Original Article

A Study of Prognostic Indicators in Oral Cavity Squamous Cell Carcinoma in a Tertiary Care Institution

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Abstract

Background: Oral carcinoma is ranked as the sixth most common type of cancer worldwide, with India harboring one-third of the overall burden. Factors like smoke, tobacco, asbestos, silica, and other carcinogenic components may play a part. Late-stage detection leads to five-year survival rates of around 20% only. Hence, this study was designed to analyze the prognostic factors for oral squamous cell carcinoma (OSCC) at a tertiary care hospital. The aims were to assess the prevalence and frequency of OSCC, identify prognostic indicators in the specimens received to predict outcomes, and follow up wherever possible.

Materials and Methods: Parameters like depth of invasion, worst pattern of invasion, lymphocyte response, perineural invasion, resection margin status, lymphovascular invasion, and extranodal extension were studied.

Results: The majority of the study had a type 1 WPOI and type 1 LHR response. Perineural invasion, lymphovascular invasion, and extranodal spread were seen in advanced cases.

Conclusion: Key factors contributing to poor prognosis included age, smoking or tobacco use, and a higher depth of invasion (>10 mm). Perineural or lymphovascular/extranodal spread and a higher grade of WPOI were significantly associated with poor prognosis.

Keywords:

Oral squamous cell carcinoma, worst pattern of invasion, depth of invasion, prognosis

Introduction

Any uninhibited growth of cells that infest and lead to impairment of the adjacent tissue is called cancer. Oral cancer is ranked as the sixth most common type of cancer worldwide, with India harboring one-third of the overall burden. Oral carcinoma establishes a severe health issue in countries experiencing economic transition [1]. Tobacco consumption, including smokeless tobacco (SLT), excessive alcohol consumption, betel-quid chewing, a nutrient-deficient diet, poor oral hygiene, and persistent viral infections, i.e., human papillomavirus (HPV), are a few of the risks related to oral cancer. Numerous socio-ecological and behavioral factors like smoke, asbestos, silica, and other carcinogenic components may play a part in causing cancer.

The buccal mucosa is commonly affected due to the prolonged placement of betel quid in the buccal pouch. Tobacco generates carcinogens such as tobacco-specific nitrosamines (e.g., N-nitrosonornicotine, nicotine-derived nitrosamine ketone, N-nitrosoanatabine, and N-nitrosoanabasine) and free radicals that can impede antioxidant enzymes such as glutathione S-transferase, glutathione reductase, superoxide dismutase, catalase, and glutathione peroxidase. Potentially malignant disorders (PMDs), such as inflammatory oral submucosa, erythroplakia, fibrosis, leukoplakia, dyskeratosis congenita, candidal leukoplakia, and lichen planus, are markers of the preclinical stage of oral carcinoma [2].

Upon early diagnosis, timely and proper management of the patient can be initiated, which may enhance the survival rate up to 90%. However, if discovered in the late phase, the prospects of a cure are very low, leading to five-year survival rates of around 20% only [3].

While ascertaining the prognosis of a person with oral squamous cell carcinoma (OSCC), all factors, including demographic, clinical, general physical, histological, and molecular factors, must be taken into consideration [4].

Hence, this study was designed to assess the prevalence and frequency and to analyze the prognostic factors for OSCC at a tertiary care hospital. This will help in adding valuable evidence that can contribute to better patient care for OSCC.

Numerous conventional clinical techniques, such as physical and histopathological examinations, biopsy, and radiological modalities, are consistently used to identify oral cancer. The identification of cancer in the early phase is a key factor in preventing further physical, psychological, and financial losses for the patient. Upon early diagnosis, timely and proper management of the patient can be initiated, which may enhance the survival rate up to 90%.

Materials and Methods

This cross-sectional observational study was conducted in the Department of Pathology at a tertiary care teaching hospital in India on 70 subjects over a period of 7 years.

The mandibulectomy specimens and referral cases with complete details of the gross specimen and availability of all microscopic slides were included in the study.

Demographic data such as age, gender, occupation, and socio-economic status were noted. Clinical examination (both local and systemic), as well as investigations/procedures performed, were obtained from the clinical data available. The specimens were processed following standard guidelines, and histo-morphological parameters were assessed as follows:

Depth of Tumor Invasion: Measured from the surface of the tumor to the deepest point of invasion in paraffin-embedded sections. The cutoff criterion to differentiate between low-risk and high-risk is 4 mm. A DOI of 4 mm is regularly used as a threshold based on precedent literature positing this as an optimal cutoff depth [15–18].

