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Nomogram for Predicting Survival for Oral Squamous Cell Carcinoma

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Abstract

An accurate system for predicting the survival of patients with oral squamous cell carcinoma (OSCC) will be useful for selecting appropriate therapies. A nomogram for predicting survival was constructed from 96 patients with primary OSCC who underwent surgical resection between January 1994 and June 2003 at the Yonsei Dental Hospital in Seoul, Korea. We performed univariate and multivariate Cox regression to identify survival prognostic factors. For the early stage patients group, the nomogram was able to predict the 5 and 10 year survival from OSCC with a concordance index of 0.72. The total point assigned by the nomogram was a significant factor for predicting survival. This nomogram was able to accurately predict the survival after treatment of an individual patient with OSCC and may have practical utility for deciding adjuvant treatment.

Keywords: c-index, nomogram, oral squamoue cell carcinoma, predictive model, survival

Introduction

Oral cancer is the sixth most common cancer in men and the twelfth most common cancer in women (Sudbo and Reith, 2005). According to statistics from 1999 to 2002, the annual incidence rate of oral cancer is 5.9% in men and 2.2% in women in South Korea (based on data from the National Cancer Center in Korea). The approximately 90% of oral is squamous cell carcinoma (Pisani *et al.*, 1999). Patients with oral squamous cell carcinoma (OSCC) are often asymptomatic, but may experience minimal pain in the early stage (Epstein *et al.*, 2007). Despite the availability of advanced clinical diagnostic systems, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT) imaging and improved therapy, the overall 5-year survival rates of OSCC over the past two decades are still poor (Myoung *et al.*, 2006). Therefore, it is necessary to develop novel prognostic tools for predicting the OSCC patients' status, which could improve survival by allowing enough time for the appropriate therapy to be implemented.

Stephenson *et al.* (2005) showed that the prediction accuracy was improved by the integration of clinical variables and gene expression (Stephenson *et al.*, 2005b). It has already been shown that the expression level of specific genes influence survival. Specific protein expression was used to predict survival in various cancers including clear cell renal carcinoma (Kim *et al.*, 2004). The relationship between p53 and the survival in OSCC has been studied by many researchers (Galli *et al.*, 2009; Goulart *et al.*, 2009; Shah *et al.*, 2009; Smith *et al.*, 2009). In these studies, some reported that p53 predicted the survival of OSCC (Galli *et al.*, 2009; Shah *et al.*, 2009) while others did not (Goulart *et al.*, 2009; Smith *et al.*, 2009), and Smith *et al.* (2009) concluded that p53 does not predict the progression of OSCC after an extensive review of the previous studies.

In this study, significant clinical factors for predicting survival were identified and a nomogram was constructed using these factors. In addition, we evaluated the effect of p53 on the survival of OSCC patients, by embedding it into the nomogram. The created nomogram was evaluated by c-index.

Nomogram is a graphical representation of a statistical model and provides the probability of a particular clinical outcome, such as death or recurrence (Kattan *et al.*, 1998). It has been constructed for predicting survival in prostate cancer (Kattan *et al.*, 1999; Stephenson *et al.*, 2005a), vulvar cancer (Rouzier *et al.*, 2006), osteosarcoma (Kim *et al.*, 2009), renal cancer (Karakiewicz *et al.*, 2007), breast cancer (Rouzier *et al.*, 2005), and advanced Non-Small-Cell Lung cancer (Hoang *et al.*, 2005). Furthermore, nomograms have been shown to be superior to the traditional staging systems in predicting the features of various cancers (Hoang *et al.*, 2005; Karakiewicz *et al.*, 2007; Kattan *et al.*, 1999; Kim *et al.*, 2009; Rouzier *et al.*, 2006; Rouzier *et al.*, 2005; Stephenson *et al.*, 2005a).

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Methods

Patients

We retrospectively investigated 96 patients (71 men and 25 women) with primary OSCC who underwent surgical ablation between January 1994 and June 2003 at the Yonsei Dental Hospital in Seoul, Korea.

The tumor location was the tongue in 26 cases, gingiva in 56 cases, and other sites in 14 cases, which included the buccal cheek, floor of mouth and lower lip. The pathological stage was divided into two groups, early and advanced. The I and II stages were grouped into the early group, and the III and IV stages were grouped into the advanced group. The pathologic (pTMN) classification and staging were classified according to the 6^{th} edition of AJCC (American Joint Committee on Cancer).

