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Clinicopathological correlation of histological grade and depth of invasion in oral squamous cell carcinoma: A retrospective case series from a tertiary care centre

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Abstract
Aim: To evaluate the association between histological grade and depth of invasion in OSCC and to analyse its distribution with respect to gender, tumour site, and tobacco-related habits.
Materials and Methods: This retrospective study included 50 cases of histopathologically confirmed OSCC diagnosed between January 2023 and January 2025. The specimens consisted of 40 biopsies and 10 resection specimens received in the Department of Pathology, KVG Medical College and Hospital, Sullia. Tumours were graded according to the WHO classification into well-differentiated (9 cases), moderately differentiated (38 cases), and poorly differentiated carcinomas (3 cases). Depth of invasion was assessed according to AJCC 8th edition criteria and categorized into ≤5 mm, 6–10 mm, and >10 mm. Statistical analysis was performed using Fisher's exact test.
Results: Among the 50 cases studied, males constituted the majority with 39 cases (78%), while females accounted for 11 cases (22%). Buccal mucosa was the most common tumour site, observed in 26 cases (52%), followed by tongue in 13 cases (26%), lip in 6 cases (12%), and other sites in 5 cases (10%). A history of tobacco use was noted in 36 patients (72%). Histologically, moderately differentiated OSCC was the most frequent subtype, accounting for 38 cases (76%), followed by well-differentiated carcinoma in 9 cases (18%) and poorly differentiated carcinoma in 3 cases (6%).
Regarding depth of invasion, 19 cases (38%) showed DOI ≤5 mm, 18 cases (36%) had DOI between 6–10 mm, and 13 cases (26%) demonstrated DOI >10 mm. A significant correlation was observed between histological grade and depth of invasion. All well-differentiated tumours showed DOI ≤5 mm, whereas poorly differentiated tumours consistently demonstrated deeper invasion (>10 mm). Fisher's exact test revealed a statistically significant association between higher histological grade and increased DOI ($p < 0.05$).
Conclusion: Higher histological grade is significantly associated with increased depth of invasion in OSCC. These findings support the importance of routinely reporting both parameters in histopathological evaluation, as they provide valuable prognostic information and may help guide clinical management.

Keywords: Oral squamous cell carcinoma, Depth of invasion, Histological grade, Case series, Tumor aggressiveness

Introduction

Oral squamous cell carcinoma accounts for nearly 90% of all malignant tumours of the oral cavity. It remains one of the most common cancers in India due to widespread tobacco consumption in smoked and smokeless forms. Despite advances in surgical and adjuvant therapies, overall survival has not improved significantly, largely due to late diagnosis and aggressive tumour behaviour.

The biological behaviour and prognosis of the patient of OSCC is influenced by multiple clinicopathological factors including tumour size, lymph node status, histological grade, lymphovascular invasion, perineural invasion, and depth of invasion.

Histological grading reflects tumour differentiation and degree of resemblance to normal squamous epithelium. Well-differentiated tumours show abundant keratinization, whereas poorly differentiated tumours exhibit marked atypia and minimal keratin production.

Depth of invasion represents the vertical measurement of tumour infiltration from the basement membrane of adjacent normal mucosa to the deepest invasive tumour front. DOI differs from tumour thickness, as it specifically measures true stromal invasion.

The inclusion of DOI in the AJCC 8th edition staging system underscores its independent prognostic value. Tumours with greater DOI are associated with increased risk of cervical lymph node metastasis and poorer outcomes. Many studies have included investigation on tumor thickness and depth of invasion as prognosis predictors. However, in the literature, the depth of invasion and tumor thickness are often not very clear. According to the American Joint Committee on Cancer Classification (AJCC) 8th edition, DOI is measured from the level of the basement membrane of the closest adjacent normal mucosa. A vertical line is drawn from this plane to the deepest point of tumor invasion. Therefore, depth of invasion is not the same as tumor thickness and neither of the two are interchangeable. Tumor thickness could be larger than DOI in exophytic tumors, and lower than DOI in an endophytic/ulcerated growth pattern.