Worst Pattern of Invasion (WPOI): Small tumor islands of fewer than 15 cells and satellite tumors located at least 1 mm away from the main tumor are considered high risk.

Lymphocytic Host Response (LHR): No response is considered high risk.

Perineural Invasion (PNI): Large perineural invasions are considered high risk.

Surgical Resection Margins: <5 mm is considered high risk.

Lymphovascular Invasion: Presence is considered high risk.

Extranodal Extension: Presence is considered high risk.

Data analysis was performed using the statistical software GraphPad InStat v3.0. The association between various histo-morphological parameters and patient outcomes was evaluated using the chi-square test.

Results

A total of 70 cases were enrolled. The mean age was noted to be 50.11 ± 11.09 years, with the range being 27–79 years. The total proportion of males was noted to be 81.43% in the study. The majority of the cases enrolled in the study belonged to the 51–60 years age group, followed by the 41–50 years age group (n = 22). Thirteen patients were between 31–40 years of age, followed by eight cases between 61–70 years and three patients between 71–80 years (Table 1).

Table 1: Outcomes of patients followed up in study (n=29)

Outcome noted	*Number of patients*	*% Of cases*
Death	9	31.04%
Recurrence	2	6.9%
No recurrence	18	62.07%

Forty-three of the enrolled cases (61.42%) did not have any history of smoking, while the remaining 27 cases (38.58%) did. Fifty-two of the enrolled cases (74.28%) had a history of tobacco use, while the remaining 18 cases (25.72%) did not have a history of tobacco use (Table 2).

Table 2: Impact of various parameters on prognosis in study

Parameter assessed	*Good prognosis (n=18)*	*Poor prognosis (n=11)*	*P value*
Mean age (years)	51.83 ± 9.42	56.72 ± 12.38	<0.01^
Age status			
Age ≥60 years	2 (11.11%)	6 (54.55%)	
Age <60 years	16 (88.89%)	5 (45.45%)	**0.03***
Gender			
Male	13 (72.22%)	11 (100%)	0.12
Female	5 (27.78%)	0	
Smoking or tobacco habit			
Present	12 (66.67%)	11 (100%)	**0.04***
Absent	6 (33.33%)	0	**0.05#**
Depth of invasion			
≥10 mm	3 (16.67%)	7 (63.64%)	**0.01***
<10 mm	15 (83.33%)	4 (36.36%)	
WPOI Type			
Type 1	17 (94.44%)	5 (45.45%)	**0.01***
Greater than type 1	1 (5.56%)	6 (54.55%)	
Perineural invasion			
Present	1 (5.56%)	5 (45.45%)	**0.02***
Absent	17 (94.44%)	6 (54.55%)	
Lymphovascular / Extranodal invasion			
Present	2 (11.11%)	6 (54.55%)	**0.03***
Absent	16 (88.89%)	5 (45.45%)	
***p<0.05 was found to be significant by chi-square test, ^p<0.05 considered significant by unpaired t test #p<0.05 significant by Fisher exact test**			

The resection margin was >5 mm in 69 of the 70 enrolled cases, while only one patient had a resection margin <5 mm. The left buccal mucosa was most commonly involved, i.e., in 20% of the cases. This was followed by the right buccal mucosa in 17.14% of cases, the right lateral border of the tongue in 14.29%, the left gingivobuccal (GB) sulcus in 12.86% of cases, the right GB sulcus in 11.43% of cases, and 10% of cases had the rest of the oral cavity involved.

The majority of the study cases (n = 48, 68.57%) had a type 1 WPOI, followed by type 2 (n = 7, 10%) and types 3 and 5, with six patients each (8.57%). A total of 98.57% of the cases enrolled in the study were noted to have a type 1 LHR response.

Perineural invasion for lesions was noted in eight of the enrolled cases (11.43%). Lymphovascular invasion for lesions was noted in 12 of the enrolled cases (17.14%), while the remaining 58 cases (82.86%) had no lymphovascular invasion. Extra-nodal spread for lesions was noted in five of the enrolled cases (7.14%).

