

# Validation of a multifactorial risk assessment system in a homogeneous group of early oral tongue carcinomas

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## Abstract

**Objective:** This study aims to validate the prognostic performance of the Brandwein-Gensler histologic risk assessment system in a homogeneous cohort of early-stage oral tongue squamous cell carcinomas (SCC). Specifically, it evaluates the system's ability to predict overall survival and the presence of occult metastases.

**Materials and Methods:** A total of 72 patients with early-stage (T1–T2) oral tongue SCC were retrospectively analyzed. Sixty of these cases were classified using the Brandwein-Gensler risk system, which considers three histologic parameters: worst pattern of invasion (WPOI), lymphocytic host response (LHR), and perineural invasion (PNI). Overall survival (OS) was assessed using Kaplan-Meier and Cox regression analysis. The system's prognostic accuracy was tested using receiver operating characteristic (ROC) analysis. Correlations with occult metastases were also examined.

**Results:** Statistically significant differences in OS were observed between risk groups ( $p = 0.01$ ), with high-risk patients exhibiting a threefold increased mortality risk ( $p = 0.012$ ). The ROC analysis demonstrated moderate discriminatory power ( $AUC = 0.702$ ). However, the system did not show a statistically significant correlation with the development of occult metastases ( $p = 0.49$ ).

**Conclusion:** The Brandwein-Gensler system is a valid prognostic tool for overall survival in early-stage oral tongue SCC, successfully identifying patients at increased risk of death. Its role in predicting occult metastases remains inconclusive and warrants further investigation.

**Keywords:** oral tongue cancer, squamous cell carcinoma, histologic risk model, Brandwein-Gensler, prognosis, survival, occult metastasis

## Introduction

Squamous cell carcinoma (SCC) of the oral tongue is the most common malignancy among intraoral subsites of oral cavity tumors (11,2,13). Clinical experience indicates that tumors at this location often demonstrate aggressive biological behavior (11,2,13). The T category at the time of diagnosis is an independent prognostic factor for cervical metastasis and overall survival (21).

However, aggressive tumor behavior is occasionally observed even in patients with small primary lesions.

In an effort to better predict and assess tumor aggressiveness, multiple histopathological grading systems and prognostic models have been developed over the years (6,12,14,1,10,7,8,19,16,5,4).

In 1920, Broders (6) introduced the concept of histological grading for malignant tumors based on cellular differentiation. This work laid the foundation for further classifications. Over time, various histological scoring systems have been proposed for oral SCC, including those by Eneroth (1972) (12), Jakobson (1973) (14), Crissman et al. (1984) (10), Anneroth (1987) (1), Bryne et al. (1989) (8,7), and Woolgar et al. (1995) (19).

In 2005, Brandwein-Gensler et al. (4) proposed a histologic risk assessment model that stratifies patients into low-, intermediate-, and high-risk categories based on well-established histopathologic features. The system incorporates three main parameters: perineural invasion, host lymphocytic response, and the pattern of invasion at the tumor-host interface. (Table 1.)

**Table 1. Brandwein-Gensler et al. (3), Histologic Risk Assessment System**

Variable		Score
WPOI	WPOI 1	0
	WPOI 2	0
	WPOI 3	0
	WPOI 4	1
	WPOI 5	3
Lymphoplasmacytic Infiltrate	Intense	0
	Moderate	1
	Mild	3
Perineural Invasion	Absent	0
	Involving small nerve fibers	1
	Involving large nerve fibers	3

Unlike the linear scoring systems proposed by Jakobson (14) and Bryne et al. (8,7), the Brandwein-Gensler model is non-linear. The most unfavorable histological features are weighted more heavily—assigned 3 points rather than 2—to reflect the disproportionately increased risk associated with WPOI 5, perineural invasion of large-caliber nerves, and absence of host lymphocytic response (4,3). This model was the first histologic risk system validated specifically for early-stage oral cancers (15).