Understanding the relationship between histological grade and DOI may provide insight into tumour aggressiveness and aid in clinical management.

Materials and methods

This retrospective observational study was conducted in the Department of Pathology, KVG Medical College & Hospital, Sullia, from January 2023 to January 2025.

Sample Size

50 histopathologically confirmed cases of primary OSCC.

- Biopsy specimens: 40
- Resection specimens: 10

Inclusion Criteria

- Primary OSCC cases
- Adequate tissue for grading
- Available clinical data

Exclusion Criteria

- Recurrent tumours
- Previously treated cases

Histopathological Evaluation

Specimens were fixed in formalin, processed routinely, and stained with hematoxylin and eosin (H&E).
Tumours were graded into:

- Well differentiated (9 cases)
- Moderately differentiated (38 cases)
- Poorly differentiated (3 cases)

Measurement of Depth of Invasion

DOI was measured from the reconstructed basement membrane of adjacent normal mucosa to the deepest invasive tumour front using ocular micrometry.
DOI was categorized into:

- ≤5 mm
- 6–10 mm
- 10 mm
- And above 10 mm

Statistical Analysis

Data were analysed using Fisher's exact test. $p < 0.05$ was considered statistically significant.

Results

Gender Distribution

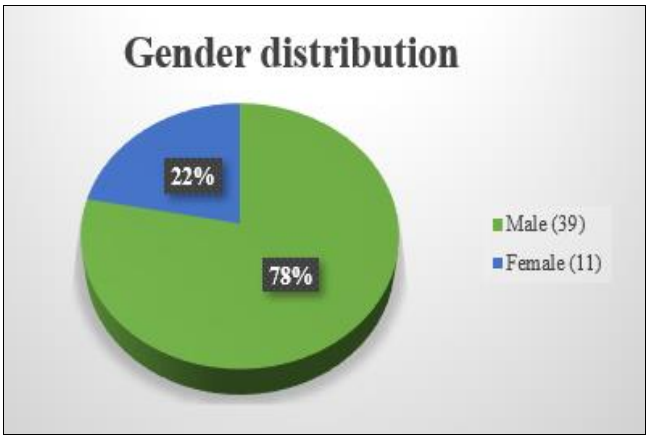

Fig 1: Pie chart showing gender distribution

Male predominance was noted compared to female in this study.

Site Distribution

Table 1: Site Distribution, Buccal mucosa was the commonest one followed by tongue, lip and other sights.

Site	Number	Percentage
Buccal mucosa	26	52%
Tongue	13	26%
Lip	6	12%
Others	5	10%

Tobacco Habit

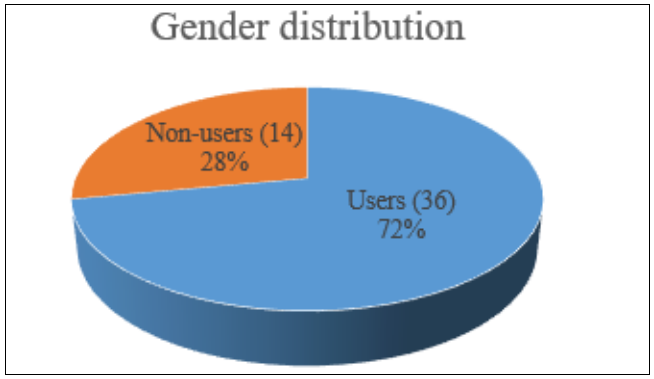

Fig 2: Pie chart showing tobacco habit distribution, in which the users were more compared to the non-tobacco users

Histological Grade

Table 2: Histological Grade Distribution

Grade	Number	Percentage
Well differentiated	9	18%
Moderately differentiated	38	76%
Poorly differentiated	3	6%

