

## Original Research Article

# Invasive tumor front in oral squamous cell carcinoma: an independent prognostic factor

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### ABSTRACT

**Background:** Head and neck squamous cell carcinoma (HNSCC) is one of the most aggressive and invasive cancer types. Squamous cell carcinomas of the oral cavity are among the ten most common cancers in the world, and accounts for almost 3-5% of all malignancies. The invasive edges of head and neck squamous cell carcinomas often display different morphological and molecular characteristics than more superficial parts of the same tumor.

**Methods:** In our 2 year retrospective study, carried at a tertiary care centre of north India, main aim was to evaluate the prognostic significance of several parameters of the modified Bryne's grading system along with probability of survival in OSCC patients.

**Results:** Out of 60 cases 40 were males and 20 were females. Tumor differentiation was assessed which showed that 90% of the tumors were well differentiated, 6.6% of the tumors were moderately differentiated and 3.4% of the tumors were poorly differentiated. The predominant POI in the primary OSCC was pattern 2 (63.4% in 38 cases) followed by pattern 3, pattern 1 and pattern 4 (28.4% in 17 cases, 6.6% in 4 cases and 1.6% in 1 case) respectively.

**Conclusions:** Distributing all the cases according to the Bryne's prognostic groups we found that 13 (21.7%) cases belonged to group with a score of <9, and 47 cases (78.3%) had a score of >9. The 5-year tumour-specific survival in OSCC patients with invasive front score of <9 was 95% compared to 46.25% in patients with high invasive front score >9.

**Keywords:** OSCC, Invasive tumor front, HNSCC, Prognostic factor, TNM

### INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is one of the most aggressive and invasive cancer types.<sup>1</sup> Squamous cell carcinomas of the oral cavity is among the ten most common cancers in the world, and accounts for almost 3-5% of all malignancies.<sup>2</sup> Oral squamous cell carcinoma (OSCC) corresponds to 95% of all head and neck cancers and is associated with increasing morbidity and mortality.<sup>3</sup> It has been documented to have high frequency in Central and South East Asian countries (India, Bangladesh, Sri Lanka, Thailand, Indonesia, Pakistan).<sup>4,5</sup> Five year survival rate has been seen to be 50-60%.<sup>6</sup>

The invasive edges of head and neck squamous cell carcinomas often display different morphological and molecular characteristics than more superficial parts of the same tumor.<sup>7</sup> Histopathological grading of squamous cell carcinoma (SCC) was first introduced in 1920 by Broders.<sup>8</sup> Broders evaluated his grading system using a number of epithelial malignancies from various body sites and recommended it for the prognostication of epithelial malignancies.<sup>9</sup> Initially it was used to predict clinical behaviour and the prognosis of oral squamous cell carcinomas (OSCCs). Subsequently many studies have revealed that the correlation between prognosis and the degree of differentiation of oral tumours as assessed by the Broders' classification was poor.<sup>10</sup> So with time

many other malignancy grading systems were developed for evaluation of prognosis and the behaviour of OSCC.

Bryne et al modified the Anneroth grading system, which hypothesized that the morphological features within the invasive fronts are important in prediction of clinical behaviour and prognosis of the tumor. Brynes' modified grading system included grading at the most anaplastic areas at the invasive fronts of the tumor.<sup>11</sup> The parameters for evaluation include: nuclear pleomorphism, mitotic index, lymphocytic response, tumor growth pattern, degree of Keratinization. Assessing included not only the tumour cell population but also the histological relationship of the neoplasm to the host tissue.<sup>12</sup>

In OSCCs extensive local invasion and frequent regional lymph node metastases are usually present at the initial stage of the diagnosis, resulting in the unpredictable prognosis of these tumors.<sup>13</sup> General agreement has been deduced that the invasive front is the most useful area in the tumor for prognostic information, where the deepest and presumably most aggressive cells reside.<sup>14</sup>

In our retrospective study, main aim was to evaluate the prognostic significance of several parameters of the modified Bryne's grading system along with probability of survival in OSCC patients and loco-regional metastasis.

## METHODS

It was a 2 year retrospective study conducted in the department of pathology Government Medical College, Srinagar from August 2011 to July 2013. The study material included both tongue and other intra-oral SCCs. The case history of 68 patients was transcribed from patient's individual clinical records.