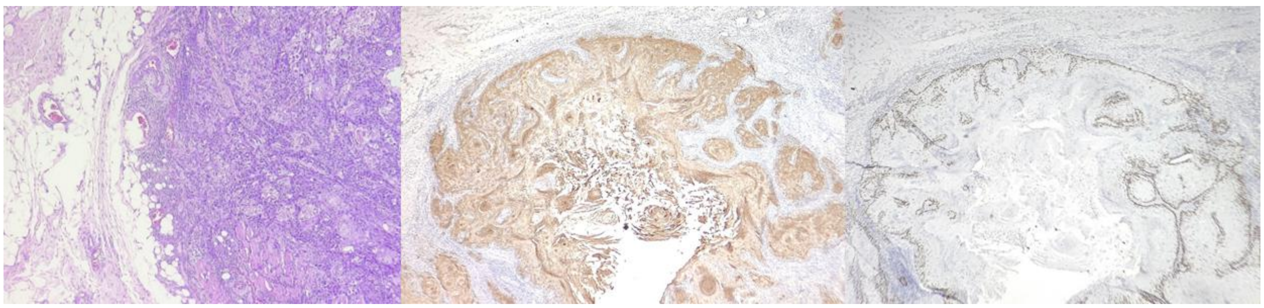

Figure 1: Haematoxylin and eosin (20X) – WPOI 1: Non-aggressive tumors with a broad, pushing margin. Pan-cytokeratin and p-40 highlighting the pattern of invasion. The majority of the study (n = 48, 68.57%) showed type 1 WPOI on histopathology.

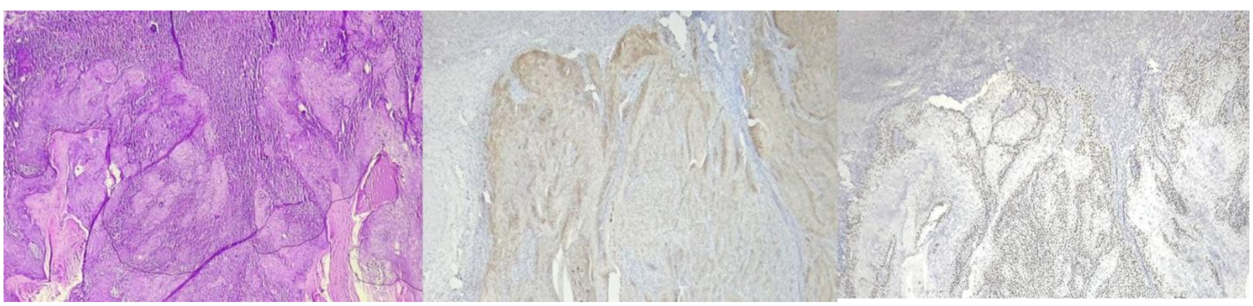

Figure 2: Haematoxylin and eosin (20X) – WPOI 2: Broad, finger-like projections. WPOI-2 (n = 7, 10%). Pan-cytokeratin and p-40 highlighting the pattern of invasion.

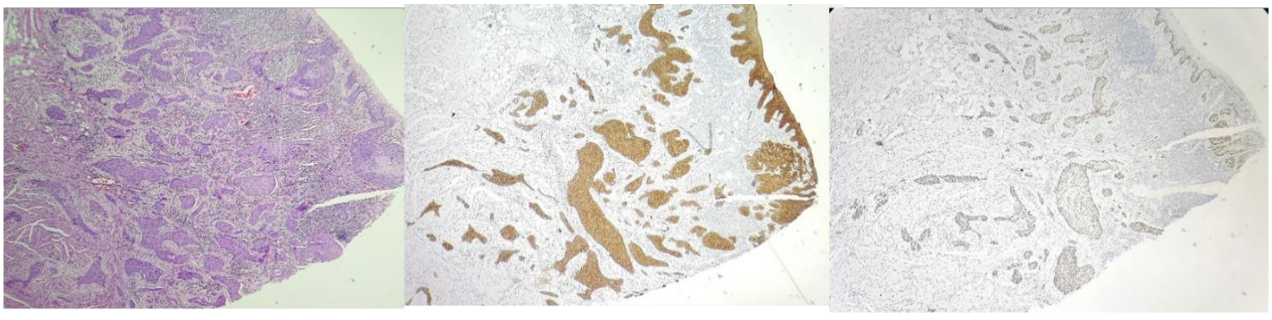

Figure 3: Haematoxylin and eosin (20X) – WPOI 3: Invasive islands of tumor cells (> 15 cells per island). Pan-cytokeratin

and p-40 highlighting the pattern of invasion.