Depth of Invasion

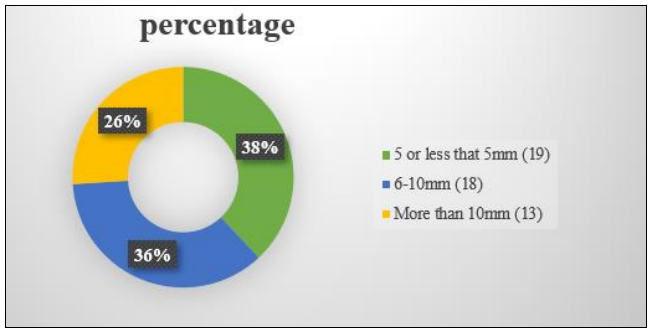

Fig 3: Pie chart showing DOI distribution, in which 5mm or less than 5 mm of DOI is predominant

Correlation Between Grade and DOI

Table 3: Grade vs DOI Correlation ($P < 0.05$)

Grade	≤5 mm	6–10 mm	>10 mm	Total
Well	9	0	0	9
Moderate	10	18	10	38
Poor	0	0	3	3
Total	19	18	13	50

Fisher's exact test revealed a statistically significant association between higher histological grade and increased DOI ($p < 0.05$).

Histopathological features

Well Differentiated OSCC

Microscopy revealed tumour islands with prominent keratin pearl formation and intercellular bridges. Nuclear pleomorphism was mild and mitotic Figs were few.

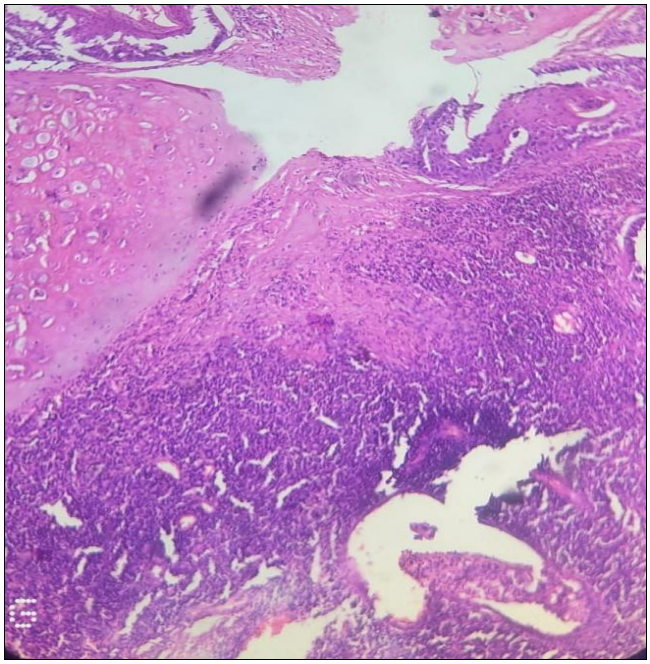

Fig 4: Well differentiated OSCC showing keratin pearls (H&E, ×10)

Moderately Differentiated OSCC

Sections showed irregular nests and cords with reduced keratinization. Moderate nuclear pleomorphism and increased mitotic activity were noted.

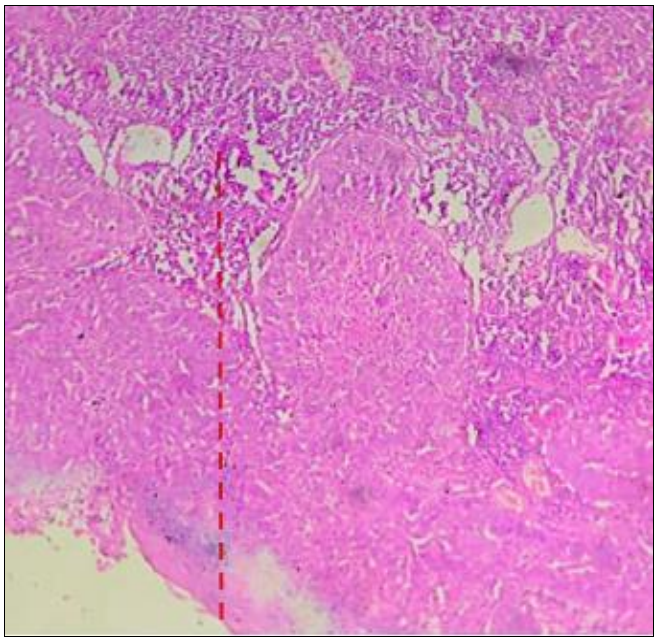

Fig 5: Moderately differentiated OSCC (H&E, ×10)

Poorly Differentiated OSCC

Tumours displayed sheets of highly atypical cells with minimal keratinization, marked pleomorphism, and frequent atypical mitoses.

