

RESEARCH ARTICLE

Validation of the Invasive Pattern Grade Score as an Independent Prognostic Factor in Oral Squamous Cell Cancers

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ABSTRACT

Aim: To prove the validity of an invasive pattern grade score (IPGS) as an independent prognostic factor in oral squamous cell carcinomas.

Introduction: Oral squamous cell carcinomas are the most common type of cancers in Indian males and their treatment is associated with morbidity and socioeconomic losses to the individual and society. In spite of advances in diagnosis and therapy, prognosis and survival remain dismal: One, due to late clinical presentation and two, due to the unpredictable biological behavior of these cancers. Validation of IPGS as an independent prognostic factor may reduce the uncertainty involved in treatment.

Materials and methods: A retrospective analysis of the records of all patients with oral cavity squamous cell carcinomas treated with surgery between July 2010 and June 2012 was done. A total of 54 patients were analyzed with respect to various clinicopathological parameters including IPGS.

Results: Statistically significant associations were established between IPGS and tumor recurrence ($p < 0.004$) and death due to cancer ($p < 0.02$). Invasive pattern grade score was not influenced by age, tumor size, gender, site, clinical stage, or histologic grade.

Conclusion: Our study indicates the validity of IPGS as an independent prognostic factor that can be used to predict disease behavior in oral cavity squamous cell carcinomas. Further studies are required to establish this score as a routine part of the histopathological examination and to help us in choosing treatment modalities.

Keywords: Invasive front, Oral cavity, Prognostic factor, Squamous cell carcinoma.

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INTRODUCTION

Head and neck malignancies are the commonest cancers in Indian males. The prevalence of oral cavity cancers in our country is extremely high and is one of the highest in the world.¹ In spite of advances in diagnosis and management, the morbidity and mortality due to disease and therapy are significant. Most patients present with locoregionally advanced tumors, which translate to poor treatment outcomes.

The tumor–node–metastasis (TNM) staging system is most commonly used to define the disease burden, choose the treatment modality, and also prognosticate disease recurrence and patient survival.^{1,2} However, the TNM system has no scope to assess the histologic features of the tumor, which determine the biological behavior of these cancers.

There have been numerous attempts to define markers (histological, immunochemical, and genetic) that would prognosticate oral squamous cell cancers and attempt to predict disease recurrence.³ Most of these markers of tumor behavior are not only expensive to perform on a routine basis but are also time-consuming to replicate.

Consequent to the paper by Chang et al,⁴ we attempted to validate a histopathologic method called the invasive pattern grade score (IPGS) in oral squamous cell cancers. This is similar to the Gleason's score used in prostatic cancers, and is a simple technique that can be assessed on light microscopy with hematoxylin and eosin staining.

Because of the histological heterogeneity within the tumor, studies have shown that the most useful prognostic information is obtained from the invasive front of the tumor, where presumably the most aggressive tumor cells reside.^{5,6} Invasive pattern grade score divides the invasive front of the tumor into four different patterns of infiltration, and is expressed as the sum of the two most prevalent patterns.

The aim of this study was to validate the use of IPGS as an independent prognostic factor by attempting to correlate the score with various clinical parameters.

MATERIALS AND METHODS

The case records of all patients with oral squamous cell cancers, who underwent surgery at our institute between July 2010 and June 2012 were reviewed. Tissue specimen blocks and slides were retrieved from the Department of Oncopathology. A total of 54 patients underwent definitive surgical resection of oral squamous cell cancers during this period.

Histopathological analysis included a review of the slides and blocks by two qualified oncopathologists, who evaluated the tumors independently. Invasive pattern grade score was defined based on Gleason's scoring system for prostatic malignancies.^{7,8} The patterns of invasion were classified as per the work of Jakobsson et al⁹ and defined further by Bryne et al.^{5,6,10,11}

To explain in detail, pattern of invasion 1 (*POI-1*) represented tumor invasion in a "pushing manner" with a smooth outline; *POI-2* referred to tumor invasion with broad pushing "fingers," or separate large tumor islands, with a stellar appearance; *POI-3* was invasive islands of tumor cells, more than 15 cells per island; *POI-4* was individual tumor cells or tumor islands with less than 15 cells per island (Fig. 1).