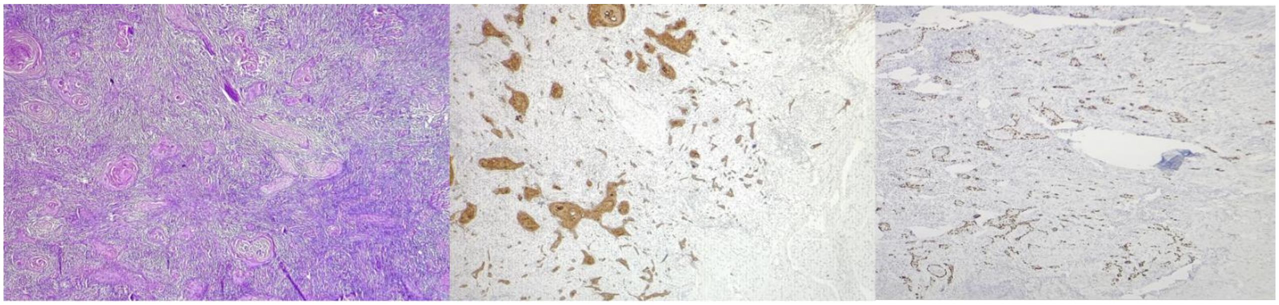

Figure 4: Haematoxylin and eosin (20X) – WPOI 4: Islands of tumor cells (< 15 cells). Pan-cytokeratin and p-40 highlighting the pattern of invasion.

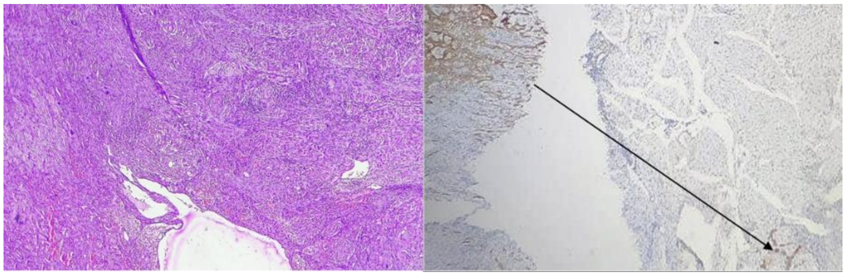

Figure 5: Haematoxylin and eosin (20X) – WPOI 5: Tumor satellite separate from the main tumor (at a distance of > 1 mm). Immunohistochemical markers easily identify smaller foci of tumor cells.

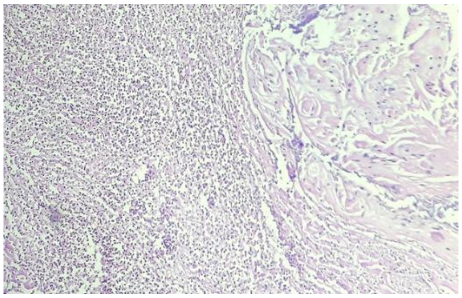

Figure 6: Haematoxylin and eosin (40X) – Strong lymphocytic host response (LHR-1) showing a complete host response, with a dense lymphocytic infiltrate rimming the tumor at the advancing edge.

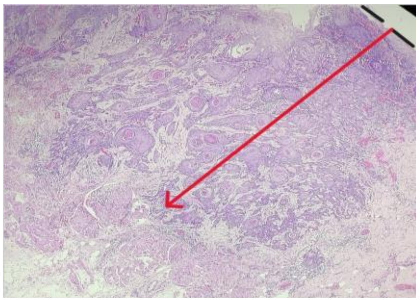

Figure 7: Measurement for depth of invasion (DOI), indicated by a red arrow, with the "horizon" marked as a dashed line.

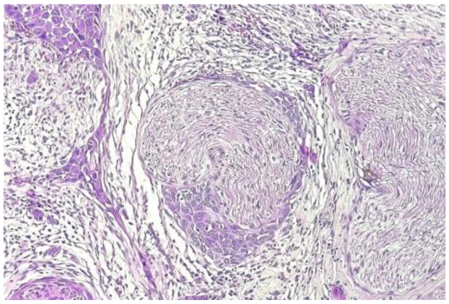

Figure 8: Haematoxylin and eosin (40X) – Perineural invasion: Tumor cells completely surround a nerve and invade its perineurium.

