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Original Research Article

A Comparative Study between Broders and Brynes Grading System of Oral Squamous Cell Carcinoma in Relation to Histopathological Prognostic Factors

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Abstract

Background: Squamous cell carcinoma is most common malignancy of the oral cavity occurring in 5th and 8th decades of life. Histopathological grading of the tumour is important to assess the biological behaviour of the tumour which has prognostic significance**.** ***Aim:*** To evaluate the prognostic significance of Broder's and Bryne's grading system in oral squamous cell carcinoma by comparing with histopathological prognostic factors**.** ***Materials and methods:*** This is a retrospective study of 45 cases of oral squamous cell carcinoma received from department of General surgery and ENT during January 2016 to June 2019. Broders and Bryne's grading systems were compared with different prognostic factors like tumour budding, worst pattern of invasion and mitotic activity. ***Results:*** Review of 45 cases of oral squamous cell carcinoma showed tongue to be common site (51.11%).Common age of occurrence was 50-70 years with male predominance (66.67%) on analysing worst pattern of invasion in both grading system Bryne's grading showed correlation with WPOI (P value-0.00001) and tumour bud/low power field (P value 0.001). Broders grading didn't show prognostic significance when compared to Bryne's grading. ***Conclusion:*** TNM staging system cannot assess aggressive clinical behaviour of oral squamous cell carcinoma. Broders histopathological grading system did not have prognostic significance when compared to Brynes invasive front grading system which is multifactorial grading.

Keywords: Oral squamous cell carcinoma, Broders, Brynes, Histopathological grading.

INTRODUCTION

Oral carcinoma is the 3rd most common malignancy in developing countries and 8 th most common cancer in developed countries [1]. Squamous cell carcinoma constitutes 95% of all the oral malignancies [2]. Most common age of occurrence is 5th to 8th decades of life and is common in men In India tobacco chewing or smoking, chewing of betel nuts and reverse smoking also increases the incidence of oral cancer [3]. Tongue and floor of the mouth are the common sites of this cancer [4].

Death in cases of oral squamous cell carcinomas are due to failure in controlling the primary lesion and its metastasis [5]. Though the patient is at early clinical stage, yet the tumor has very aggressive course leading to the mortality of patient [6].

Histopathological grading is based on Broders criteria (1920) defined by WHO which does not have major impact on patient outcome and hence does not have prognostic significance, Bryne's invasive front grading system has better prognostic significance than Borders grading. In our study we tried to compare the significance of Broders and Bryne's grading system by comparing with histopathological prognostic markers like tumor budding, worst pattern of invasion (WPOI) and mitotic activity.

AIM

To evaluate the prognostic significance of Broder's and Bryne's grading systems by comparing with histopathological prognostic factors that would help in assessing the clinical behaviour of tumour.

MATERIALS AND METHODS

A retrospective study of 45 cases of oral squamous cell carcinoma received from department of General surgery and ENT from January 2016 to June 2019 were undertaken.

Inclusion Criteria

The adequate histologic material from lesions arising from cheek, tongue, Buccal mucosa, palate Alveolus, Valecula and Maxilla were included.

Exclusion Criteria

Tumor arising from the pharyngeal complex and the vermilion border of the lip were excluded as these sites are not from oral cavity proper.

General clinical information like patient age, sex and site of the lesion were noted. All the biopsy specimens were fixed in 10% formalin. After processing, the sections were stained by Haematoxylin & Eosin and were graded according to Broders grading and Bryne's deep invasive front grading system.

Broders system of classification (1920) [1]

According to this system, the tumour is graded depending on the degree of differentiation and tumor cell keratinisation into

Grade I: Well differentiated tumour with cells producing much keratin. 75-100% of tumor cells are well differentiated.

Grade II: Moderately differentiated tumours with, 50-75% of tumour showing differentiated cells.

Grade III: Poorly differentiated tumours, 25-50% of cells showing differentiation

Grade IV: Tumour with anaplastic cells, 0-25% of tumour cells show differentiation

Bryne's *et al*.,deep invasive front grading system (1992)[1]

Morphologic features	**Tumour scores**			
	1	**2**	**3**	**4**
Degree of keratinisation	Highly Keratinized (more than 50% of the cells)	Moderately keratinized (20-50% of the cells)	Minimal keratinisation (5-20% of cells)	No Keratinization (0-5%)
Nuclear pleomorphism	Little nuclear pleomorphism (>75% mature cells)	Moderately abundant nuclear pleomorphism (50-75% mature cells)	Abudant nuclear pleomorphism (25-30% mature cells)	Extreme nuclear pleomorphism (0-25% mature cells)
Pattern of invasion	Pushing well differentiated infiltrating borders	Infiltrating, solid cords, bands and or strands	Small groups or cords of infiltrating cells (n>15)	Marked and wide spread cellular disassociation in small groups of cells (n<15) and or in single cells
Host response (lymphoplasmacytic infiltrate)	Marked	Moderate	Slight	None