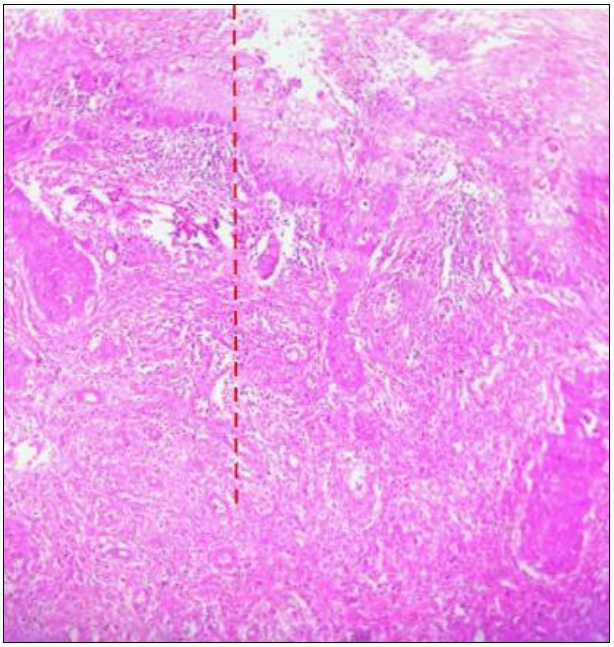

Fig 6: Poorly differentiated OSCC (H&E, ×10)

Perineural Invasion

Perineural invasion (PNI) was identified in higher grade tumours in focal areas. In our study one of the poorly differentiated variant had the perineural invasion. PNI is recognized as an adverse prognostic factor and is associated with increased local recurrence and reduced survival. Its identification during routine histopathological examination is essential as it may influence adjuvant therapy decisions.

Discussion

Oral squamous cell carcinoma remains one of the most common malignancies of the oral cavity and represents a major health burden in developing countries, particularly in South Asia. The high prevalence in this region has been attributed largely to widespread consumption of tobacco in both smoked and smokeless forms [1, 2]. The present study evaluated the clinicopathological characteristics of oral squamous cell carcinoma and examined the correlation between histological grade and depth of invasion.

In the present study, a clear male predominance was observed, with males accounting for 78% of cases while females constituted 22%. Similar findings have been reported in several earlier studies. Rai *et al*. [3] reported that approximately 75% of OSCC cases occurred in males, which was attributed to higher tobacco consumption among men. Akhter *et al*. [4] also observed a male predominance in their study of oral squamous cell carcinoma. The gender difference is likely related to lifestyle factors such as tobacco chewing, smoking, and alcohol consumption, which are more common among males in many parts of India.

The buccal mucosa was the most commonly involved site in the present study, accounting for 52% of cases. This finding is consistent with earlier reports from the Indian subcontinent. Rai *et al*. [3] also reported buccal mucosa as the most frequent site of oral carcinoma. The predominance of buccal mucosa in Indian populations is often linked to the habit of placing smokeless tobacco or betel quid in the buccal vestibule for prolonged periods. Chronic exposure of the mucosa to carcinogens in tobacco leads to epithelial dysplasia and eventually malignant transformation.

Tongue was the second most common site in the present study (26%). Several international studies have reported tongue as the most common site of OSCC, particularly in Western populations. [5] This difference in anatomical distribution may reflect variations in lifestyle habits and carcinogenic exposures between different geographic regions.