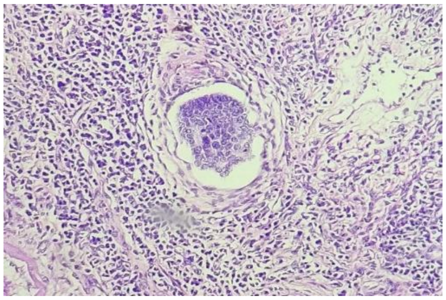

Figure 9: Vascular invasion: Vessel filled by a rounded islet of tumor cells (haematoxylin and eosin).

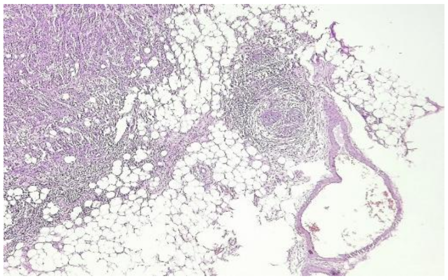

Figure 10: Lymph node with metastasis, showing extranodal extension into the surrounding fat.

Discussion

A total of 70 cases were enrolled. The mean age was noted to be 50.11 ± 11.09 years, range being 27–79 years. Though the majority of the cases were of the age group after 50 years, there was a pretty large proportion of cases of the younger age group. Early exposure to pan-tobacco products is the foremost cause of the higher rates of disease being recorded in younger individuals in this area. The total proportion of males was noted to be 81.43% in the study.

Forty-three of the enrolled cases (61.42%) were non-smokers, while the remaining 27 cases (38.58%) were smokers. Fifty-two of the enrolled cases (74.28%) were having a history of tobacco use in the study, while the remaining 18 cases (25.72%) lacked it. The buccal mucosa was most commonly involved in our case, as in other studies. The left buccal mucosa in 20% of cases, the right buccal mucosa in 17.14% of cases, the right lateral border of the tongue in 14.29% of cases, while the left GB sulcus in 12.86% of cases. 11.43% of cases had right GB sulcus involvement, while 10% of cases had rest of the oral cavity involvement.

In the study by Acharya et al. [5], buccal mucosa (47%) was the most frequently affected site, followed by the gingiva/alveolar process (24%) and tongue (22.78%). Regardless of age, the most frequently affected site was the buccal mucosa. In another study by Tandon et al. [6], the commonest sites for OSCC were noted to be the buccal mucosa and gingivobuccal sulcus (GBS) (45.92%) and alveolus (24.49%). Singh et al. [7] noted similar findings, where buccal mucosa and gingivobuccal sulcus were the most affected sites both in males (49%) and females (40%), followed by alveolus, which was 25% and 31%, respectively.

Amongst histopathological findings, depth of invasion (DOI), in the present study, 18 cases showed DOI < 5 mm, 28 cases showed DOI ≥ 5 mm–10 mm, and 24 cases had DOI > 10 mm. In the present study, amongst the cases which had poor prognosis, the majority, i.e., 6 cases belonged to DOI between 5 to 10 mm, 3 cases were having DOI < 5 mm, and only 2 showed DOI > 10 mm, which are comparable to Chaturvedi et al. [11].

The majority of the study (n = 48, 68.57%) had a type 1 WPOI, which was followed by type 2 (n = 7, 10%), type 3, and type 5 with 6 patients each (8.57%). Shimizu et al. [8] found half of the patients (46/91, 50.5%) with small invasive tumor islands with a size < 15 cells per island, including single-cell invasion (WPOI-4), 20 (22.0%) with invasive tumor islands larger than 15 cancer cells (WPOI-3), and 15 (16.5%) with tumor satellites at a distance of more than 1 mm from the main tumor (WPOI-5).

In the study by Li et al. [8], on evaluating the pattern of invasion, non-aggressive WPOI (WPOI-1 to WPOI-3) was noted in 99 of 299 cases (33.11%). WPOI-4 in 51.17% and WPOI-5 in 16.05%. In the same study by Li et al. [9], it was noted that WPOI was significantly predictive for loco-regional recurrence (LRR) of oral cavity cancers in the study ($p < 0.05$). In the 2019 study by Chatterjee et al. [10], on assessing the WPOI pattern, 102 of the 126 cases (80.95%) had an infiltrative pattern. In the study by Chaturvedi et al. [11], the majority of cases had a non-aggressive pattern of WPOI (45.6%), just like our study.