## Aim

The aim of this study was to evaluate the prognostic utility of the Brandwein-Gensler histologic risk assessment system in a homogenous cohort of patients with early-stage squamous cell carcinoma of the oral tongue. Specifically, we sought to determine its predictive value for mortality and occult metastasis.

## Material and Methods

A cohort of 72 cases of early-stage oral tongue SCC was analyzed. All cases were diagnosed and treated at the Department of Maxillofacial Surgery, University Hospital “Alexandrovska.” Patients with clinical staging cT3 and cT4 or those who had received preoperative radiotherapy or chemoradiotherapy were excluded. Only cases meeting the criteria for early-stage tumors (T1 and T2) were included.

Out of 116 patients initially evaluated for oral tongue carcinoma, 72 met the inclusion criteria, and of these, 60 were successfully classified according to the Brandwein-Gensler scoring system (4). The cohort consisted of 43 males (59.7%) and 29 females (40.3%). Tumor localization was on the lateral border in 53 cases (73.6%), ventral tongue in 17 (23.6%), and dorsal tongue in 2 (2.8%).

Histopathologic diagnosis and tumor morphology were reviewed and confirmed by pathologists at the Department of General and Clinical Pathology, University Hospital “Alexandrovska.” Missing or ambiguous data were reviewed and updated. All tumors were scored using the Brandwein-Gensler model. A cumulative risk score and risk category were assigned to each case. Due to lack of precise data on nerve diameter, all cases with perineural invasion were conservatively scored with 3 points.

Statistical analysis was performed using SPSS software. Overall survival was evaluated using Kaplan–Meier analysis, with comparisons made via the log-rank test and Cox regression. The predictive value of the scoring system was assessed via ROC curve analysis and AUC calculation.

## Results

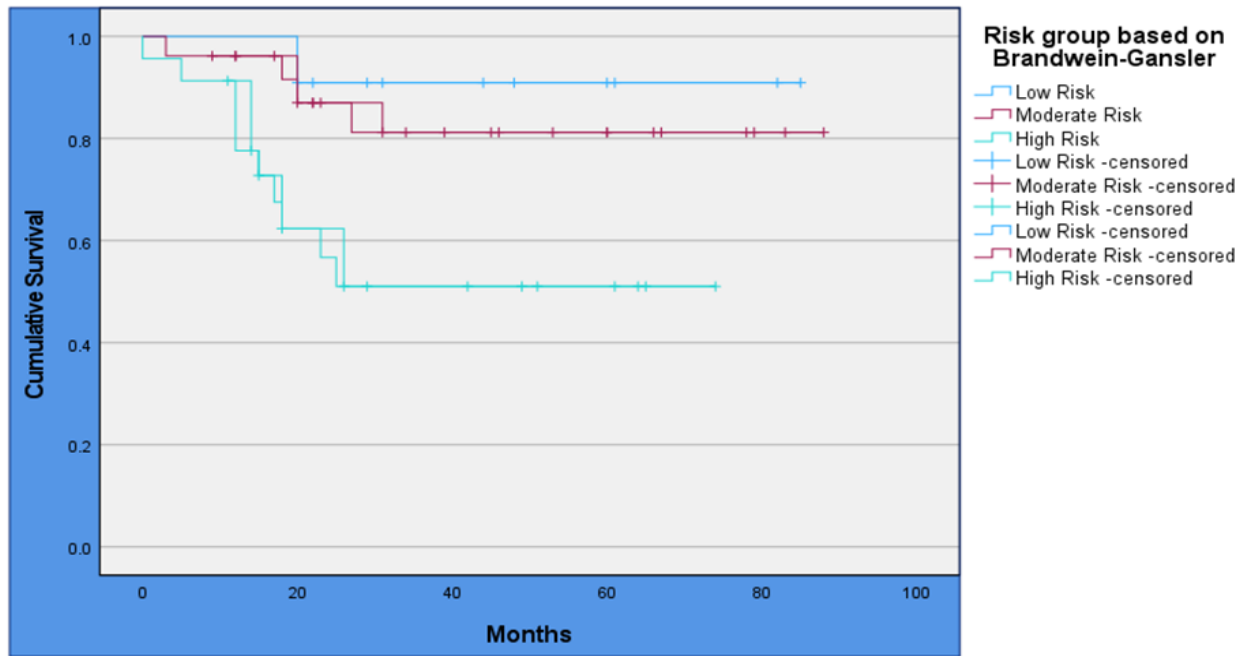
Among the 60 evaluated patients, 15 deaths were recorded, while 45 patients remained censored (survived through the follow-up period). The proportion of censored cases ranged from 56.5% in the high-risk group to 90.9% in the low-risk group. (Table 2.)