The pathology material for the study was obtained from the pathology department of Government Medical College, Srinagar, which included paraffin- embedded sections. Eight cases were excluded because of inadequate representation of the deepest invasive front. Thus, 60 cases were included in the study.

Six-micrometre sections were cut on a rotary microtome from the selected blocks. All the hematoxylin and eosin (H&E) stained histo-pathological slides that represented deep invasive fronts in the cut sections were selected and examined concurrently by two pathologists and consensus was reached by discussion.

Histopathological malignancy grading was done on H&E-stained sections according to the criteria described by Bryne et al.<sup>11</sup>

**Table 1: Modified Bryne's malignancy grading system used in our study.**

Morphologic parameters	Score			
	1	2	3	4
<b>Degree of keratinization</b>	Highly (>50%)	Moderately (20–50%)	Minimal (5-20%)	No (0–5%)
<b>Nuclear pleomorphism</b>	Little	Moderately	Abundant	Extreme
<b>Number of mitoses (per HPF)</b>	0–1	2–3	4–5	>5
<b>Pattern of invasion (POI)</b>	Pushing borders	Infiltrating cords/bands or strands	Small cell groups (n>15)	Single cells/tiny groups (n<15)
<b>Lymphocytic infiltration</b>	Marked	Moderate	Slight	None

### Statistical analysis

The prognostic significance of selected parameters on survival was determined Fisher's exact test was used to determine the statistical significance and p<0.05 was considered to be statistically significant.

## RESULTS

All 60 cases were of primary oral squamous cell carcinoma. Out of 60 cases 40 were males and 20 were females. 50 patients were more than 50 years in age whereas rest of the patients belonged to age group of 50 years or less. The mean age of presentation being 59 yrs. 60% of the patients had associated history of tobacco use. Tongue was the commonest site of involvement contributing to 33.3% of the oral SCC. 22 cases with

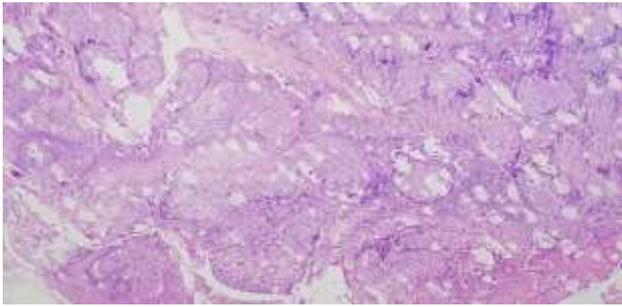
pathologically confirmed regional lymph node metastasis were observed (Table 2).

Tumor differentiation was assessed which showed that 90% (54 cases) of the tumors were well differentiated, 6.6% (4 cases) of the tumors were moderately differentiated and 3.4% (2 cases) of the tumors were poorly differentiated.

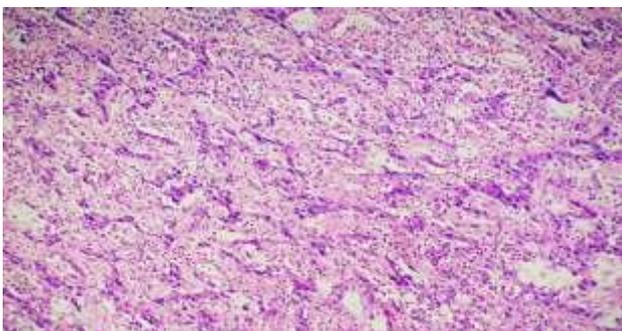
The predominant POI in the primary OSCC was pattern 2 (63.4% in 38 cases) followed by pattern 3 (Figure 2), pattern 1 (Figure 1) and pattern 4 (Figure 3) (28.4% in 17 cases, 6.6% in 4 cases and 1.6% in 1 case) respectively.

Status of inflammation in the primary OSCCs showed a predominance of moderate grade of inflammation in 30 cases (50%) followed by slight lympho-plasmacytic

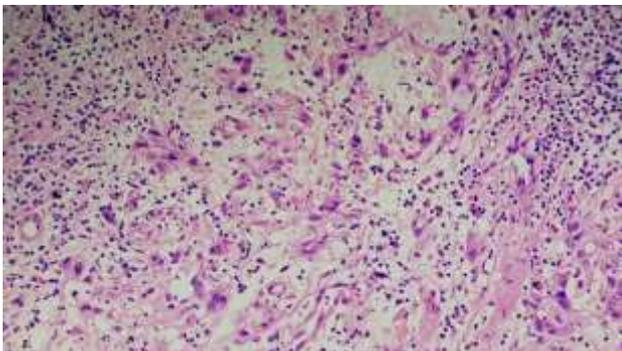
infiltrate in 20 cases (33.3%). 7 cases (11.7%) were not associated with inflammation.