The sum of scores were grouped as

Grade I: 4-8

Grade II: 9-12

Grade III: 13-16

The prognostic significance of these two different grading systems were analysed by using 3 histopathological parameters i.e, tumour budding, worst pattern of invasion (WPOI) and mitotic activity.

To assess the tumour budding we selected the areas with high density of tumour budding under low power. Then the number of tumour buds were counted and maximum count per slide were used as bud number. Tumour budding intensity was categorised into 3 groups with less than 5 buds/low power field as low intensity, 5- 10 tumor buds/low power field as intermediate intensity and more than 10 buds/field as high intensity. This budding intensity categorization was according to ITBCC (International Tumor Budding consensus conference) 2016 recommendation [7].

Yamamoto et al has evaluated the mode of invasion at the invasive front of the tumor and graded it from Grade 1 to 4D. Tumors with well defined borders were categorized as Grade 1. Tumours with cords or less marked borderlines were graded as Grade 2. Grade 3 tumours had no distinct borderline and had groups of tumour cells infiltrating at border. Grade 4 was sub classified into grade 4C showing diffuse invasion of Cord like type and grade 4D with diffuse invasion of diffuse type. Grade 4 was considered to be powerful parameter in predicting lymphnode metastases [8]. Brandwein *et al.*, has proposed worst pattern of invasion (WPOI) depending upon the previous descriptions of mode of invasion. WPOI 4 tumors were defined as having tumor islands ≤ 15 cells per island which are discontinuous or separated from main tumor mass. WPOI 5 in tumors are defined by dispersed and discontinuous growth pattern [9]. The degree of tumor dispersion exceeds that of WPOI 4 with defined cutoff of 1mm. In our study we have taken WPOI-4 and WPOI-5 as they have been considered to be related with worse prognosis [10].

Mitotic activity was assessed by counting mitotic figures in 10 continuous high power fields (HPF) in the area having high mitotic activity. The cut off value was taken as ≤ 13/10hpf (low mitotic count) versus ≥ 14/10hpf.

Association between the grading systems and morphological parameters were calculated by using Chi square test. P values ≤ 0.05 were considered significant.

RESULTS

A total of 45 cases of oral squamous cell carcinomas are reviewed in our study. Tongue was found to be more common site (51.11%) and base of the tongue was more commonly involved. Other sites in the decreasing order of frequency are buccal mucosa, palate, Alveolus, cheek and maxilla (Table-1).

Table-1: Sites of involvement in squamous cell carcinoma

Tumour site		No. of cases
Cheek		2(4.44%)
Tongue	Base	13(28.89%)
	Side	10(22.22%)
Buccal mucosa		11(24.44%)
Palate		4(8.89%)
Alveolus,valecula		4(8.89%)
Maxilla		1(2.22%)
Total		45

Males comprised of 66.7% of cases and females comprised of 33.33% of cases. In males maximum number of case were seen in the age group of 50-70 years whereas in females maximum cases were seen in 40-50 years age group (Table-2).

Table-2: Tumour distributions in various age groups and sex

Age (in yrs)	Male	Female
20-30	-	1(6.67%)
30-40	1(3.33%)	2(13.33%)
40-50	6(20%)	10(66.67%)
50-60	10(33.33%)	-
60-70	11(36.37%)	2(13.33%)
>70	2 (6.6%)	-
Total (n=45)	30 (66.67%)	15 (33.33%)

Chi – Square: 17.5096; P-value – 0.0036 (significant)

After grading the tumors in Broders and Brynes grading system, 30 cases were in Broders Grade I out of which maximum cases had 9 -13 score in Brynes grading system. Borders Grade II and Grade III tumors showed maximum number of cases with score 9-13 in Brynes grading (Table-3).