Immunohistochemical staining

Immunohistochemical staining for p53 was performed using an EnVision-HRP detection system (Dako, Carpinteria, CA, USA). The primary antibody was the p53 monoclonal antibody, which specifically stained p53 (Dako). Sections (3 μm thick) were cut from tumor tissue blocks mounted on slides and sections were dried for 1-2 hours at 56°C. Briefly, sections were deparaffinized in xylene and were rehydrated in graded alcohol. After antigen retrieval by the addition of citrate buffer (pH, 6.0) with the use of an autoclave at full power for 4 min, tissue sections were treated with 3% hydrogen peroxide for 10 min to block endogenous peroxidase. Sections were incubated with p53 (1:50) in a humid chamber overnight at 4°C.

Slides were then incubated with Envision reagent followed by incubation with Diaminobenzidine (DAB) chromogen, slides were counterstained with Mayer's hematoxylin, and then mounted. All of the stained sections were imaged by a light microscope.

Immunohistochemical analysis

Immunohistochemical staining was evaluated by an investigator who did not know the clinicopathological characteristics or the clinical outcome of the patients. Specimens were considered positive for staining when the tumor cells had dark brown nuclei, and specimens were considered negative for staining when the tumor cells had only blue nuclei. The percentage of stained tumor cells was graded using a four-point scale (0, +1, +2, +3, +4) as follows: 0, none of the tumor cells were stained; +1, ≤25% of the tumor cells were stained; +2, 25% to ≤50% of the tumor cells were stained; +3, 50% to ≤75% of the tumor cells were stained; +4, >75% of tumor cells were stained. The intensity was divided into negative, weak, moderate and strong (0, +1, +2, +3).

Histological grading

OSCC tissue specimens were subjected to routine hematoxylin and eosin (H & E) staining. Specimens were graded into well (G1), moderately (G2) and poorly (G3) differentiated squamous cell carcinomas using the World Health Organization (WHO) grading system. Thirty-one cases were well differentiated, 49 cases were moderately differentiated, and 16 cases were poorly differentiated.

Statistical analysis

The relationships between the clinical factors were tested using the Chi-square statistic. Univariate and multivariate analyses were performed to assess the effects of various factors on the prediction of survival. The Cox proportional hazard model was used to perform the multivariate analysis.

Nomogram for the prediction of survival of OSCC patients was created with the selected significant variables and evaluated by the concordance index (c-index). Calibration was assessed by plotting the predicted versus the actual probability. All statistical analyses were performed using R with the Design, eha and Hmisc libraries.

Results and Discussion

The clinical features and p53 expression of the 96 patients used in this study are summarized in Table 1. They underwent surgical resection between January 1994 and June 2003 at the Severance Hospital in Seoul, Korea. The association of clinical factors and pathological groups was shown using p-values from chi-square test in Table 1.

Tumor site, LN metastasis and T stage were significantly and differentially distributed between the early and advanced groups. The outcome pattern was also significantly different. This result indicated that early and advanced groups have different clinical characteristics; therefore, the predictive model should be identified for each stratified groups. In regards to tumor sites, 32.5% of gingiva was in the early stage while 77% was in the advanced group. Lymph node metastasis was not observed in the early group while over 60% was in the ad-

Table 1. Characteristics of patients with OSCC (N=96)

Clinical variables	Patients (n=96)	Early stage (n=40)	Advanced stage (n=56)	p-value (Early vs. Advanced)
Age				
＜60	42 (56%)	16 (40%)	26 (46%)	
≥60	54 (44%)	24 (60%)	30 (54%)	0.6764
Sex				
Female	25 (26%)	9 (22.5%)	16 (29%)	
Male	71 (74%)	31 (77.5%)	40 (71%)	0.6654
LN metastasis (n=73)				
N (−)	62 (65%)	40 (100%)	22 (39%)	
N (+)	34 (35%)	0 (0%)	34 (61%)	3.304e-09
Tumor site				
Gingiva	56 (58%)	13 (32.5%)	43 (77%)	
Tongue	26 (27%)	18 (40%)	8 (14%)	
Other	14 (25%)	9 (22.5%)	5 (9%)	7.793e-05
Histopathologic grade				
G1	31 (32%)	13 (32.5%)	18 (32%)	
G2	49 (51%)	22 (55%)	27 (48%)	
G3	16 (17%)	5 (12.5%)	11 (20%)	0.6295
Distant metastasis				
No	89 (92%)	37 (92.5%)	52 (93%)	
Yes	7 (8%)	3 (7.5%)	4 (7%)	0.74
Pathologic stage (P stage)				
Early	40 (42%)	40 (100%)	0 (0%)	
Advanced	56 (58%)	0 (0%)	56 (100%)	NA
T stage				
T1	19 (20%)	16 (40%)	3 (5.5%)	
T2	33 (34%)	24 (60%)	9 (16%)	
T3	23 (24%)	0 (0%)	23 (41%)	
T4	21 (22%)	0 (0%)	21 (37.5%)	1.127e-12
p53				
−+	37 (39%)	26 (60%)	32 (57%)	
++ +++	59 (61%)	14 (40%)	24 (43%)	0.3755
Disease outcome				
Survived	45 (47%)	24 (60%)	21 (37.5%)	
Dead	51 (53%)	16 (40%)	35 (62.5%)	0.04878

vanced group.

