical resection for oral cavity squamous cell carcinoma, adjuvant radiotherapy may be recommended for patients at higher risk for locoregional recurrence, but it can be difficult to predict whether a particular patient will benefit.

Objective: To construct a model to predict which patients with oral cavity squamous cell carcinoma would benefit from adjuvant radiotherapy.

Design and Setting: We constructed several types of survival models using a set of 979 patients with oral cavity squamous cell carcinoma. Covariates were age, sex, tobacco use, stage, grade, margins, and subsite. The best performing model was externally validated on a set of 431 patients.

Participants: The model was based on a set of 979 patients with oral cavity squamous cell carcinoma, including 563 from Memorial Sloan Kettering Cancer Center, New York, New York, and 416 from the Hospital AC Camargo, São Paulo, Brazil. The validation set consisted of 431 patients from Princess Margaret Hospital, Toronto, Ontario, Canada.

Main Outcome and Measure: The primary outcome measure of interest was locoregional recurrence-free survival.

Results: The lognormal model showed the best performance per the Akaike information criterion. An online nomogram was built from this model that estimates locoregional failure-free survival with and without postoperative radiotherapy.

Conclusions and Relevance: A web-based nomogram can be used as a decision aid for adjuvant treatment decisions for patients with oral cavity squamous cell carcinoma.

ORAL CANCERS ARE THE sixth most common type of cancer worldwide,[1] with an estimated 41 380 new cases expected to be diagnosed in the United States in 2013.[2] Of these, half are oral cavity squamous cell carcinoma (OCSCC). For OCSCC, surgery is the preferred primary therapy, but because of the high rate of locoregional recurrence, adjuvant radiotherapy or chemoradiotherapy is often recommended. Risk factors have been identified for patients with head and neck cancer that result in higher rates of recurrence,[3] and patients who are thought to be at higher risk are often offered postoperative radiotherapy to reduce this risk.

It is likely that only certain subsets of high-risk patients will gain benefit from adjuvant therapy, but determining which patients will benefit remains a challenge.

Because of the multitude of potential risk factors for recurrence, it would not be practical to conduct prospective clinical trials to test every permutation of risk factors to determine which specific patients would benefit from adjuvant therapy. In these settings, multivariate survival prediction models may be able to provide insight into these important clinical questions.

We previously published a prediction model[4] to estimate the risk of locoregional recurrence after treatment of OCSCC. The nomogram was built from a series of patients with OCSCC from Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, New York, and externally validated with data from Hospital AC Camargo (HACC) in São Paulo, Brazil. The specific aim of the present study was to enhance this model by explicitly adding the effects of adjuvant radiotherapy to the model. Using data from

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Princess Margaret Hospital (PMH) in Toronto, Ontario, Canada as an external validation data set allowed pooling of data from MSKCC and HACC for a larger sample size to construct an improved nomogram that enables a quantitative comparison of the risk of locoregional failure with and without adjuvant radiotherapy. The purpose was to provide additional information to clinicians and patients to aid in the decision-making process for adjuvant therapy.

Figure 1. Kaplan-Meier plot of locoregional recurrence-free survival for all cases, grouped by T classification.

METHODS

STUDY POPULATION

The training cohort for this survival model consisted of a combined set of 563 patients with OCSCC from the MSKCC and 416 patients from the HACC. The test cohort used to validate the model was a set of 431 patients from the PMH.

STATISTICAL ANALYSIS

All statistical analyses were performed using the R software package (http://www.r-project.org). Covariates included age, sex, tobacco use, oral cavity subsite (floor of mouth, oral tongue, or other), T classification, N classification, grade, and margin status. Margins were defined as "close" if tumor cells were found within 1 high-powered field of the resection margin. The primary outcome measure of interest was locoregional recurrence-free survival (LRFS), where an event was defined as any locoregional recurrence or death from any cause. All covariates were treated as discrete and converted to binary variables, except for age, which was modeled as a continuous variable and fitted to a smoothed restricted cubic spline function as per Harrell.[5(p20-23)] We used a model-building approach promoted by Harrell[5(p53-86)] in which all covariates are included in the final model with no variable selection performed.