**Figure 1: Squamous cell carcinoma showing well delineated pushing borders of the invasive front**



**Figure 2: Photomicrograph showing tumor infiltrating in small groups and cords.**



**Figure 3: Photomicrograph showing single cell infiltration pattern at the advancing tumor edge.**

Moderate amount of nuclear pleomorphism was observed in 32 cases (53.3%), followed by mild nuclear pleomorphism in 24 cases (40%) and abundant and extreme nuclear pleomorphism in 3 (5%) and 1 (1.7%) case respectively.

All the 60 cases were graded at the invasive front according to the modified Bryne’s parameters. Which showed that about 93% of cases in our study were non-keratinized or minimally keratinized at the invasive fronts. About 11% of the cases showed absence of lymphoid response at the tumor invasive front while as 89% of the cases showed slight to marked lymphoid

response at the invasive front. 90% of the cases had <5 mitosis/HPF at the invasive edge of the tumor (Table 3).

**Table 2: Characteristics of the study group.**

Features	No. of cases	%
<b>Age at presentation (years)</b>		
≤50	10	16.7
>50	50	83.3
<b>Gender</b>		
Male	40	66.7
Female	20	33.3
<b>Tobacco (smoking/chewing)</b>		
Yes	36	60
No	24	40
<b>Anatomical site</b>		
Tongue	20	66.7
Other oral site	40	33.3
<b>T stage</b>		
T1+T2	19	31.6
T3+T4	41	68.4
<b>Nodes</b>		
N0	38	63.3
Nodes clinically/ pathologically present	22	36.7
<b>Depth of invasion</b>		
<4 mm	6	10
≥4 mm	38	63.3
INA*	16	26.7
<b>Perineural invasion</b>		
Present	03	5
Absent	55	91.7
INA	02	3.3
<b>Lymphovascular invasion</b>		
Present	25	41.7
Absent	33	55
INA	02	3.3

\*INA- information not available.

We distributed all the cases according to the Bryne’s prognostic groups and found that 13 (21.7%) cases belonged to group with a score of <9, and 47 cases (78.3%) had a score of >9 (Table 4).

Out of 60 patients 49 (81.6%) were treated with surgery alone and 4 (6.7%) were treated with both surgery and radiotherapy. Surgery together with radiotherapy and chemotherapy had been employed in 5 (8.3%), and 2 (3.4%) patients were given chemo/radiotherapy alone without surgical intervention.

5 years of follow-up, revealed that out of 60 patients, 32 patients (53.3%) did not show any evidence of recurrence. 8 (13.3%) patients were living with the disease and were under further management. 18(30%) patients had died due to the disease and 2 (3.4%) patients had died due to some other causes.

**Table 3: Percentage of cases in each grade according to the modified Bryne’s parameters.**

Morphologic parameters	Score			
	1	2	3	4
	N (%)	N (%)	N (%)	N (%)
<b>Degree of keratinization</b>	1 (1.6)	3 (5)	9 (15)	47 (78.4)
<b>Nuclear pleomorphism</b>	24 (40)	32 (53.3)	3 (5)	1(1.7)
<b>Number of mitoses</b>	18 (30)	19 (31.7)	17 (28.3)	6 (10)
<b>Pattern of invasion</b>	4 (6.6)	38 (63.4)	17 (28.4)	1 (1.6)
<b>Lympho-plasmacytic infiltration</b>	3 (5)	30 (50)	20 (33.3)	7 (11.7)

**Table 4: Distribution of patients according to Bryne's prognostic groups.**

Bryne’s groups	(n=60)	Percentage (%)
<b>5-8</b>	13	21.7
<b>9-12</b>	39	65
<b>13-20</b>	8	13.3

