

## Head and Neck Cancer

# Significance of Pattern of Invasion in Tongue Squamous Cell Carcinoma—A Retrospective Study from a Regional Cancer Center of North-East India

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## Abstract



**Introduction** Many multiparametric models and scoring systems had been proposed in oral tongue squamous cell carcinoma (OTSCC) to predict the survival and recurrence, out of which pattern of invasion (POI) is gaining focus recently.

**Objective** We conducted a retrospective study with the aim to see the prognostic significance of the POI and other parameters such as depth of invasion, perineural invasion (PNI), and lymph node status in OTSCC.

**Materials and Methods** The slides of already diagnosed OTSCC cases were prepared from January 2015 to December 2017 records and studied by two pathologists for different patterns using Brandwein-Gensler scoring system. The different clinicopathologic parameters were compared with different POI. Statistical analysis was performed to present cumulative survival outcomes and for comparison.

**Results** Most of our patients were > 40 years of age with male preponderance. Tumor differentiation pattern was assessed using Broders' system of grading that showed 85% of tumors were well, 12.5% tumors were moderately differentiated, and 2.5% tumors were poorly differentiated. The worst POI was predominantly pattern III (50%) followed by pattern II (32.5%) and pattern IV (13.8%). Most patients were in stage II (33.8%) followed by stage III (32.5%), stage IV (26.3%), and stage I (7.5%). There was an inverse relationship between POI with tumor stage and recurrence. A strong statistically significant association was found between POI with perineural infiltration and lymph node metastasis.

**Conclusion** We concluded from our study that worst POI is significantly associated with number of lymph nodes metastasis and perineural infiltration and hence can be used as an independent prognostic factor.

## Keywords

- ▶ pattern
- ▶ invasion
- ▶ worst
- ▶ prognostic
- ▶ tongue
- ▶ lymph node

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## Introduction

Broders first introduced in 1920 histopathological grading of squamous cell carcinoma (SCC) based on the proportion of differentiated cells to undifferentiated or anaplastic cells within the entire tumor cell population and graded as highly/well, moderately, poorly differentiated, and undifferentiated tumors.<sup>1,2</sup> The utility of tumor differentiation using Broders' histopathological malignancy grading system in predicting the clinical course and outcome of oral tongue squamous cell carcinoma (OTSCC) has been found to be limited and criticized because of its poor prognostic value, and lack of reproducibility, underscoring the need for more complex grading systems. Studies by Brandwein-Gensler et al,<sup>3</sup> Almagush A et al,<sup>4</sup> Anneroth et al,<sup>5</sup> Bryne et al,<sup>6</sup> and Martínez-Gimeno et al<sup>7</sup> came into being where multi-parameter prognostic models and scoring systems that include nuclear pleomorphism, mitotic index, lymphocytic response, tumor growth pattern, tumor thickness, degree of keratinization, depth of invasion, and pattern of invasion (POI) have been proposed<sup>7-10</sup> to predict the survival of patients with OTSCC and there was a general agreement that the most useful prognostic information can be deduced from the invasive front of the tumor, where the deepest and presumably most aggressive cells reside.<sup>11</sup>

SCC was encountered as the most common histological diagnosis in the malignant neoplasm of tongue; we conducted a retrospective study on 80 patients with an aim to study the prognostic significance of the POI and other clinicopathological parameters such as survival, stage, recurrence, depth of invasion, perineural invasion, and lymph node status in OTSCC.

## Materials and Methods

### Tissue Specimens

Paraffin-embedded sections of 80 patients with OTSCC collected between January 2015 and December 2017 from the hospital archives were evaluated. Only exclusion criteria used were any patients receiving preoperative chemo- or radiotherapy and recurrent cases. All the sections were from the surgical resection specimen. Patients with history of any prior treatment for OTSCC, residual or recurrent cases, and biopsy specimens were excluded.