We used a propensity score weighting method to balance observed covariates between the treatment and observation groups.[6] Propensity scores reflect the probability that a patient will receive therapy on the basis of observed covariates.[6] By assigning propensity score weights to each case and incorporating these weights into model construction, we can reduce treatment bias inherent in retrospective nonrandomized regression analyses. Propensity scores were calculated using the twang R library (http://cran.r-project.org/web/packages/twang/index.html) with adjuvant radiotherapy as the outcome of interest.

Multivariate regression survival analysis was performed using several survival modeling methods, and results were compared. We built semiparametric models (Cox proportional hazards) and accelerated failure time parametric models (Weibull, exponential, log-logistic, and lognormal). All survival models were constructed using the rms R library by Harrell (http://cran.r-project.org/web/packages/rms). Model performance was compared using the Akaike information criterion (AIC), a measure of the goodness of fit for statistical models, and the model with the best (lowest) AIC was selected.[7] To determine whether the functional form of the chosen model had an appropriate fit for this data set, we plotted the quantile function (inverse of the cumulative distribution function) of the selected model and evaluated the straight line fit.

The model with the best AIC was then externally validated using the PMH data set by measuring both discrimination and calibration. Discrimination was evaluated using the concordance index (C-index). The C-index is a commonly used measure for evaluating survival models that is well described by
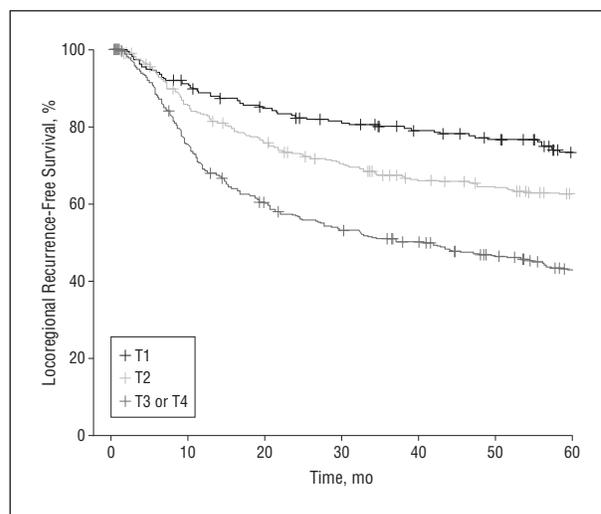
Harrell.[5(p493)] The C-index measures the probability that, given a pair of randomly selected patients, the model correctly predicts which patient will experience an event first. The value of the C-index can range between 0.5 (random chance) and 1.0 (perfect discrimination).[5(p493),8,9] Calibration, which compares predicted survival with actual survival, was evaluated with a calibration curve.[5(p493)] The final survival prediction model was then implemented into a browser-based online nomogram, where a user can enter parameters for a specific patient and obtain an estimate of the expected LRFS with or without adjuvant radiotherapy. The browser-based software tool was programmed in JavaScript.

RESULTS

A total of 979 patients (from MSKCC and HACC) were included in the training set for this study. Of these, 49% received adjuvant radiotherapy. A Kaplan-Meier plot of LRFS for all patients by T classification is shown in **Figure 1**. A comparison of the baseline characteristics between the treated and untreated groups, before and after propensity score weighting, is given in **Table 1**. Patients treated with adjuvant radiation therapy tended to have OCSCC that was of higher T classification, node positive, and higher grade and had positive margins. After propensity score weighting, all covariates were balanced and no longer had statistically significant differences.

