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# Scoring the future under microscope: Predicting early-stage oral squamous cell carcinoma recurrence with histological markers

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## ABSTRACT

**Introduction:** Oral squamous cell carcinoma (OSCC) is the sixth most common cancer globally. Despite advances in therapeutic modalities, improvements in mortality and morbidity remain limited in early-stage OSCC. This variability in prognosis is due to the tumors biological heterogeneity and challenges in accurately predicting loco-regional recurrence (LRR).

**Objectives:** The objective of the study is to evaluate the influence of the parameters that are included in Brandwein-Gensler (BG) risk model, i.e., lymphovascular invasion (LVI), lymph node metastasis, and depth of invasion (DOI) in predicting LRR in early-stage cases.

**Materials and Methods:** A retrospective analysis was conducted on patients diagnosed with early-stage (T1/T2) OSCC over a 5-year duration who underwent primary surgical resection and had complete follow-up data available. Histopathological parameters were assessed using hematoxylin and eosin-stained sections, and BG risk score was applied based on standard criteria.

**Statistical analysis:** Statistical analysis was done using Chi-square test and Fisher exact test where count is less than 5. Software used to conduct statistical analysis were MS Excel, and SPSS version 26, and $P < 0.05$ was considered to indicate statistical significance.

**Results:** A total of 101 cases were included in this study, out of which 34 cases (33.67%) showed recurrence. Among evaluated parameters, LVI ($P = 0.004$), perineural invasion (PNI) ($P < 0.001$), worst pattern of invasion (WPOI) ($P < 0.001$), DOI ($P < 0.001$), lymphocytic host response (LHR) ($P < 0.001$), and risk score ($P < 0.001$) were found to be statistically significant predictors of LRR.

**Conclusions:** The integration of histopathological factors such as LVI, PNI, WPOI, and LHR, particularly when evaluated using BG risk model, offers a valuable framework for identifying high-risk patients. Routine incorporation of this scoring system into initial diagnostic assessment can enhance prognostication and inform the selection of candidates for post-surgical adjuvant therapy, ultimately improving patient management and outcomes in early-stage OSCC.

**Keywords:** Brandwein-Gensler risk model, Early stage, Lymphocytic host response, Oral cavity squamous cell carcinoma, Recurrence

## INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the sixth most common type of cancer in the world, with a total of around 575,000 cases/year. In India, 40% of the total cancer cases are of oral cancer,

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and it is also a major cause of death.[1] Incidence of oral cancer in Kolar is 29.66% of the total cancer incidence.[2,3]

Although there have been many recent advancements in treatment, mortality and morbidity rates have remained high over the past few decades. Poor prognosis of OSCC is attributed to its early metastasis, poor sensitivity to chemotherapeutic agents, and its aggressive behavior.[1]

Early-stage OSCC, which includes T1 and T2 cases, is managed with primary resection followed by nodal dissection, with positivity of margins being the key factor for prognosis. However, due to the variable prognosis of these tumors, many patients experience the loco-regional recurrence (LRR), leading to shorter disease-free survival (DFS) and higher mortality.[4]

The current treatment guidelines for OSCC recommend surgical resection. The latest (8$^{th}$ edition) American Joint Committee on Cancer (AJCC) classification now includes depth of invasion (DOI) and extranodal extension (ENE) in its staging system. According to these criteria, every 5 mm increase in DOI up to ≥10 mm raises the T category by one level, while the presence of pathologic ENE upgrades the nodal category by one level.

The Brandwein-Gensler (BG) risk model, introduced in 2005, assesses histologic risk based on three key factors: Worst pattern of invasion (WPOI), lymphocytic host response (LHR), and perineural invasion (PNI), to predict the recurrence.[5] The BG risk model given in Table 1 shows the scoring pattern for the 3 parameters and their sum is taken as the total score. A total score of 3 or higher indicates high risk, while 1-2 signifies intermediate risk, and a score of 0 represents low risk.[4,10]

### Objectives

To evaluate the influence of the three parameters used in BG risk model, i.e., (1) lymphovascular invasion (LVI), (2) lymph node metastasis, and (3) DOI to predict LRR in early-stage cases.

