

## Review Article

# Assessing the Utility of Tumor Budding and Worst Pattern of Invasion Score in the Histopathological Reporting Formats for Prognostication in Patients of OSCC with and without OSMF- A Retrospective Study

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## Abstract

OSCC is the most common malignant epithelial tumor affecting the oral cavity. The global incidence of OSCC subsidize for 2% to 4% of all cancer and Oral Submucous Fibrosis (OSMF) is premalignant condition of oral cavity which can concomitantly present along with OSCC or present before the exhibition of squamous cell carcinoma of oral cavity. Squamous cell Carcinoma of oral cavity is projected in more than 90% of all tumors. It is the 6<sup>th</sup> most common cancer and has a wide geographic variation. In South-East Asia especially in India the disease is more rampant owing to consumption of smokeless tobacco (betel quid). Moreover, OSCC and OSMF share the same line of etiology. For investigation of preventive approach this premalignant condition can serve as a good example. Age, gender, and socioeconomic characteristics, as well as clinical and pathological parameters of the tumor, such as anatomical location, histological grading, and treatment method, have all been identified as predictive factors in people with OSCC. Nevertheless, the findings on the relationship between survival time and prognostic and predictive parameters are yet to be defined. It's a huge challenge to identify patterns of recurrence in these cases. Tumor budding has been identified as a promising prognostic indicator. One of the most notable results in OSCC is a substantial connection between a high tumor budding count and the incidence of lymph node metastases and in early stage OSCC, there was a link between tumor budding and occult lymph node metastases. Because occult metastasis is the leading cause of relapse and poor prognosis in early-stage cancers, it's critical to confirm this link in other large multicenter cohorts.

Oral cavity cancer is on the rise worldwide as a result of tobacco use, and it has become a public health issue in emerging nations like India. The prognosis for these patients is not very convincing in general. Multiple clinical, pathological and site of tumor influence the prognosis of oral cavity malignancies. DOI, WPOI, tumor budding, PNI and entrance pathways were all linked to a lower overall survival rate, albeit this was not statistically significant. To summarize, WPOI and tumor budding are key risk factors for LN metastasis in all stages of OSCC and are linked to worse prognosis in early-stage malignancies. These are simple and dependable prognostic indicators that should be reported in histopathologically. If an information of relevance can be collected retrospectively regarding tumor budding and routes of entry, further evaluation of collected results can yield unknown facts about tumor entry, routes, pattern of invasion, secondary metastasis and a treatment plan for future cases in patients with OSCC with or without OSMF.

## Aim

Evaluation and correlation of Tumor budding, worst pattern of invasion, histopathological grading, lymphovascular invasion and perineural invasion as a prognostic indicator in patients of Oral squamous cell carcinoma with and without Oral submucous fibrosis.

## Objectives

1. To evaluate the tumor budding and worst pattern of invasion score in the histopathological reporting formats for prognostication in patients of OSCC with OSMF.
2. To evaluate the tumor budding and worst pattern of invasion score in the histopathological reporting formats for prognostication in patients of OSCC without OSMF.
3. To correlate and compare the aforementioned factors with survival (overall, Disease free, Disease specific) in patients with OSCC with and without OSMF.

## Review of Literature

Shimzu et al. [1] discussed the importance of tumor budding as an independent prognostic marker in early-stage oral squamous cell carcinoma with special reference to the mode of invasion and worst pattern of invasion. Tumor budding is a highly essential parameter in identifying nodal metastasis in early-stage cancer, according to the retrospective study. In The study patients were followed up after ablative procedures with careful wait-and-see follow-up at short intervals such as every week or every two weeks for 6 months with or without the use of imaging modalities, if there are symptoms of

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developing nodal relapse, perform neck dissection as soon as possible, but if budding with more than ten buds and the grade 4D mode of invasion, or WPOI-5 are observed in the same section, perform neck dissection as soon as possible.

The study discussed the Depth of invasion, tumor budding, and worst pattern of invasion as main prognostic indicator for early-stage oral cancer. Samples of carcinoma of tongue were evaluated under light microscope by two independent investigators. Using cox proportional hazard regression model for assessing the prognostic strength of each marker. Using Kaplan-Meier plots for calculating cumulative survival outcomes [2].

This study compiled the results of Ovid Medline, PubMed, Scopus and Web of Science for articles that studied tumor budding in OSCC. Reported recommendations for tumor marker (REMARK) criteria to evaluate the quality of studies eligible for meta-analysis. According to the analyses, there was strong evidence for tumor budding to be considered as a promising prognostic marker for OSCC. The study conducted included meta-analysis of 2 studies that included only early-stage oral cancers. The results were suggestive of budding as an important prognostic factor but with wide confidence interval. The results lacked strong statistical proof and requires further validation [3].

### Study Protocol

1. Study Design- Retrospective analytical Study.
2. Study Duration- February 2022- January 2024.
3. The study will be conducted in the department of oral and maxillofacial surgery at Sharad Pawar Dental College and Hospital & Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha.
4. Study Hypothesis- Null Hypothesis.

### Ethical Approval

The detailed study synopsis would be subjected to approval from Institutional Ethical Committee Sharad Pawar Dental College DMIMS (DU) and initiated after its approval.

### Declaration

The study procedure described in the study is in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Inclusion Criteria

Patients who underwent Surgical Intervention for Oral Squamous Cell Carcinoma with and without OSMF. All the slides available in the archive section of General Pathology from 2017 to December 2019 of patients with Oral squamous cell carcinoma with and without Oral submucous fibrosis. Patients with Grade III and IV OSMF.