Tobacco use was reported in 72% of patients in the present study, highlighting the strong association between tobacco exposure and oral squamous cell carcinoma. Tobacco contains numerous carcinogenic substances such as nitrosamines and polycyclic aromatic hydrocarbons that can induce genetic mutations in epithelial cells [6]. Long-term exposure to these carcinogens promotes dysplastic changes in oral mucosa, which may eventually progress to invasive carcinoma.

Regarding histological grading, moderately differentiated squamous cell carcinoma was the most common subtype observed in this study, accounting for 76% of cases. Well differentiated carcinomas accounted for 18%, while poorly differentiated tumours constituted 6% of cases. This distribution is consistent with findings reported in previous studies. Akhter *et al.* [4] reported that moderately differentiated carcinoma was the most frequent histological type in their study population. Similar observations were made by Niculescu *et al.* [7] in a histopathological review of oral squamous cell carcinoma cases.

Histological grade is considered an important indicator of tumour aggressiveness. Well differentiated tumours typically show abundant keratin production and relatively mild nuclear atypia, whereas poorly differentiated tumours display marked cellular atypia, increased mitotic activity, and minimal keratinization. Poorly differentiated tumours tend to exhibit more aggressive biological behaviour and have been associated with poorer clinical outcomes.

Depth of invasion has emerged as one of the most important prognostic factors in oral squamous cell carcinoma. DOI reflects the vertical extent of tumour infiltration into the underlying connective tissue. Tumours with greater depth of invasion are more likely to metastasize to cervical lymph nodes and are associated with poorer survival rates [8]. Recognition of the prognostic importance of DOI has led to its inclusion in the AJCC 8th edition staging system.

In the present study, the distribution of depth of invasion showed that 38% of cases had DOI ≤5 mm, 36% had DOI between 6–10 mm, and 26% had DOI greater than 10 mm. A statistically significant association between histological grade and depth of invasion was observed. All well differentiated tumours demonstrated superficial invasion, whereas poorly differentiated tumours consistently showed deeper infiltration.

These findings are consistent with the observations reported by Lee *et al.* [9] who evaluated the prognostic significance of tumour thickness and depth of invasion in oral squamous cell carcinoma. Their study demonstrated that tumours with greater DOI were associated with increased risk of lymph node metastasis and poorer clinical outcomes.

Another important histopathological feature observed in the present study was the presence of perineural invasion in one case of poorly differentiated carcinoma. Perineural invasion is considered an adverse prognostic factor in oral cancer and is associated with increased risk of tumour recurrence and decreased survival rates. [10] Identification of perineural invasion during routine histopathological examination is therefore clinically important.

The correlation between tumour differentiation and invasive behaviour has been investigated in several previous studies. Poorly differentiated tumours tend to lose intercellular adhesion and exhibit increased proliferative activity, which facilitates stromal invasion. This may explain the greater depth of invasion observed in poorly differentiated carcinomas in the present study.

Overall, the findings of this study support the importance of routine assessment of depth of invasion in oral squamous cell carcinoma. Accurate measurement of DOI provides valuable prognostic information and may help clinicians in determining the need for neck dissection or adjuvant therapy.

Table 4: Comparison of Present Study with Previous Studies

Study	Sample Size	Common Site	Common Grade	Key Finding
Akhter *et al* [4]	50	Buccal mucosa	Moderately differentiated	Grade associated with metastasis
Rai *et al* [3]	60	Buccal mucosa	Moderately differentiated	Tobacco strongly associated
Lee *et al* [9]	72	Tongue	Moderately differentiated	DOI predicts lymph node metastasis
Niculescu *et al* [7]	80	Tongue	Moderately differentiated	Histological grading important
Present study	50	Buccal mucosa	Moderately differentiated	Significant correlation between grade and DOI

Limitations

This study was conducted in a single tertiary care centre with a relatively small sample size. Long-term follow-up data were not available to correlate histological findings with survival outcomes.

Conclusion

Higher histological grade is significantly associated with increased depth of invasion in oral squamous cell carcinoma. Both parameters serve as essential prognostic indicators and should be carefully evaluated in routine histopathological reporting to guide clinical management

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