## MATERIALS AND METHODS

This was a laboratory-based observational study performed on 101 cases of patients with histopathologically confirmed early-stage OSCC patients who were classified as T1 and T2 cases, classified as per the 8$^{th}$ edition of AJCC, and who were treated by surgical resection and had follow-up data for 5 years.

### Inclusion criteria

Early-stage T1/2 OSCC patients with follow-up data were included.

### Exclusion criteria

Late stage (T3/T4) OSCC patients, patients on neoadjuvant chemo and radiotherapy, and patients with no follow-up data were excluded.The demographic parameters, such as sex and age, were recorded from the records department and from the archives. Hematoxylin and eosin (H&E)-stained slides were taken from archives, and the risk score was calculated using the BG risk model. Histological parameters such as grade, DOI, WPOI, PNI, LHR, LVI, lymph node metastases, and pathological stage in cases showing recurrence were reviewed and documented. The pathologist conducting the scoring was blinded to patient outcomes and clinical data variables. LRR was evaluated depending on whether there was recurrence of OSCC at the original site or in the remaining lymph nodes. Figures 1 and 2 show gross images of T1 and T2 OSCC cases, respectively.

**Figure 1:** Gross image of T1-oral squamous cell carcinoma case.

**Figure 2:** Gross image of T2-oral squamous cell carcinoma case. Red arrow depicts the tumor growth.

Tumors classified as WPOI-1, WPOI-2, or WPOI-3 were given a score of 0, as they are considered nonaggressive.[5] These tumors can display broad pushing borders, finger-like projections, or large separated islands (>15 cells per island), but they are not thought to extend beyond the tumor's perimeter. WPOI-4 is characterized by small, discontiguous tumor islands (≤15 cells per island) that are clearly separated from the main tumor mass. WPOI-5 reflects a more aggressive, dispersed growth pattern, with tumor spread exceeding that of WPOI-4, specifically defined by a separation distance of more than 1 mm. Figures 3-7 show microphotographs of different patterns of invasion.