In comparing the performance of the survival models, the lognormal model had the most favorable (lowest) AIC of 6888 (**Table 2**), indicating a better overall fit than the other models. For a lognormal model, the appropriate quantile function plot is

$$\Phi^{-1}[1 - \hat{S}(t)] \text{ vs } \ln(t),$$

where Φ^{-1} is the inverse of the standard normal cumulative distribution function, $\hat{S}(t)$ is the Kaplan-Meier estimate of the survival function, and $\ln(t)$ is the natural logarithm of time. A plot of this quantile function approximated a straight line, indicating a reasonable fit for these data. The lognormal model was then externally validated with the PMH data set, and it was found to have

Table 1. Patient and Tumor Characteristics Before and After Propensity Score Weighting to Balance Covariates Between Untreated and Treated Groups

Characteristic (N = 979)	Original			PS Weighted		
	No RT	RT	P Value	No RT	RT	P Value
Age, mean, y	60	57	<.001	58	57	.48
Female sex, %	38	27	<.001	19	27	.12
Tobacco use, %						
Yes	67	77		84	77	
No	15	10	.001	8	10	.22
Unknown	18	12		8	12	
Site, %						
Floor of mouth	21	23		23	23	
Oral tongue	52	42	.004	43	42	.99
Other	27	35		34	35	
T classification, %						
T1	42	5		4	5	
T2	41	32	<.001	26	32	.33
T3 or T4	17	63		70	63	
N classification, %						
N0	92	34		36	34	
N1	4	24	.001	25	24	.91
N2 or N3	3	42		40	42	
Grade, %						
G1	39	30		30	30	
G2 or G3	35	45	.003	40	45	.57
Unknown	25	24		30	24	
Margins, %						
Positive or close	12	30		34	30	
Negative	88	70	<.001	66	70	.64

Abbreviations: PS, propensity score; RT, radiotherapy.

Table 2. Comparison of Survival Models

Model	Akaike Information Criterion[a]
Cox proportional hazards	11 671
Weibull	6964
Exponential	7000
Log-logistic	6893
Lognormal	6888

[a] The Akaike information criterion is a measure of goodness of fit of the model. Lower values indicate a better fit.

good discrimination, with a C-index of 0.71. This C-index compares favorably with those of other prediction models that are commonly used for other cancer sites.[10-14] The calibration curve also showed good agreement between predicted and observed outcomes for the lognormal model. The β coefficients for the lognormal model are shown in **Table 3**. Note that for a lognormal model, a negative β coefficient indicates a worse hazard.

Figure 2 shows an example comparison of how the lognormal model curve approximates the Kaplan-Meier survival plot for an example patient with T2N0 oral tongue cancer with positive margins.

The lognormal model was implemented as an online survival prediction nomogram that calculates the expected survival benefit from adjuvant radiotherapy. This browser-based software tool is available at http://skynet.ohsu.edu/nomograms (**Figure 3**). Using the nomogram, we can estimate the LRFS for an individual patient on the basis of their specific parameters, and we can estimate the incremental benefit of adjuvant radiotherapy. For example, a 60-year-old female smoker with T2N2 moderately differentiated oral tongue cancer with positive margins would be expected to see a 13% absolute improvement in 5-year LRFS (from 16% to 29%) with adjuvant radiotherapy. In contrast, a 55-year-old male nonsmoker with T1N1 well-differentiated floor of mouth cancer with close margins would be predicted to see only an 8% absolute benefit from radiotherapy (improvement from 48% to 56%). In general, the nomogram demonstrates that patients with positive margins, higher N classification, and lower T classification, younger patients, and female patients seem to obtain more absolute benefit from adjuvant radiotherapy.

DISCUSSION

Clinical prediction calculators and nomograms are becoming increasingly popular decision aids in predicting cancer risk, prevention, and therapeutic outcomes.[15] There are a number of important cancer risk prediction models being used today for prostate,[11,13,14,16,17] breast,[12,18-21] pancreas,[22] and other cancer sites.[23] Clinical prediction tools are useful for individualizing therapeutic recommendations for a specific patient. Although prediction models can never substitute for evidence from prospective randomized clinical trials, these tools are useful adjuncts to clinical decision making in situations where optimal therapeutic management may not be clear.