### Histological Evaluation

All the hematoxylin and eosin-stained histopathological slides were concurrently reviewed and evaluated independently by two qualified pathologists (the first observer LMK and the second observer YR) using the same type of microscope without any prior knowledge of each patient's clinical details. All the hematoxylin and eosin-stained histopathological slides were concurrently reviewed and evaluated independently by two qualified pathologists (the first observer and the second observer) using the same type of microscope without any prior knowledge of each patient's clinical details. A set criterion was formulated for the evaluation of the slides as follows:

- All the sections of the tumor were evaluated microscopically by the two pathologists (LMK and YR).
- The maximum depth of infiltration was calculated microscopically under 40x and would be taken for consideration.
- The POI was taken for consideration in the section of maximum depth of thickness at its infiltrating edge following the criteria set by Brandwein-Gensler et al<sup>3</sup> (details mentioned in the next paragraph) under high power resolution (40X).
- Extratutural angiolymphatic invasion as mentioned in College of American Pathologist (CAP) guidelines was not taken into consideration as worst POI (WPOI) 5 in this study.

When the opinions of the two evaluators differed selecting the sections or maximum depth of invasion, consensus was reached by discussion.

### Histologic Variables and Invasion Pattern Grading

Tumor differentiation was done using Broders' grading system. Variables like depth of invasion, lymph node metastasis, perineural invasion, and POI were evaluated.

Depth of invasion was measured from the base of adjacent normal epithelium to the deepest point of invasive tumor.

Tumor POI was examined at the host-tumor interface. Invasive tumor front scoring system defined by Brandwein-Gensler et al<sup>3</sup> was used in our study comprising patterns I to V. Pattern I represents tumor invasion in a broad pushing manner. Pattern II represents tumor invasion with broad pushing "fingers," or separate large tumor islands, with a stellate appearance. Pattern III represents invasive islands of tumor >15 cells per island. Pattern IV represents invasive tumor islands <15 cells per island, including single cell invasion and single-cell filing pattern. Pattern V represents tumor satellites of any size at distance of 1 mm or more from intervening normal tissue (not fibrosis) at the invasive tumor front.

### Statistical Analysis

Frequency tables of demographic and clinicopathological parameters were established. Kaplan-Meier plot was constructed to present cumulative survival outcomes and compared using the log-rank test. A *p*-value of <0.05 was considered to be statistically significant.

## Results

The distribution of patients by demographic and clinicopathologic factors is shown in [Table 1](#). The mean follow-up period was 35 months (range: 1-60 months). Out of the 80 patients, 18 patients died of OTSCC because of recurrence, whereas 40 were alive at the end of the follow-up period, while remaining 22 patients were lost to follow-up.

OTSCC was more common in patients age  $\geq 40$  years (82.5%) in comparison to <40 years (17.5%). It had male preponderance (71.3%) over female (28.7) with male to female ratio of 2.5:1.

**Table 1** Demographic and clinicopathological features of 80 patients with oral tongue squamous cell carcinoma

Parameters	Number of patients	(%)	Parameters	Number of patients	(%)
Age			Perineural invasion		
<40 years	14	17.5	Present	31	38.7
≥40 years	66	82.5	Absent	49	61.3
Gender			Lymph Node Metastasis		
Male	57	71.3	Present	31	38.7
Female	23	28.3	Absent	49	61.3
M:F	2.5:1				
Differentiations			Recurrence		
WDSCC	68	85	Present	18	22.5
MDSCC	10	12.5	Absent	62	77.5
PDSCC	2	2.5			
Status			Tumor Depth		
Alive	40	50	≤5mm	22	27.5
Dead	18	22.5	>5–10mm	39	48.8
Lost to follow-up	22	27.5	>10mm	19	23.8
Stage			Pattern		
Stage I	6	7.5	Pattern I	0	0
Stage II	27	33.8	Pattern II	11	13.8
Stage III	26	32.5	Pattern III	40	50.0
Stage IV	21	26.3	Pattern IV	26	32.5
			Pattern V	3	3.8

Abbreviations: MDSCC, moderately differentiated squamous cell carcinoma; PDSCC, poorly differentiated squamous cell carcinoma; WDSCC, worst differentiated squamous cell carcinoma.

Tumor differentiation pattern assessed using Broders' system of grading showed that 85% of tumors were well differentiated, 12.5% tumors were moderately differentiated, and 2.5% tumors were poorly differentiated.

Tumor depth of >5 to 10 mm was seen in 48.8% followed by ≤5 mm in 27.5% and >10 mm in 23.8% of patients.