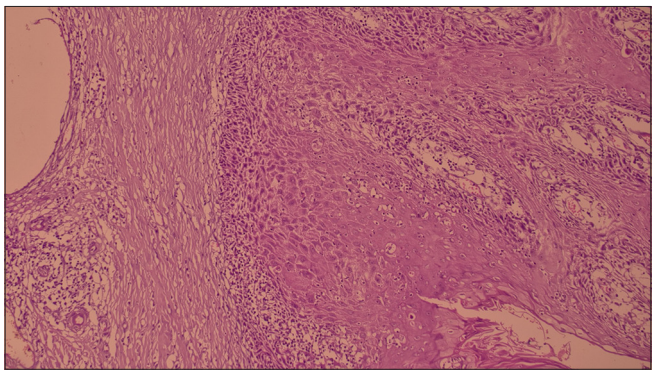

**Figure 3:** The worst pattern of invasion 1. (H&E, x400), Black arrow shows the pushing border of the tumor.

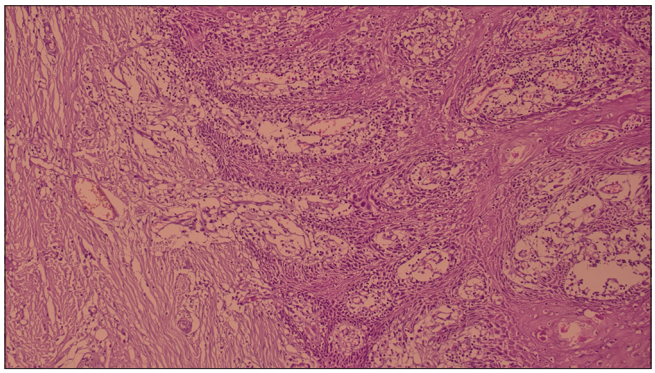

**Figure 4:** The worst pattern of invasion 2. (H&E, x400), Black arrow showing the finger like growth of the tumor.

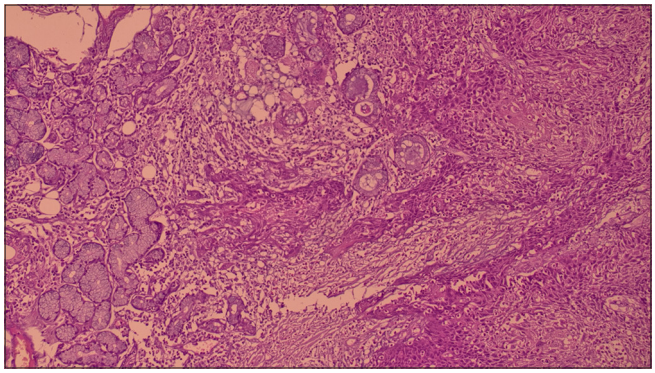

**Figure 5:** Worst pattern of invasion 3. (H&E, x400), Black arrow showing the large islands of the tumor cells separated from the tumor.

PNI was considered when carcinoma encircled or tracked along a nerve. Therefore, cases where SCC is merely close to or in contact with nerves without actual encasement were not considered PNI.

LHR was evaluated under light microscopy at the leading edge of the tumor and is based on the overall most intense immune reaction observed. This assessment is currently qualitative and does not involve counting specific types of lymphocytes. However, previous studies have shown that T cells are the main type of lymphocyte present at the advancing edge of the tumor.[6]

For statistical analysis, all the collected data were coded into Microsoft Excel. Analysis was done on the categorical variables using the Chi-square test of significance. $P < 0.05$ was considered statistically significant. Statistical Package for Social Sciences 22 version was used for the analysis of data.

## RESULTS

Of 101 participants in this study, the majority of cases were female (73 cases, 72.27%), and the main cause of cancer was

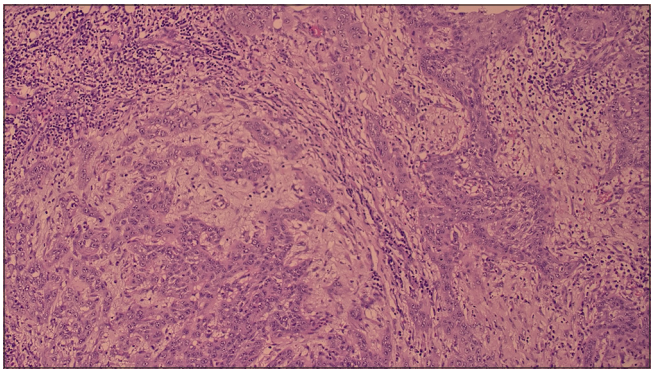

**Figure 6:** The worst pattern of invasion 4. (H&E, x400), Black arrow showing the small tumor islands (<15 cells) at the tumor margin.

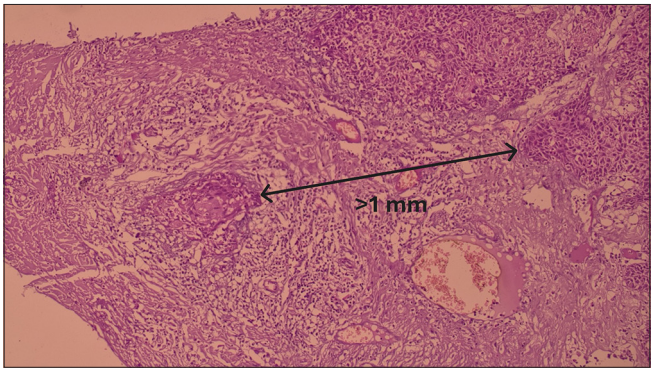


**Figure 7:** The worst pattern of invasion 5. (H&E, x400), Black arrow showing the tumor satellites > 1 mm away from main tumor.