Pattern of invasion, being one of the important prognostic factors of carcinoma, we compared the distribution of cases among the various other studies conducted by others. Though the sample size was different, the frequency was comparable to these studies. The majority of the authors with which we have compared our study have the highest number of cases belonging to the infiltrative pattern (WPOI-4 and WPOI-5). 98.57% of the cases enrolled in the study were noted to have type 1 LHR response, while only 1 other patient had type 3 LHR response. Of the 69 with type 1 LHR, 17 cases showed poor prognosis, i.e., recurrence or death, and 11 showed good prognosis, i.e., no recurrence. Chaturvedi et al. [11] showed 42.3% type 1 LHR, which is comparable to our study.

Lymphovascular invasion for lesions was noted in 12 of the enrolled cases (17.14%), while the remaining 58 cases (82.86%) were noted to have no lymphovascular invasion, which was comparable to Chatterjee et al. [10] and Li Yu Lee et al. [9]. Resection margin was > 5 mm in 69 of the 70 enrolled cases, while only one patient had an inadequate resection margin. The studies by Li Yu Lee et al. [9] and Chaturvedi et al. [11] had similar findings as in our study.

Extranodal spread for lesions was noted in 5 of the enrolled cases (7.14%). This is similar to Muhammad Faisal et al. [12]; only 1 out of 118 cases showed extranodal spread, and 117 did not show any extranodal spread.

Follow-up was obtained in 29 of the enrolled cases. It was found that 18 of these cases (62.07%) had no recurrence, while 9 patients died (31.04%) and 2 patients had a recurrence (6.9%). The patients with recurrence had WPOI-4 with lymphovascular invasion in their original excision specimen. Out of 9 patients who died, 2 had recurrence, and 3 died of old age. Causes for the remaining 4 could not be traced. The mean age was significantly higher in the poor-prognosis group ($p < 0.05$). The proportion of patients with age > 60 years was significantly higher in the poor-prognosis group ($p < 0.05$). The gender distribution was statistically comparable between the good-prognosis and poor-prognosis groups ($p > 0.05$). The proportion of patients with smoking or tobacco habit was significantly higher in the poor-prognosis group ($p < 0.05$). The proportion of patients with depth of invasion > 10 mm was significantly higher in the poor-prognosis group ($p < 0.05$). The proportion of patients with perineural or lymphovascular/extranodal spread was significantly higher in the poor-prognosis group ($p < 0.05$). The proportion of patients with WPOI type 1 was significantly higher in the good-prognosis group ($p < 0.05$).

The prognostic findings were similar to those noted in some of the other identical studies. In the study by Suresh et al., the patients who belonged to the younger age group (< 65 years) were noted to have better survival in comparison to the older age group, a finding replicated in our study. In addition, extranodal status was associated with poor outcomes, like in our study. Recurrence was noted in 11 of the 148 enrolled patients in this study, with 2 deaths reported because of postoperative pneumonia. There was no significant difference in the disease-specific survival rate by gender, another finding identical to our study. Various studies have suggested that both perineural and vascular invasion are known predictors of poor outcomes in OSCC patients. In a study (571 OSCC patients), it was observed that, relative to vascular invasion, lymphatic invasion was significantly related to poorer overall survival, disease-specific survival, and disease-free survival [13,14].

There were a few limitations in the study. The follow-up period was limited, due to which the outcomes were not evaluated in all enrolled cases. The sample size was limited, and the study was conducted in only one hospital. Future studies with a larger sample size, a multi-center study design, and longer follow-up can help in validating our study findings.

Conclusion

OSCC is noted more commonly in elderly males. Most of them had significant tobacco use or smoking. More than one-third of the enrolled cases of OSCC either died or suffered from recurrence. Key factors contributing to poor prognosis included age, smoking or tobacco use, and higher depth of invasion (> 10 mm). Perineural or lymphovascular/extranodal spread and a higher grade of WPOI were significantly associated with poor prognosis. Most of the patients with early-stage SCC have a poor prognosis despite small tumor size. The TNM staging used for reporting does not provide information on the aggressive clinical behavior of the tumor. These indicators are easy and reliable factors and should be routinely evaluated and be a part of the standard reporting format.

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