The different patterns were predominantly pattern III (50%) followed by pattern II (32.5%), pattern IV (13.8%), and the least was pattern V (3.8%). The pattern I was not seen in our study (→Fig. 1).

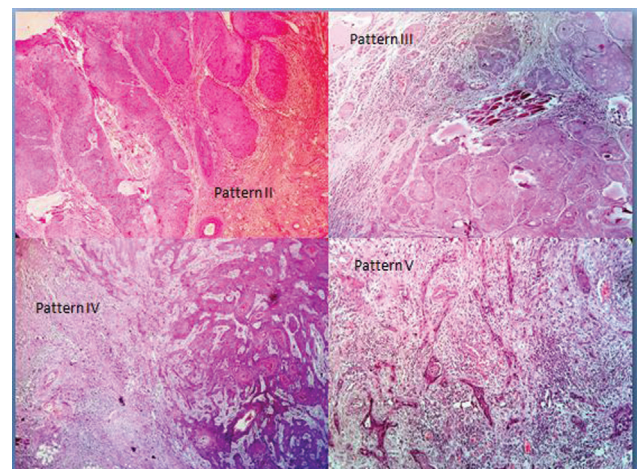
Most patients were in stage II (33.8%) followed by stage III (32.5%) and stage IV (26.3%). Least common was stage I (7.5%).

Perineural invasion and lymph node metastasis were seen in 38.7% each, while recurrence occurred in 22.5% of patients.

### Survival Outcomes

The overall survival of patients with OTSCC at 1 year, 3 years, and 5 years was 92.9, 58.5, and 50.5, respectively. Depth of invasion, perineural invasion, nodal metastasis, and POI correlate well with the overall survival in patients with OTSCC; however, no statistically significance ( $p < 0.05$ ) was seen.

There was an inverse relationship between POI with tumor stage and recurrence; however, it did not show strong statistical association (→Table 2).



**Fig. 1** The different patterns of infiltration, hematoxylin and eosin, 20X.

A strong statistically significant association was found between POI with perineural infiltration ( $<0.013$ ) and lymph node metastasis ( $<0.0001$ ; →Table 3).

### Discussion

The present study assessed the effectiveness of clinicopathological parameters in predicting the mortality as well as the

## POI vs STAGE

pattern	Stage					Total	p value
	Stage I	Stage II	Stage III	Stage IV	Stage V		
II	3	6	2	0	11		
	50.00%	22.20%	7.70%	0.00%	13.80%		
III	3	13	14	8	40		
	50.00%	55.60%	53.80%	38.10%	50.00%		
IV	0	6	9	11	26	0.17	
	0.00%	22.20%	34.60%	52.40%	32.50%		
V	0	0	1	2	3		
	0.00%	0.00%	3.80%	9.50%	3.80%		
Total	6	27	26	21	80		
	100.00%	100.00%	100.00%	100.00%	100.00%		

## POI VS Recurrence

pattern	Recurrence			Total	p value
	No	Yes	Total		
II	11	0	11		
	17.70%	0.00%	13.80%		
III	28	12	40	0.147	
	45.20%	66.70%	50.00%		
IV	20	6	26		
	32.30%	33.30%	32.50%		
V	3	0	3		
	4.80%	0.00%	3.80%		
Total	62	18	80		
	100.00%	100.00%	100.00%		

Table 2 Relationship between pattern of invasion (POI) on oral tongue squamous cell carcinoma with stage and recurrence.

## POI vs PNI

pattern	PNI		Total	p value
	absent	present		
II	9	2	11	
	18.40%	6.50%	13.80%	
III	29	11	40	
	59.20%	35.50%	50.00%	
IV	10	16	26	0.013
	20.40%	51.60%	32.50%	
V	1	2	3	
	2.00%	6.50%	3.80%	
Total	49	31	80	
	100.00%	100.00%	100.00%	

## POI vs LN status

pattern	LN		Total	p value
	Absent	Present		
II	11	0	11	
	22.40%	0.00%	13.80%	
III	28	12	40	
	57.10%	38.70%	50.00%	
IV	10	16	26	<0.0001
	20.40%	51.60%	32.50%	
V	0	3	3	
	0.00%	9.70%	3.80%	
Total	49	31	80	
	100.00%	100.00%	100.00%	

Table 3 Relationship between pattern of invasion (POI) on oral tongue squamous cell carcinoma with perineural invasion (PNI) and lymph node (LN) metastasis.

prognostic significance of the POI at the host-tumor interface of patients with OTSCC.