**Table 1:** Scoring pattern for the Brandwein-Gensler risk scoring model.

| Variable | Definition | Score |
|---|---|---|
| WPOI | | |
| Type 1 | Pushing border | 0 |
| Type 2 | Finger-like growth | 0 |
| Type 3 | Large separate islands, >15 cells per island | 0 |
| Type 4 | Small tumor islands, ≤15 cells, per island | +1 |
| Type 5 | Tumor satellites, >1 mm from the main tumor or the next closest satellite | +3 |
| LHR | | |
| Type 1 | Strong, lymphoid nodules in each 4x field at advancing edge of tumor. | 0 |
| Type 2 | Intermediate, lymphoid nodules at some but not all 4x fields at advancing edge of tumor | +1 |
| Type 3 | Weak | +3 |
| PNI | | |
| None | None | 0 |
| Small nerves | Small nerves <1 mm in diameter | +1 |
| Large nerves | Large nerves > 1 mm in diameter | +3 |

WPOI: Worst pattern of invasion, LHR: Lymphocytic host response, PNI: Perineural invasion

tobacco chewing. The most common site was buccal mucosa (55 cases, 54.45%), followed by the gingivobuccal sulcus (26 cases, 25.74%).

Table 2 provided a broader analysis of recurrence rates across multiple variables, including demographic and pathological factors. LVI and PNI stand out as critical predictors, with recurrence rates of 100% when present (5/5 cases for LVI and 10/10 for PNI), compared to significantly lower rates in their absence (30.21% for LVI-negative cases and 26.37% for PNI-negative cases). Both factors had highly significant *P*-values (0.004 for LVI and <0.001 for PNI). Similarly, higher LHR, WPOI, and PNI scores were strongly associated with recurrence (e.g., 72% recurrence for WPOI 1, 68.42% for LHR 1, and 100% for PNI 1), all with $P < 0.001$. In contrast, variables such as sex, tumor grading, and bone invasion did not show significant associations with recurrence ($P > 0.05$).

The BG Score, a histopathological grading system, in relation to recurrence was calculated. It shows a strong association between higher BG scores (ranging from 0 to 5) and increased recurrence rates. Notably, none of the cases with BG scores of 0 or 1 recurred, whereas 15 out of 21 cases had a score of 2, 11 out of 13 had 3, and all 4 cases had 5 experienced recurrence. The $P < 0.001$ confirms the statistical significance of this trend, indicating that higher BG scores are a robust predictor of recurrence [Table 3].

**Table 2:** Association of clinicopathological parameters with recurrence.

| Variable | Group | Total | Recurrent | Recurrence rate (%) | *P*-value |
|---|---|---|---|---|---|
| Sex | F | 73 | 25 | 34.24 | 0.157 |
| | M | 28 | 9 | 32.14 | |
| Tumor grading | MDSCC | 23 | 7 | 30.43 | 0.903 |
| | WDSCC | 78 | 27 | 34.62 | |
| Lymphovascular invasion | No | 96 | 29 | 30.21 | 0.004 |
| | Yes | 5 | 5 | 100.00 | |
| Perineural invasion | No | 91 | 24 | 26.37 | <0.001 |
| | Yes | 10 | 10 | 100.00 | |
| Bone invasion | No | 98 | 32 | 32.65 | 0.261 |
| | Yes | 3 | 2 | 66.67 | |
| WPOI score | 0 | 62 | 21 | 33.87 | <0.001 |
| | 1 | 25 | 18 | 72.00 | |
| | 3 | 14 | 5 | 35.71 | |
| LHR score | 0 | 81 | 29 | 35.80 | <0.001 |
| | 1 | 19 | 13 | 68.42 | |
| | 3 | 1 | 1 | 100.00 | |
| PNI score | 0 | 91 | 24 | 26.37 | <0.001 |
| | 1 | 9 | 9 | 100.00 | |

WPOI: Worst pattern of invasion, LHR: Lymphocytic host response, PNI: Perineural invasion, MDSCC: Moderately Differentiated Squamous Cell Carcinoma, WDSCC: Well Differentiated Squamous Cell Carcinoma. Chi square test and Fishers exact test were used.

Together, these findings underscore the importance of histopathological markers, particularly the BG score, LVI, PNI, and invasive growth patterns, in predicting cancer recurrence. The results suggest that patients with these high-risk features may benefit from closer surveillance or more aggressive adjuvant therapies to mitigate recurrence risk.