The primary end point was survival time. The free-survival interval was defined as the time between the date of surgery to the last visit or the date when the patient died. Univariate and multivariate analyses were carried out to identify the characteristics associated with survival. Table 2 shows the results of the univariate and multivariate Cox regression analysis for the whole dataset.

P stage and LN metastasis were significant factors in the univariate analysis and no significant factors were identified in the multivariate analysis. Therefore, it would be desirable to construct a predictive model separately using the P stage. It would also be possible to construct separate models using LN metastasis, because LN metastasis was shown to be a significant factor in the univariate analysis.

To explore the association of p53 expression with other clinical factors, a chi-square test was performed. The results were summarized in Table 3.

From Table 3, p53 was shown to not be significantly associated with any clinical factors in the whole dataset and advanced group, and it was only significantly associated with the Tumor Site in the early group. These results indicated that p53 can be a novel and independent predictor in the prediction model. In the separate analysis of the early and advanced groups, LN metastasis had only one category, 'negative', in the early group; therefore, we excluded this variable from the model (Table 4).

No significant factors were identified in the advanced group. However, Grade was significant and p53 was shown to be slightly significant in the early group, even though the p-value was only marginally larger than 0.05. Therefore, we constructed a nomogram for the early stage of OSCC.

Table 2. Univariate and multivariate analysis using the whole dataset (n=96)

Variables	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
LN metastasis				
− : +	1.90 (1.10, 3.3)	0.0225	1.27 (0.50, 3.20)	0.619
Histopathologic Grade				
G1 : G2	0.84 (0.44, 1.59)	0.591	0.82 (0.41, 1.64)	0.566
G3 : G2	1.23 (0.58, 2.60)	0.350	1.66 (0.74, 3.74)	0.133
Distant Metastasis				
N : Y	0.44 (0.11, 1.80)	0.250	0.32 (0.07, 1.57)	0.160
P stage				
early : advanced	0.54 (0.3, 0.98)	0.044	0.89 (0.20, 3.26)	0.861
Tumor site				
Tongue : gingiva	0.72 (0.36, 1.44)	0.359	1.09 (0.47, 2.53)	0.837
Other : gingiva	1.14 (0.54, 2.40)	0.732	1.99 (0.79, 5.03)	0.145
T stage				
T1 : T2	0.62 (0.25, 1.57)	0.3147	0.66 (0.25, 1.74)	0.401
T3 : T2	1.09 (0.53, 2.25)	0.2655	1.53 (0.48, 4.88)	0.243
T4 : T2	1.77 (0.88, 3.56)	0.1333	2.08 (0.73, 5.89)	0.098
p53				
−+:++ +++	1.26 (0.73, 2.20)	0.409	1.58 (0.84, 2.99)	0.150

Table 3. Relationship between p53 & clinical characteristics

Variables	p53		p-value		
	− + (n=37)	++ +++ (n=59)	Whole data set (n=96)	Early (n=40)	Advanced (n=56)
LN matastasus (N=73)					
n (−)	27 (73%)	35 (59%)	0.2535	NA	0.5495
n (+)	10 (27%)	24 (41%)			
Tumor site					
Gingiva	23 (62%)	33 (56%)			
Tongue	10 (27%)	16 (27%)	0.6911	0.01633	0.4086
Other	4 (11%)	10 (17%)			
Histopathologic grade					
G1	15 (41%)	16 (27%)			
G2	17 (46%)	32 (54%)	0.3802	0.1794	0.4652
G3	5 (13%)	11 (19%)			
Distant metastasis					
No	35 (95%)	54 (92%)	0.8732	0.3051	0.8756
Yes	2 (5%)	5 (8%)			
P stage					
Early	18 (49%)	19 (32%)	0.3755	NA	NA
Advanced	19 (51%)	37 (68%)			
T stage					
T1	7 (19%)	12 (20%)			
T2	15 (41%)	18 (31%)	0.6654	0.8457	0.4697
T3	9 (24%)	14 (24%)			
T4	6 (16%)	15 (25%)			

A nomogram predicting the 5-year and 10-year survival with clinical factors and p53 expression was constructed for the early group (Fig. 1). Metastasis was excluded from the model identification because it was highly unbalanced between the two categories (Y and N).