**Table 2. Overall Survival Assessment According to Risk Category (Brandwein-Gensler) – Kaplan-Meier Method**

Risk Category (Brandwein-Gensler)	Total (n)	Deaths	Survivors	Mean Survival	95% CI	Log-rank
Low risk	11	1	10 (90.9%)	79.1 months	68.0-90.1	$\chi^2 = 8.56$ p = 0.01
Moderate risk	26	4	22 (84.6%)	74.9 months	63.2-86.6	
High risk	23	10	13 (56.5%)	44.9 months	31.7-58.1	
Total	60	15	45 (75.0%)	67.4 months	58.5-76.3	

A statistically significant difference in survival was observed across risk groups (p = 0.01). (Figure 1.)

**Figure 1. Kaplan–Meier Survival Curves According to Risk Category Based on the Risk Assessment System Proposed by Brandwein-Gensler**



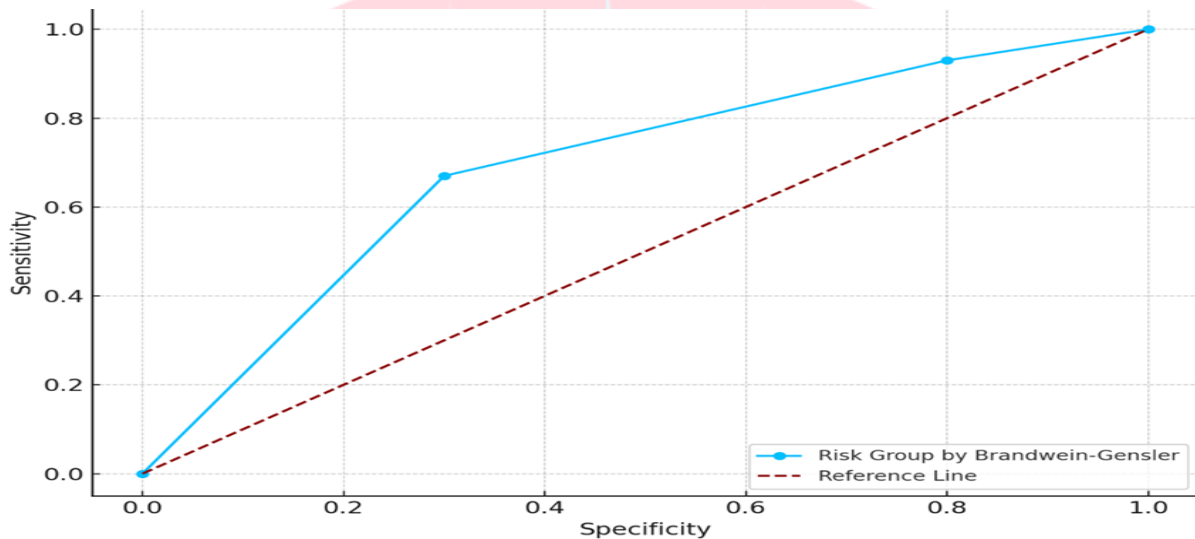
Kaplan–Meier curves demonstrated significantly reduced survival among patients classified in the high-risk category.