The association between the DOI, measured in millimeters, and disease recurrence in a sample of 101 cases was analyzed. Of these, recurrence was absent in 67 (66.3%) and present in 34 (33.7%). The data suggest a non-linear but significant relationship between DOI and recurrence, with deeper invasion generally correlating with higher recurrence rates. The $P = 0.038$ indicates that this association is statistically significant, implying that DOI may be a meaningful predictor of recurrence. These findings suggest that while deeper invasion tends to increase recurrence risk [Table 4].

The association between tumor staging (T and N classification) and disease recurrence was studied, which showed that T staging (T1 and T2) shows no significant correlation with recurrence, with nearly identical proportions of recurrence observed in both groups ($P = 0.990$). In contrast, N staging demonstrates a strong and clinically meaningful relationship with recurrence ($P < 0.001$). Patients without nodal involvement (NO) had substantially lower recurrence rates (8/63 cases, 12.7%) compared to those with nodal disease. Notably, more advanced nodal stages (N2b, N3, and N4) showed universal or near-universal recurrence, with all 10 N2b cases and all 4 N3 cases experiencing recurrence. The findings highlight that while primary tumor size (T stage) may not independently predict recurrence in this cohort, the presence and extent of lymph node metastasis (N stage) serve as a powerful prognostic indicator, with progressively higher nodal stages correlating with dramatically increased recurrence risks [Table 5].

A Kaplan-Meier survival analysis was performed [Figure 8] to evaluate DFS among patients with OSCC across different TNM stages. DFS was defined as the time from definitive treatment to the occurrence of local recurrence, regional recurrence, distant metastasis, second primary tumor, or death, whichever occurred first. Patients without an event at the last follow-up were censored.

The Kaplan-Meier curves demonstrated a clear stage-dependent difference in DFS, with lower stages (Stage I and Stage II) exhibiting better DFS rates compared to higher stages (Stage III and Stage IV).

**Table 3:** Brandwein-Gensler score.

| Recurrence | Low risk | Intermediate risk | High risk | Total | *P*- value |
|---|---|---|---|---|---|
| Absent | 41 | 15 | 11 | 67 | <0.001 |
| Present | 0 | 15 | 19 | 34 | |
| Total | 41 | 30 | 30 | 101 | |

*P*<0.001, Chi square test.

**Table 4:** Recurrence based on depth of invasion.

| DOI (mm) | Recurrence | | Total |
|---|---|---|---|
| | Absent | Present | |
| 2 | 2 | 1 | 3 |
| 3 | 5 | 2 | 7 |
| 4 | 11 | 0 | 11 |
| 5 | 12 | 2 | 14 |
| 6 | 13 | 10 | 23 |
| 7 | 3 | 6 | 9 |
| 8 | 7 | 5 | 12 |
| 9 | 12 | 4 | 16 |
| 10 | 2 | 4 | 6 |
| Total | 67 | 34 | 101 |

*P*=0.038. DOI: Depth of invasion

## DISCUSSION

Patients diagnosed with early-stage OSCC often display considerable variation in their clinical outcomes, with DFS ranging widely among individuals.[7] In a study done by Yuen *et al.*[8] it was reported that out of the 63 patients having early-stage oral tongue cancer, 33 patients who were treated with elective nodal dissection showed a better neck recurrence rate compared to 30 patients who did not receive radiotherapy.[8]

This observed heterogeneity in prognosis underscores the need for further research aimed at identifying and validating reliable prognostic markers. A deeper understanding of factors that contribute to tumor recurrence could significantly enhance risk stratification and treatment planning in early-stage OSCC.

**Table 5:** Recurrence and T and N staging.

| Staging | Recurrence | | Total | *P*-value |
|---|---|---|---|---|
| | Absent | Yes | | |
| T staging | | | | 0.990 |
| 1 | 2 | 1 | 3 | |
| 2 | 65 | 33 | 98 | |
| N staging | | | | <0.001 |
| 0 | 55 | 8 | 63 | |
| 1 | 12 | 10 | 22 | |
| 2 | 0 | 2 | 2 | |
| 2b | 0 | 10 | 10 | |
| 3 | 0 | 4 | 4 | |