Hence, as is obvious, the cohesiveness of tumor cells decreases from pattern 1 to pattern 4 and degree of anaplasia increases.

The two most common patterns at the invasive front of the tumor (the point where the tumor had the greatest microscopic depth) were identified, and the IPGS calculated as the sum of the two patterns. This summation was done to account for the histological variation within the tumor; 15% or more of the invasive front had to demonstrate a particular pattern for it to be considered. If only a single pattern predominated, it was doubled to arrive at the IPGS.

Statistical Analysis

Chi-square test was used to assess the significance between the various clinical parameters and the IPGS. Odds ratio was calculated to determine the chances of recurrence with respect to the IPGS, as also the chances of death due to disease.

RESULTS

The demographic data of our patient cohort are summarized in Table 1. Most patients were male [$n = 35$ (64.81%)], with an overwhelming 92.59% reporting tobacco usage for a minimum of 3 to 5 years, either in the form of smoking or chewing. Nearly 44.4% ($n = 24$) of the patients presented with the primary site being the oral tongue, followed by the buccal mucosa with a percentage of 33.33% ($n = 18$).

Patient groups were classified as low IPGS if the score was 4 or less, and high IPGS if it was 5 or more. Thirty-two of the 54 (59.25%) patients had a high IPGS score, whereas 22 (40.74%) had a low score. The two most common scores were 5 and 7.

Table 1: Demographic and clinicopathologic features of the patient cohort ($n = 54$)

Clinicopathologic parameters	Number of patients, n (%)
Age	
<45 years	15 (27.7%)
>45 years	39 (72.2%)
Gender	
Male	35 (64.8%)
Female	19 (35.1%)
Tobacco use	
Yes	51 (94.4%)
No	3 (5.5%)
Site of the primary	
Tongue	24 (44.4%)
Buccal mucosa	18 (33.3%)
Gingiva	12 (22.2%)
TNM stage	
I	22 (40.7%)
II	20 (37.03%)
III	10 (18.5%)
IV	2 (3.7%)
Tumor grade	
I	13 (24.07%)
II	28 (51.8%)
III	13 (24.07%)
Recurrence	
Yes	40 (74.07%)
No	14 (25.9%)

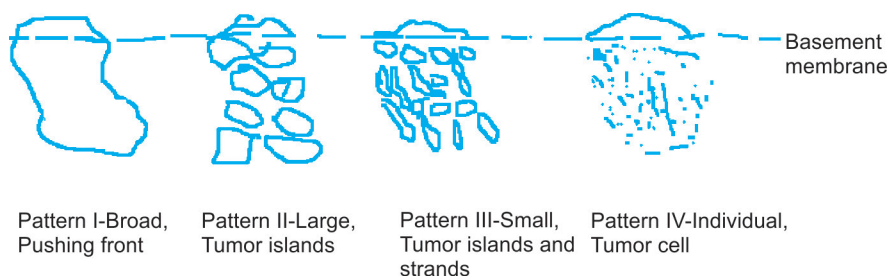


Fig. 1: Different patterns of the invasive front of the tumor

Table 2: Correlation between IPGS and clinicopathologic parameters

Clinicopathologic parameter	Low IPGS (<4) n = 22	High IPGS (>5) n = 32	p-value
Age			
<45 years	7	8	NS
>45 years	15	24	
Gender			
Male	15	20	NS
Female	7	12	
Primary site			
Tongue	10	14	
Buccal mucosa	8	10	NS
Gingiva	4	8	
TNM stage			
I	9	13	
II	9	11	NS
III	4	6	
IV	0	2	
Tumor grade			
I	6	7	
II	12	16	NS
III	4	9	
Nodal metastasis			
N0	12	10	NS
N+	10	22	
Recurrence			
No	21	19	
Yes	1	13	<0.02
Death due to disease (n = 13)			
	2	11	<0.04

NS: Not significant

On comparison of the IPGS with various clinical and pathological parameters, there was no significant correlation between IPGS and age, gender, size of the tumor, TNM stage, and grade of the tumor or lymph node metastasis. Statistical significance was found with respect to tumor recurrence ($p < 0.004$) and death due to distant metastasis ($p < 0.02$) (Table 2).