Table-3: Tumour distribution in Broders and Brynes grading systems

Broders grading	Bryne's invasive front grading		
	Less than 8 score	9-13 score	14-16 score
Grade I (n=30)	11(24.44%)	12(26.67%)	7(15.56%)
Grade II (n=8)	-	5 (11.11%)	3 (6.67%)
Grade III(n=7)	-	5 (11.11%)	2 (4.44%)
Grade IV	-	-	-
Total (n=45)	11 (24.44%)	22(48.89%)	12 (26.67%)

Chi-Square-10.352; P-value – 0.035 (significant)

Worst pattern of invasion in different Broders grades were analysed. Maximum Grade I tumors showed WPOI-5 (57.14%), Grade II tumours showed WPOI -4 (71.43%) and all the Grade III tumours showed WPOI -4 (Table-4).

Table-4: Tumours with worst pattern of invasion

Broders grading	WPOI 4	WPOI 5
Grade I (n=14)	6 (42.86%)	8(57.14%)
Grade II (n=7)	5 (71.43%)	2 (28.57%)
Grade III (n=2)	2 (100%)	-
Grade IV	-	-
Total (n=23)	13(56.52%)	10(43.48%)

Chi-square – 3.2352; P-value – 0.1984 (not significant)

Tumors with worst pattern of invasion were analyzed according to Brynes grading which showed that tumors with score less than 8 had WPOI 4 pattern and all the cases with score 14 – 16 had WPOI -5 pattern (Table-5).

Table-5: Tumours with worst pattern of invasion (WPOI) in Bryne's grading

Bryne's grading	WPOI 4	WPOI 5
Less than 8	2(8.7%)	-
9-13 score	11(47.8%)	1(4.35%)
14-16 score		9 (39.13%)
Total (n=23)	13(56.62%)	10(43.48%)

Chi square – 19.2699; P-value – 0.0001 (significant)

When both grading system were compared in cases with WPOI 5, Broders grading did not show correlation with WPOI where as Brynes grading showed correlation. In Broders grading even the Grade I tumors showed WPOI -5 where as in Brynes grading all the tumors with score more than 14 -16 showed WPOI 5 (Table-6).

Table-6: Comparison of Broders and Bryne's grading in cases with WPOI -5

Broders grading	Bryne's grading		
	Less than 8	9-13 score	14-16 score
Grade I	-	1 (10%)	7 (70%)
Grade II	-	-	2(20%)
Grade III	-	-	
Grade IV			
Total (n=10)	-	1 (10%)	9 (90%)

Chi-square – 0.278; P-value – 0.598 (not significant)

Broders grading was compared with mitotic activity in tumor. Maximum number of cases in Grade I, Grade II and Grade III had less than 13 mitotic activity. In cases where activity was more than 14 maximum cases were of Grade I (Table-7).

Table-7: Cases with Broder's grading and mitotic activity /10hpf's

Broders grading	Mitotic activity /10hpf	
	Less than 13	More than 14
Grade I (n=29)	17(58.62%)	12(75%)
Grade II (n=8)	7 (24.14%)	1(6.25%)
Grade III (n=8)	5 (17.24%)	3(18.75%)
Grade IV	-	-
Total (n=45)	29 (64.44%)	16(35.56%)

Chi-square- 2.2983; P-value – 0.3169 (not significant)

When mitotic activity was compared with Brynes grading maximum number of cases with score less than 8 had mitotic count less than 13/10hpf and maximum number of cases with score 14 – 16 had mitotic count more than 14/10hpf (Table-8).

Table-8: Cases with Bryne's grading and mitotic activity/10hpf

Bryne's grading	Mitotic activity /10hpf	
	Less than 13	More than 14
Less than 8	8 (27.59%)	3(18.75%)
9-13 score	20 (68.96%)	2 (12.5%)
4-16 score	1 (3.45%)	11(68.75%)
Total (n=45)	29 (64.44%)	16(35.56%)

Chi-square- 23.5426; P-value – 0.00001 (significant)

Broders and Brynes grading were compared in cases with mitotic activity more than 14mitotic count/10hpf. Maximum number of Broders Grade I tumor were in this group and maximum number of Brynes grading tumors with score 14 – 16 were in this group**.** This showed that there is no prognostic significance of Broders grading.

Table-9: Comparison of Broder's and Bryne's grading in cases with mitotic activity more than 14/10hpf

Broders grading	Bryne's grading		
	Less than 8	9-13 score	14-16 score
Grade I	3(18.75%)	1(6.25%)	8 (50%)
Grade II	-	-	1 (6.25%)
Grade III	-	-	3 (18.75%)
Grade IV	-		
Total (n=16)	3(18.75%)	1 (6.25%)	12 (75%)

Chi-square – 17.510; P-value – 0.004 (significant)

Tumor buds were seen in 17 cases. Remaining cases have well delineated borders. Broders grading was compared with tumor buds/ low power field by categorizing into three groupsi.e, less than 5/low power field, 5 – 10 tumor buds/ low power field, more than 10/ low power field. Maximum number of Grade I, Grade II and Grade III tumors were having less than 5 tumor buds/ low power field (Table-10).