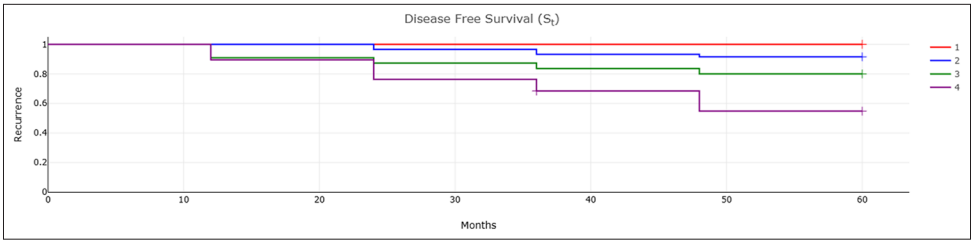


**Figure 8:** The Kaplan–Meier curve comparing the disease-free survival with TNM staging of the patients.

In this context, the present study aims to assess the applicability and prognostic utility of the BG risk model in OSCC cases classified according to the 8th edition of the AJCC staging system, with particular emphasis on early-stage tumors. In addition, the study examines the relationship of DOI, LVI, and lymph node metastases with tumor recurrence, to explore their potential as independent predictors of disease outcome.

In our study with a DOI cutoff value at 5 mm, we found a significant increase in recurrence ($P = 0.038$), which supports the recommendation to give adjuvant radiotherapy to these patients. In a study by Tandon *et al.*, they found that the use of postoperative radiotherapy for patients with DOI >5 mm improved the overall survival, loco-regional control, and DFS.[9]

It was identified that LVI ($P = 0.004$), PNI ($P < 0.001$), WPOI Score ($P < 0.001$), and LHR Score ($P < 0.001$), are significant risk factors for predicting recurrence in early-stage OSCC cases. Furthermore, the BG risk model demonstrates significant utility in predicting the likelihood of recurrence in early-stage OSCC cases. In our study, we also identified a significant correlation between the nodal status of the patient and the risk of recurrence ($P < 0.001$).

The challenge faced for the assessment of these histological parameters is the study of the advancing tumor margins, which requires extensive sampling so that these parameters can be adequately assessed, especially in early-stage cases. For these early-stage cases, it is recommended to submit the resection margin planes and the advancing tumor edge entirely.

The BG risk model gives the scoring based on the WPOI, PNI, and LHR. When considering WPOI, WPOI 1-3 have all been given a score of 0, which indicates that these patterns are considered nonaggressive patterns of invasion. The most commonly seen pattern is the WPOI 3. Hence, these patterns can be considered as not extending beyond the tumor perimeter.

For WPOI 4 and WPOI 5, these patterns show tumor islands that are present separately from the main tumor mass, showing a predilection of these patterns to show spread away from the primary site.

The Kaplan-Meier analysis shows that early-stage OSCC patients enjoy improved DFS, highlighting the critical importance of early detection and timely intervention.

In a study done by Li *et al.*, LHR ($P = 0.0297$), WPOI ($P = 0.0002$), and the BG risk model ($P = 0.0012$) were identified as significant histological risk factors associated with locoregional recurrence (LRR).[4]

In another study by Amalangush *et al.*,[4] they found that WPOI and DOI were the best factors for predicting LRR. In a study by Hori *et al.*, LVI, WPOI, tumor budding, and depth emerged as factors for the prediction of DFS.[11]

Early-stage OSCC presents with a markedly heterogeneous prognosis, making individualized risk assessment essential. Several histopathological parameters, including WPOI, DOI, LVI, presence of nodal metastases, LHR, and PNI, have emerged as significant independent predictors of LRR.

## CONCLUSIONS

The BG histological risk model has shown particular promise in integrating multiple high-risk features into a single prognostic framework. Routine evaluation of these parameters on standard H&E-stained sections, when combined with the BG scoring system at the time of initial diagnosis, can enhance prognostication accuracy. This integrated approach allows for better identification of patients at elevated risk of recurrence, thereby guiding the selection of individuals who may benefit from adjuvant therapy following surgical resection.

**Author's contributions:** GMS : Concept, data collection, analysis and interpretation of data, Drafting manuscript. S.MD: Data Analysis, Manuscript editing. AK: Data Analysis, Manuscript editing.

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**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical

information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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