Table 3. Gamel Boag Lognormal Multivariate Regression Model Parameters

Covariate	β Coefficient	P Value
Intercept (β_0)	6.039	<.001
Age[a]	−0.015	.24
Age'[a]	0.012	.69
Age"[a]	−0.101	.49
Male sex	−0.333	.003
Tobacco use		
No	0 [Ref]	
Yes	0.026	.87
Unknown	−0.324	.09
Margins		
Negative	0 [Ref]	
Positive or close	−0.738	<.001
T stage		
T1	0 [Ref]	
T2	−0.424	.002
T3 or T4	−0.818	<.001
N stage		
N0	0 [Ref]	
N1	−0.185	.32
N2 or N3	−1.435	<.001
Grade		
1	0 [Ref]	
2 or 3	−0.099	.34
Unknown	0.240	.04
Site		
Floor of mouth	0 [Ref]	
Oral tongue	−0.072	.53
Other	0.317	.02
RT	0.059	.64
RT with pos margins	0.448	.03
RT with N1	−0.190	.46
RT with N2 or N3	0.229	.29
log (σ)	0.456	<.001

Abbreviations: pos, positive; Ref, reference; RT, radiotherapy.

[a] Age was modeled using a restricted cubic spline function with 4 knots, requiring 3 independent coefficients: age, age', and age".
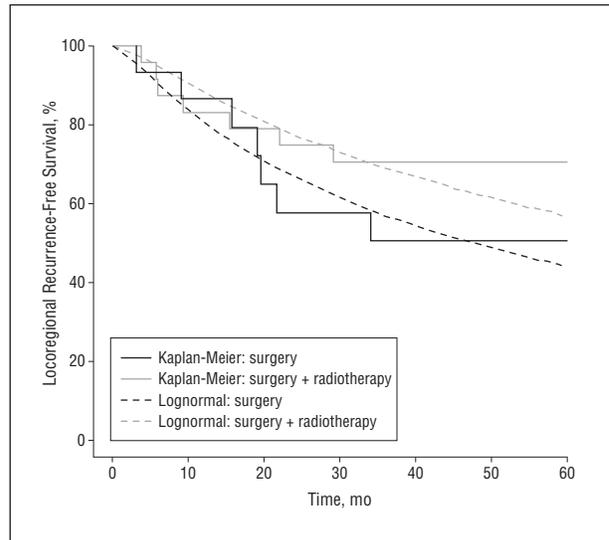

Figure 2. Comparison of lognormal survival model curve with actual Kaplan-Meier data for an example patient with T2N0 oral tongue cancer with positive margins.
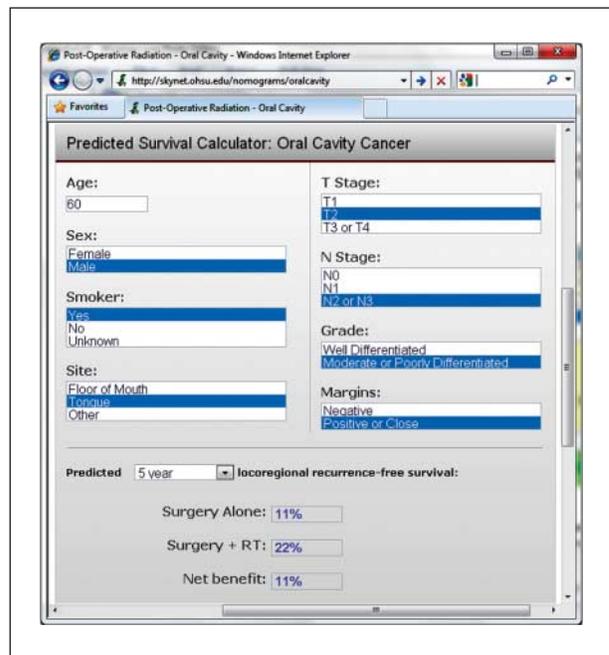

Figure 3. Online prediction calculator that estimates the benefit of adjuvant radiotherapy for an individual patient. This web-based tool is available at http://skynet.ohsu.edu/nomograms.