When tumor recurrence was compared with various clinicopathological variables, statistical significance was achieved with IPGS, TNM stage, and lymph node metastasis (Table 3).

Follow-up of the patient's cohort was done for 48 months, with a loss to follow-up of 4 patients (7.4%). Distant metastasis was noted in 4 patients, with lung being the most common site and one patient with vertebral metastasis. Thirteen patients died due to disease – 10 of whom had locoregional recurrence. At the time of publication, 33 patients are alive and free of disease (Table 4).

There was a good interobserver agreement between the two oncopathologists in scoring the tumors, and in 8 patients, where there was a difference of opinion, the average IPGS was taken into consideration.

Table 3: Correlation of clinicopathologic parameters and IPGS with tumor recurrence

Clinicopathologic parameter	Number of cases			p-value
	Recurrence	No (n = 40)	Yes (n = 14)	
Age				
<45 years	15	9	6	
>45 years	39	31	8	NS
Gender				
Male	35	24	11	
Female	19	16	3	NS
TNM stage				
I + II	42	38	4	
III + IV	12	2	10	<0.02
Nodal metastasis				
N0	22	20	2	
N+	32	20	12	<0.03
Tumor grade				
I + II	41	29	12	
III	13	11	2	NS
IPGS				
Low (2–4)	22	21	1	
High (5–8)	32	19	13	<0.01

NS: Not significant

Table 4: Follow-up of the patient cohort (n = 54)

Patient status	Number	Site of recurrence
Alive and free of disease	33	None
Alive with disease [#]	8	Local/regional; on treatment
Death due to disease	13	Distant metastases – 5 (lung, bone) Locoregional – 8

[#]4 patients were lost to follow-up after diagnosis of locoregional recurrence

DISCUSSION

Oral squamous cell cancers are characterized by histological heterogeneity, not only between tumors but also within the same tumor itself.¹² This is further compounded by difference in biological behavior, depending on the primary site of origin of the tumor.¹³ Hence, prognostication of these tumors is extremely difficult and, most of the times, subjective.

Various authors have made innumerable attempts to objectively assess the biological behavior of oral squamous cell cancers and to develop predictive models.¹⁴ Borders¹⁵ was the first to establish a system of classification, based on the tumor differentiation, in 1920. However, the grading system established by him could not assess survival or the chances of tumor dissemination.

Jakobsson et al⁹ proposed a multifactorial grading system that included tumor and patient characteristics. This system, however, proved useful only for primary tongue cancers. Anneroth et al¹⁶ modified Jakobsson's system by including the degree of keratinization, nuclear

pleomorphism, pattern of invasion, host response, and mitosis activity. Bryne et al^{5,6} wrote the first paper focusing on a grading system based on the invasive front of the tumor.¹⁷

Invasive pattern grade score was developed by Chang et al⁴ as a method of objectively grading the invasive front of the tumor, which theoretically has the most aggressive cells.¹⁸ We have attempted to replicate the same system in our study, wherein the IPGS is used in a similar fashion to Gleason's score in prostate cancers.¹⁹

In our study, we have demonstrated that the IPGS as used by us does not interact with and is independent of clinicopathologic variables like tumor site, tumor size, grade, lymph node metastasis, or tumor extent. Statistically significant correlation between IPGS and disease recurrence and death due to metastases points to the fact that IPGS can be used as an independent prognostic factor.

Invasive pattern grade score is a parameter that can be measured on light microscopy with hematoxylin and eosin staining. It does not require additional testing or immunochemical staining techniques. Interobserver variance is also minimal. Hence, it is our belief that IPGS can be performed routinely and replicated easily.

CONCLUSION

Summarizing, we found that patients with low IPGS (<4) had fewer recurrences and a longer disease-free survival, when compared with those with high scores (>5). Favorable prognosis could thus be linked to a low IPGS. Though the study had a smaller number of patients, we propose the IPGS as a novel, useful, and easily replicable prognostic indicator in oral squamous cell cancers.

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