The C-index was 0.72 in the nomogram for the early group and p53 was not an influential factor in prediction

Table 4. Multivariate Cox regression for early stage (n=40) and advanced stage (n=56)

Variables	Early stage		Advanced stage	
	HR (95% CI)	p	HR (95% CI)	p
LN metastasis				
− : +	NA	NA	0.55 (0.21, 1.42)	0.2139
Histopathologic grade				
G1 : G2	0.24 (0.06, 0.94)	0.0392	1.72 (0.73, 4.03)	0.2135
G3 : G2	6.56 (1.22, 35.40)	0.0016	1.37 (0.50, 3.71)	0.6838
Distant merastasis				
Y : N	0.51 (0.05, 5.52)	0.57808	0.38 (0.05, 3.14)	0.3694
Tumor site				
Tongue : gingiva	1.20 (0.33, 4.33)	0.7825	1.30 (0.42, 4.08)	0.6486
Other : gingiva	3.32 (0.76, 14.59)	0.1589	3.26 (0.87, 12.21)	0.0797
T stage				
T1 : T2	0.41 (0.11, 1.54)	0.18639		
T1 : T3			0.24 (0.03, 1.87)	0.3005
T2 : T3			0.66 (0.19, 2.29)	0.1721
T4 : T3			1.44 (0.57, 3.65)	0.0805
p53				
−+ : ++ +++	2.66 (0.87, 8.11)	0.08570	1.30 (0.59, 2.85)	0.5174

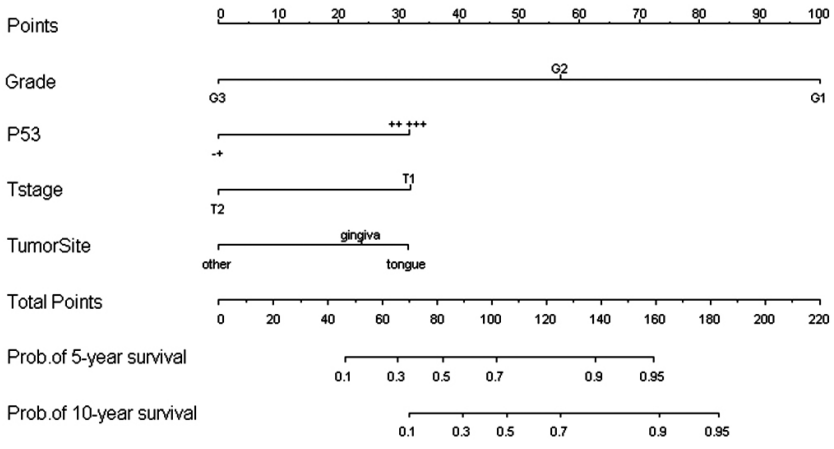

Fig. 1. Nomogram for predicting the 5-year and 10-year survival after surgery on OSCC patients.

even though it was slightly significant in the multivariate analysis. The nomogram operates by summing the points of each independent covariate. The probabilities of 5-year and 10-year survival are identified by the calculated total point (Fig. 2).

Fig. 2 shows that the probability of free-survival increased as the total points increased. For example, if the total point was 140 for a patient, the probabilities of 5 and 10 year survival would be 90% and 78%, respectively. We also investigated if the total point calculated by the nomogram would be a novel predictor. The mean of total points assigned by the nomogram was 116.5 and we stratified patients into two groups using this value. The sample size for the early stage was 40, which was not sufficient to identify subsets; however, we examined if the total points derived from the nomogram could significantly classify the survival of OSCC. For this, the Kaplan-Meier survival curve was plotted and the Log-Rank test was performed (Fig. 3).

Fig. 3 shows the stratification of the survival curves based on total points assigned by the nomogram, and those curves were significantly different (p-value < 0.05). This p-value should be considered as a measure of curve separation. Based on the results shown in Figure 3, the total point calculated by nomogram could be a combined marker for predicting survival.