When observational data is used to model treatment effects, there will always be inherent selection bias between treated and untreated groups because patient selection for treatment can be influenced by patient or tumor characteristics. Propensity score methods can be used to reduce the impact of this treatment selection bias.[6,24-27] The propensity score is defined as the probability of receiving treatment conditional on the patient's observed baseline covariates.[24,25] There are several methods in which propensity scores have been incorporated into statistical modeling, including stratification, matching, covariate adjustment, and inverse probability of treatment weighting. Austin[6] compared these 4 methods and found that matching and inverse treatment weighting performed better than the other 2 methods. We chose to implement the inverse treatment weighting approach because this method yields a final survival model whose parameters can be readily incorporated into an interactive web tool.

We used the AIC to compare the relative performance of the models. The AIC is a measure of the goodness of fit of regression models that is based on the concept of entropy.[7] It can be viewed as the amount of information lost when a model is used to describe a set of observations. The AIC includes a penalty for number of model parameters and thus represents the tradeoff between bias and variance. Lower AIC values indicate a better model fit, and in our analysis, the lognormal model had the lowest AIC.

The lognormal survival is an accelerated failure time parametric survival model that has a long history of usage in cancer survival analysis.[28] Although not as popular as the semiparametric Cox proportional hazards model, for many situations where the proportionality assumption does not hold, , such as for breast cancer[28-31] and for lung cancer,[32] the lognormal model has been shown to be a more appropriate survival model. Gamel and McLean[33] developed an extension to the original Boag

model that allows prognostic covariates to be incorporated into the lognormal model. In this type of lognormal survival model, the log of the survival time has a normal distribution and is a linear function of covariates. In this implementation, the hazard function is not constant over time but rises quickly to a peak and then declines over time.

In general, our prediction model indicates that patients with positive margins and/or N2 to N3 disease will derive the most benefit from adjuvant radiotherapy, although the relative magnitude of this benefit will vary depending on the other patient and tumor characteristics entered into the model. These findings are consistent with generally accepted indications for postoperative radiotherapy seen in other head and neck cancers[34,35] and are in agreement with NCCN guidelines[36] for adjuvant therapy for oral cavity cancers. Treatment of this cohort predated the era of postoperative concurrent chemoradiation. Therefore, none of the patients included in this study received concurrent chemotherapy with postoperative radiotherapy. It is presumed that the addition of chemotherapy in high-risk patients would amplify the impact of radiotherapy observed in our study. Thus, it is possible that the estimates provided by the nomogram represent the minimum potential benefit of adjuvant therapy after surgery for OCSCC.

In some cases, our model predicts only a small relative improvement from the addition of adjuvant therapy. We did not specify a specific threshold at which adjuvant therapy should be recommended. We believe that the final decision of whether adjuvant therapy should be given should be made after a careful discussion between the clinician and patient, accounting for multiple factors, many of which cannot be accounted for in a prediction model. Quality of life and specific patient preferences are additional important considerations in treatment decision making.

There are several limitations to this study. Some known prognostic tumor factors were not available in our data set and so could not be included in our multivariate survival models. For example, information on extracapsular extension, lymphovascular space invasion, and perineural invasion were not available in this data set, and some of these are known to be important prognostic factors.[34,35] Furthermore, we would have liked to include additional patient characteristics, such as medical comorbidities and performance status, but these data were also not available. Finally, in the future, tumor molecular information such as epidermal growth factor or TP53 receptor status will likely play a prominent role in predictive nomograms.

Despite these limitations, our new updated OCSCC nomogram represents a substantial improvement over the previous version[4] because it can quantify the expected improvement in locoregional recurrence with the addition of postoperative radiotherapy. Such information can be helpful when making adjuvant therapy decisions for patients with resected OCSCC. Recently there has been a movement toward "personalized medicine," in which specific information about an individual patient is used to optimize the patient's care. We believe that these types of predictive models will become increasingly impor-

tant in the future as we attempt to improve outcomes by individualizing therapeutic recommendations.

In conclusion, we have built an interactive prediction model for OCSCC that can make an individualized estimate of locoregional recurrence with and without adjuvant radiotherapy. This tool can assist clinicians and patients with decision making about postoperative therapy for patients with OCSCC.

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