Univariate Cox regression analysis revealed that patients in higher risk categories had approximately a threefold increased risk of mortality compared to those in lower categories ( $p = 0.01$ ). (Table 3)

**Table 3. Univariate Cox Regression Analysis According to Risk Group Based on the Brandwein-Gensler System**

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI
Risk Group Based on Brandwein-Gensler	1.121	.446	6.317	1	.012	3.068	1.28- 7.35

ROC analysis demonstrated an area under the curve (AUC) of 0.702, indicating moderate discriminatory power in distinguishing between patients with high and low risk of mortality. (Figure 2.)

**Figure 2. ROC Curve of Risk Groups According to Brandwein-Gensler System**

From the results related to the prognostic value of the Brandwein-Gensler system with regard to the development of occult metastases, a weak positive correlation was observed ( $r = 0.11$ ), though not statistically significant. Despite differences in the distribution of occult metastasis across risk groups, these variations did not reach statistical significance. (Table 4.)

**Table 4. Correlation Analysis of the Prognostic Value of the Brandwein-Gensler Risk Assessment System for the Development of Occult Metastases**

Brandwein-Gensler Risk System	No Occult Metastases	Occult Metastases Present	$\chi^2$ test	Likelihood Ration	Pearson	Spearman
Low risk	9	2	$\chi^2 = 1.42$ ; $p = 0.49$	LR = 1.40 $p = 0.49$	R = 0.11 $p = 0.44$	R = 0.12 $p = 0.41$
Moderate risk	20	3				
High risk	13	5				
Total	42	10				

## Discussion

Over the past several decades, numerous efforts have been made to develop precise and easily applicable systems for risk assessment in patients with oral cavity carcinoma. The system proposed by Brandwein-Gensler et al. is one such example, incorporating key histopathological features—perineural invasion, worst pattern of invasion (WPOI), and lymphoplasmacytic infiltrate (4). Our study aimed to validate the prognostic value of this risk assessment system for mortality and the development of occult metastases in a homogenous group of early-stage oral tongue carcinomas. Our results demonstrate a statistically significant difference in overall survival among the different risk categories defined by the system ( $p = 0.014$ ). The risk of death increases approximately

threefold with each higher risk category ( $p = 0.012$ ). These findings are consistent with the study by Brandwein-Gensler et al. (3), in which a statistically significant difference in overall survival was observed when the model was validated in a cohort of early-stage head and neck tumors ( $p = 0.024$ ). Similar results were reported by Thakur et al. (17), who found that the high-risk category was predictive of both overall and disease-specific survival in oral carcinoma. The system effectively distinguishes risk in both advanced and early oral cavity tumors (9).

The ROC analysis we performed demonstrated that the system has moderate discriminatory ability in distinguishing patients at high versus low risk of death ( $AUC = 0.702$ ). This suggests that the histologic risk assessment model proposed by Brandwein-Gensler provides better discriminatory power regarding mortality than the current TNM classification. Similar conclusions were drawn by Thakur et al. (17), who emphasized that the system offers prognostic information comparable to the TNM system. According to these authors, combining the TNM classification with the histologic risk model enhances prognostic accuracy.

Several authors conducting cohort studies on oral carcinoma have found statistically significant associations between the high-risk category—according to the histologic model—and the risk of disease recurrence (Vared et al. (20),  $p = 0.011$ ; Chaturvedi et al. (9),  $p = 0.02$ ; Thakur et al. (17),  $p = 0.001$ ). In our cohort, the system did not reach statistical significance in predicting the risk of developing occult metastases. This may be attributed to the relatively small number of cases with occult nodal involvement, which limits the statistical power of the analysis.

## Conclusion

Our study validates the histologic risk assessment system proposed by Brandwein-Gensler et al. (4) in a homogenous cohort of early-stage tongue carcinomas. The system demonstrated prognostic value for survival, successfully identifying high-risk cases for mortality. In our group, however, the system did not reach statistical significance in predicting the risk of metastasis.

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