### Exclusion Criteria

1. Patients whose demographic details and tumor characteristics weren't available.
2. Patients died due to natural causes or accidents.
3. Patients who did not undergo Surgical Intervention for Oral Squamous Cell Carcinoma with and without OSMF from 2017 to December 2019, with curative intent.
4. Patients whose slides weren't available/damaged in the archive

section of general pathology department.

5. Patients with oral non-epithelial malignancies.
6. Patients of OSCC with previous history of treatment such as surgery, radiotherapy, chemotherapy and/or both.
7. Patients with residual, recurrent disease and second primary tumors of oral cavity.

### Scope

Assessment of tumor budding along with worst pattern of invasion and other parameters so as to find co-relation between them to arrive at a conclusion of progression of disease. This study can pave way for answers to progression in the disease.

### Implications

This study will determine the role of tumor budding and depth of invasion along with other parameters to co-relate the prognosis of the disease on basis of pathological examination for future treatment planning.

### Subjects and Methodology

This is a retrospective study of patients who have undergone neck dissection, lymph node removal, transoral resection of primary tumor, mandibular resection operated with curative intent from July 2017 to December 2019, for oral Squamous Cell Carcinoma (SCC) with/without Oral submucous fibrosis in the department of Oral and Maxillofacial surgery at Sharad Pawar Dental College and Hospital (SPDC) & Acharya Vinobha Bhave Rural hospital (AVBRH) were included in the study. After obtaining the Institutional Ethical Clearance (IEC) and obtaining permission to retrieve records from Medical Records Department (MRD).

Patient's demographic details like age, sex, address will be collected from the above records. The histopathological data will be retrieved from the department of general pathology at Jawaharlal Lal Nehru Medical College (JNMC) the retrieved surgical pathology report revealed the tumor's size, and stage was assigned according to the standard staging (AJCC 8<sup>th</sup> edition) of tumor approved under College of American Pathologists guidelines CAP). Histological parameters will be evaluated in each cases such as degree of differentiation, Worst Pattern Of Invasion (WPOI), tumor budding, mode of invasion, histology grading of tumor, depth of invasion, Lymphovascular Invasion (LVE) will be evaluated by examining lymphatic, arterial and venous invasion. Perineural Invasion (PNI) is defined as a tumor surrounding or infiltrating a nerve.

The tumor extent and the histopathological grading were classified according to the 8<sup>th</sup> edition of the AJCC/UICC TNM Classification. Staining will be visualized with diaminobenzidine tetrachloride. The sections will be counterstained with hematoxylin, dehydrated, cleared, and mounted. Next, serial sections from the paraffin-embedded samples will be stained with H&E and provided for assessment of the mode of invasion and WPOI. The presence or absence of lymphovascular invasion and perineural invasion will be charted according to information from routine histopathological reports.

Immunostained tumor specimens will be initially scanned with a 4x objective lens (and 10x ocular one) to select the areas with the highest density of budding. Tumor budding in the selected areas and the highest count per slide was used as the number of buds Tumor budding will be evaluated by using OLYMPUS LX21i Binocular

Research Microscope highest count per slide was used as the number of buds.

Disease-free survival defined as the time from the date of surgery to the date of evidence of tumor relapse at any site, including primary and secondary ones, death from any cause, or to the end of December 2019. Survival analyses will be performed using the Kaplan-Meier method and compared using the log-rank test for each group

### Survival analysis

All cancer cases will be investigated further with the help of slide caliper. Evaluation of patients with the help of available follow-up information in order to determine any relation between histological invasion and overall survival which is further evaluated by grouping tumors based on specific sites and its route of entry.

After getting patients past record, a telephonic conversation will be done with the patient's family or the relatives to inform about the well-being of the patient. And based on the information, study groups will be made.

Study does not require a fixed sample size as its retrospective in nature and will depend on the number of cases operated with curative intent.

### Parameters

Worst pattern of invasion according to tumor front:

1. Pattern 1- Is tumor with broad pushing margin with smooth outline.
2. Pattern 2- Broad pushing finger like projection.
3. Pattern 3- Invasive tumor islands are present with >15 cells per island.
4. Pattern 4- Invasive tumor islands are present with <15 cells per island.
5. Pattern 5- Tumor Island is present outside the main tumor at a distance of >1 mm.

International Tumor Budding Consensus Conference (ITBCC 2016) recommendations & CAP approved guidelines.

1. Tumor budding is categorized into buds <5- low
2. Intermediate intensity >5 <10 buds
3. high intensity >10 buds

Mode of invasion (mode of invasion is assessed based on the invasive morphology of the cancer cells or nests, not the cell number of the tumor island or nest).

1. Grade 1 with well-defined borderlines.
2. Grade 2 with have cords and less defined borderlines.
3. Grade 3 group of cells and no borderlines which are distinct.
4. Grade 4C tumors have diffuse invasion like cord-like type invasion. In grade 4C, tumor cells invade deeply as a cord-shaped microtumor nest.

In grade 4D tumors, a few or single tumor cells invade the deeper portion diffusely. For conventional squamous cell carcinoma- AJCC 8<sup>th</sup> edition. Histologic grade of tumor (H&E stain).

1. G1, well differentiated
2. G2, moderately differentiated
3. G3, poorly differentiated
4. GX, cannot be assessed

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