The nomogram can be a model in which known prognostic factors can be combined and used for risk prediction in cancer (Bianco, 2006). One advantage of nomograms is that they are weighted models comprised

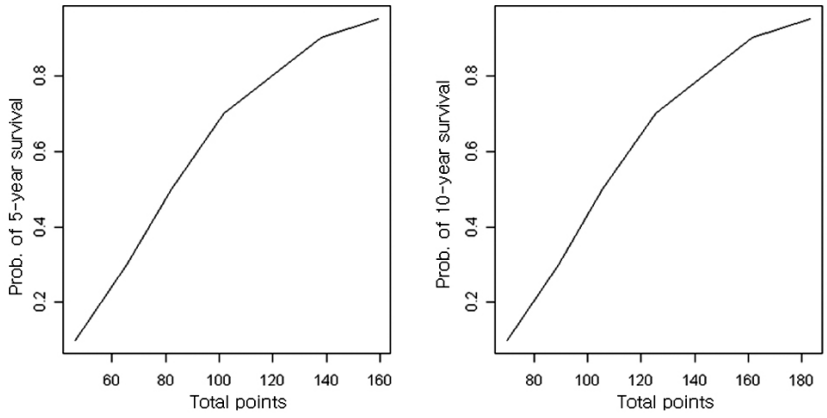

Fig. 2. The relationship between the total point derived from the nomogram and the probabilities of 5-year and 10-year survival.

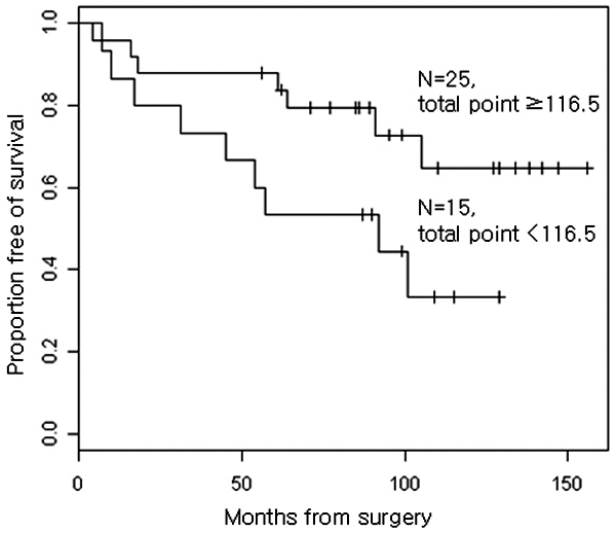

Fig. 3. Kaplan-Meier survival curves based on stratification using the total points assigned by the nomogram. The p-value comparing curves using Log rank test was less than 0.05 (Chi-square statistic was 3.9).

of independent prognostic factors, which provide an appreciation of the magnitude of impacts of individual factors on outcome probability (Kim *et al*., 2009). An accurate survival prediction model would be useful for patient counseling, planning follow-up, and selecting patients for additional treatment (Kim *et al*., 2004).

The data set that was used in this study had significantly different characteristics between early and advanced stages. In this case, identification of the predictable model for each stratified groups could be more reliable. In addition, no significant factors were detected in the advanced group when we performed multivariate analysis for each groups. Therefore, we developed and validated a nomogram for predicting 5-year and 10-year survival probability of OSCC patients in the early stage that underwent surgical resection. The nomogram predicts the probability of survival with a concordance index of 0.72.

In this study, grade was found to be a key prognostic factor in the early stage group, while it was not significant in the advanced group. p53 was slightly significant in the early stage (p=0.0857), which was previously shown not to be able to predict the progression of OSCC (Smith *et al*., 2009). However, we included p53 in the predictive model when constructing the nomogram, and explored the influence of p53. In this analysis, p53 was shown to be significant in the nomogram, and its high expression was correlated with the increased probability of survival even though it did not improve the c-index.

To evaluate the constructed nomogram, we determined whether the total points calculated by the nomogram could be used as a predictive factor, besides the c-index. The mean value of the total points was 116.5, and we divided patients into two groups using this value. A new marker based on the total points was determined to be a significant factor in the survival model ($p < 0.05$). Therefore, a factor based on the total points can be a novel predictive marker. In addition, the randomization of patients in clinical trials by composite risk factors specific to OSCC would be possible using the nomogram.

This nomogram would be a useful tool for physicians who have to make decisions in the diagnosis of OSCC patients. For example, a patient with high expression of p53, G2 and T2 stage squamous cell carcinoma of the oral tongue is predicted to have a 79.8% and 60.7% probability of 5-year and 10-year survival, respectively. If the physicians can accurately estimate the probability of survival, they could be able to improve the life of patients by choosing more appropriate treatment.

In this study, we constructed a predictive nomogram for the early stage of OSCC, based on a sample size

of 40. This sample size may not be large enough to construct a predictive model. In addition, there might be more variables that we did not include in the model. However, this is the first prognostic nomogram developed to predict the survival of Korean patients. The constructed nomogram could be improved with more data and by including biological candidates in the predictive model.

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