In the present study, the overall survival of patients with OTSCC at 1 year, 3 years, and 5 years was 92.9, 58.5, and 50.5, respectively. A reduced 5-year survival has been reported by Spiro et al for patients with oral tongue cancer.<sup>12,13</sup> We did not find a statistically significant relationship among the depth of invasion, lymph node metastasis, and perineural invasion with patient mortality. The depth of invasion by microscopic method is best evaluated only after the patient has undergone surgical treatment of the tumor and hence the usefulness in prognostication is limited. Studies done in early stage OTSCC found depth of invasion to be an independent prognostic factor. A preoperative determination of tumor depth through MRI and ultrasonography has been

suggested by several groups.<sup>14,15</sup> Possibly the small sample size and inclusion of both early (T1-T2) and late stage (T3-T4) OTSCC in the present study would explain the reason why a statistical significance was not found between depth of invasion, lymph node metastasis, and perineural invasion with overall survival.

Majority of the cases in the present study were well-differentiated SCC (85%) and no association of differentiation with the POI was found. This was also observed in study done by Nadaf et al,<sup>16</sup> and concluded that five POIs could serve as an individual prognostic marker irrespective of the histologic differentiation of tumor. Different POIs have been reported for SCCs of different sites, for example, the skin, head and neck, as well as the cervix uteri SCCs and gastric and endometrial adenocarcinomas,<sup>17-20</sup> and a high grade of

tumor cell dissociation at the invasive front has been reported to be of prognostic value in different types of carcinomas. Several studies in OTSCC have previously confirmed the relationship of unfavorable WPOI with poor prognosis in OTSCC.<sup>11,21</sup>

Bryne et al reported grading system for invasive front that was found to have prognostic significance.<sup>9</sup> In a study by Heerema et al showed that the POI (one of the features of Bryne's malignancy grading system) is an independent prognostic factor in low-stage OSCC.<sup>22</sup> Nadaf et al showed that five POIs (one component of invasive tumor front) could serve as an individual prognostic marker irrespective of the histologic differentiation of tumor.<sup>16</sup> In a study by Almangush et al, tumor budding, the depth of invasion (DOI), and WPOI were evaluated and it was found that they are significant prognostic markers for early stage (T1 and T2, N0 M0) carcinomas of tongue.<sup>23</sup>

In our study, it was observed that recurrence was most commonly seen in pattern III followed by pattern IV and there was no recurrence in pattern II. Many cases from pattern V were lost to follow-up. However, there was an inverse relationship between POI with tumor stage and recurrence, but it did not show strong statistical association, probably due to smaller sample size as well as many patients with highest POI were lost to follow-up. Similarly, Monteiro et al reported that the pattern of spread in oral cancers show little or no relation to the clinical stage at presentation.<sup>24</sup> However, in another study by Odell et al on 42 OTSCC, the prognostic significance of the invasive front grading and the close correlation between POI and metastasis as well as any recurrence of the disease were demonstrated.<sup>25</sup>

We found that LN metastasis and PNI strongly correlate with the worst POI and were found to be statistically significant. PNI was most commonly seen in association with 66.7% of pattern V followed by 61.5% of pattern IV and 27.5% in pattern III, and 18% of pattern II. Lymph node metastasis was seen in 100% cases of pattern V followed by 61.5% of pattern IV and in 30% of pattern III, but no lymph node metastasis was seen in pattern II. Several studies also support the association between POI and lymph node metastasis.<sup>25,26</sup> However, we have not found any studies that show association between perineural infiltration with the pattern of invasion. Hence, we feel the need of to test further in other studies to substantiate this strong association found in our study.

## Conclusion

In conclusion, as observed collectively from different studies mentioned above, it is well known that the most aggressive cells of tumor reside at the invasive front of tumor and show poorer prognosis in relation to worse pattern of invasion at the invasive front of tumor. The present study concluded that POI IV and V are significantly associated with number of lymph nodes metastasis and perineural infiltration, and hence can be an independent histopathologic prognostic parameter in OTSCC.

## Source of Support

Nil.

## Conflict of Interest

None.

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