**DISCUSSION**

Cancer is a condition that emerges from interaction between tumor–host microenvironment where malignant tumor cells recruit vasculature and stroma through the production and secretion of growth factors and chemokines. The locally activated host microenvironment controls the proliferation and behavior of the tumor cells. It also creates a permissive field to supply nutrients by angiogenesis and provides a way for metastasis through the vascular system.<sup>15</sup> Among the various aspects associated with cancer, factors affecting prognosis, remain the least understood and hence an accurate prediction of outcome has become extremely challenging. In patients with head and neck cancer, Multiple factors have been implicated in the overall survival and recurrence. Invasive tumor front being one of them. It refers to the pattern in which cancer infiltrates tissue at the tumor/host interface. It is patterned by multiple characteristics that include degree of keratinization, lympho-plasmacytic infiltration, nuclear pleomorphism and pattern of tumor invasion.<sup>16</sup> TNM status is routinely used for clinical staging of OSCCs and planning of treatment. The TNM classification assumes that the prognosis of small tumours without local or regional spread is better than that of larger tumours with metastasis. Several studies have been carried out which show that advanced stages of oral cancer are associated with poor prognosis.<sup>17-19</sup> It has been reported that the rate of growth and pattern of spread in oral cancers show little or no relation to the clinical stage at presentation.<sup>20</sup> Broders’ histopathological malignancy grading system, used routinely for the grading of OSCCs, has been criticized due to its poor prognostic value, and lack of reproducibility.<sup>11</sup> Their study showed that the relationship between histological, loco-regional node involvement and survival rates were statistically significant, and indicated the utility of tumour differentiation in predicting the clinical course and outcome of OSCC, underscoring the need for more complex grading systems.<sup>21</sup> The invasive

tumour front is presumed to harbour the most aggressive population of tumour cells that ultimately will invade, spread locally and metastasize.<sup>22</sup> Bryne et al reported grading system for invasive front which was found to have prognostic significance, both by the originator and later by number of other studies.<sup>23</sup> They also introduced three prognostic groups defined by the derived total malignancy grading score (5–8, 9–12 and 13–20), and statistically confirmed the value of these groups as a predictive factor for prognosis. By cross tabulating their data against patients survival data, they showed that tumours with higher malignancy gradings always ended up with a poor prognosis.<sup>11</sup> Study carried 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. However, it had moderate reproducibility, and contributory value compared to other prognostic histopathological factors when combined together.<sup>14</sup> Data from previous studies supports the hypothesis that several characteristics of the invasive front when combined together are of considerable value for the prediction of clinical behaviour of oral SCCs. In more recent studies, the POI has proven to be of high prognostic value.<sup>24</sup> One recent study carried by Kuriakose’s group showed that five POIs (one component of invasive tumor front) could serve as an individual prognostic marker irrespective of the histologic differentiation of tumour (14). In a Finnish study, tumour budding, the depth of invasion (DOI) and worst POI (WPOI) were evaluated and it was found that they are significant prognostic markers for early stage (T1 & T2, N0 M0) carcinomas of tongue.<sup>25</sup> The authors also remarked that these parameters can be rapidly and easily analysed on routine H&E stained tumour sections. Another parameter- Tumour thickness (TT) was noted to be a strong predictor for cervical lymph node involvement. In an analysis, the optimal TT cut-off point was determined at 4 mm.<sup>26</sup> More recently, other grading systems have been introduced for risk stratification of OSCC, and these need to be tested in further studies.<sup>27</sup>

## CONCLUSION

Distributing all the cases according to the Bryne's prognostic groups we found that 13 (21.7%) cases belonged to group with a score of <9, and 47 cases (78.3%) had a score of >9. The 5-year tumour-specific Survival in OSCC patients with invasive front score of <9 was 95% compared to 46.25% in patients with high invasive front score >9. Large primary tumours (pT3-4) and/or high invasive tumour front scores indicate a high probability of local recurrences. Our results indicate that features regarding the histologically invasive cells of the tumors may be most crucial for metastases and prognosis of OSCC. The probability that the system is of high prognostic value and may contribute to a more optimal treatment of cancer patients, indicates the importance of surgical removal of large and representative biopsies from the tumors. At 5 years following therapy, the proportion of cases surviving with mean Bryne's scores lower or equal to 12 was 57.2% compared to only 25% for those with scores greater than 12. Our study confirms that the Bryne's method for malignancy grading system has a prognostic significance and can be adapted to predict future outcomes.

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