Table-10: Broder's grading and Tumour bud/low power field

Broders grading	Tumor bud/low power field		
	Less than 5	5-10	More than 10
Grade I (n=9)	6(66.67%)	2(22.22%)	1(11.11%)
Grade II (n=5)	3(60%)	1(20%)	1(20%)
Grade III (n=3)	2 (66.67%)	1(33.33%)	-
Grade IV	-	-	
Total (n=17)	11(64.71%)	4(23.53%)	2(11.76%)

Chi square – 0.824; P-value- 0.935 (not significant)

In Brynes grading tumors with score 14 – 16 were having more than 5 tumor buds/ low power field. Maximum cases with score 9 -13 showed less than 5 tumor buds/low power field (Table-11).

Table-11: Bryne's grading and Tumour bud/low power field

Bryne's grading	Tumour bud/low power field		
	Less than 5	5-10	More than 10
Less than 8	-	-	-
9-13 score	11 (64.71%)	1(25%)	-
14-16 score		3(75%)	2 (100%)
Total (n=17)	11(64.71%)	4(23.51%)	2(11.76%)

Chi-square- 13.39; P-value – 0.001 (significant)

Comparison of Broders and Brynes grading was done in tumors with more than 5 tumor buds/ low power field. Maximum number of Grade I tumors and tumors with score 14- 16 in Brynes grade showed more than 5 tumor buds/ low power field (Table-12).

Table-12: Comparison of Broders and Bryne's grading in cases with more than 5 tumour buds/low power field

Borders grading	Bryne's grading		
	Less than 8	9-13 score	14-16 score
Grade I	-	-	3(50%)
Grade II	-	1(16.67%)	1(16.67%)
Grade III	-	-	1(16.67%)
Grade IV			
Total (n=6)	0	1 (16.67%)	5(83.33%)

Chi- square – 2.400; P-value – 0.301 (not significant)

DISCUSSION

In India oral cancers accounts for 50-70% of cancer mortality [3]. Khandelkar *et al.*, in his study of 80 cases on oral cancers showed male predominance (61.25%) which correlated with our study which also showed male predominance (66.67%). High prevalence of oral cancers in men may be because of tobacco consumption coupled smoking whereas females are less indulged in these habits.

In our study maximum cases were in age group ranging from 40-70 years which co-incided by the study done by Salehe Jamadar et al who showed that age distribution was in the range of 35-65 years [4].

Maximum number of cases were found on the tongue (51.11%) in our study which did not correlate with the study done by Saleha Jamadar *et al*., In their study maximum cases were found involving buccal mucosa (75%) [4].

TNM staging system is used widely for predicting the clinical outcome of oral squamous cell carcinoma. However nearly 25% of patients in T1 stage showed poor prognosis on follow up [1]. This suggested that though TNM staging is acceptable for assessing prognosis but the clinical behaviour and biological properties of tumour cannot be assessed.

In 1920 AC Broders had given a quantitative grading system depending upon the differentiation of tumour cells for the cancer of lip. Though this system of grading was widely used, limited relationship was found in between outcome of tumour and patient survival with grading system. This was probably due to the heterogeneity of tumour cell population. Due to the lack of correlation between the Broders grading and prognosis, many authors have proposed different grading system by Jakobsson *et al*., [13], Fischer [14], Lund *et al*., [15], Crissman *et al.*, [16] and Anneroth *et al*., [17].

Anneroth modified previous existing systems and has considered certain parameters like keratinisation, nuclear pleomorphism, mitoses, pattern of invasion, stage of invasion and lymphoplasmocytic infiltration. Anneroth and other grading systems used entire tumor cell population in biopsy to estimate final grading of tumor.

Bryne *et al.*, [18] modified the Anneroth grading system as he recognised that tumour has heterogeneous cell population and deep invasive margins were less differentiated than superficial part of tumour. In Bryne's grading system only the tumour cells at deep invasive margins were graded. In this grading system they omitted stage of invasion and mitotic count which were included in Anneroth's grading system. Omission of these parameters increased reproducibility of Bryne's grading system.

Intensity of tumour budding worst pattern of invasion were proved to be independent novel diagnostic biomarker for assessing the prognosis in early stage of oral squamous cell carcinoma [8]. Proliferation activity was considered as prognostic marker and was assessed by counting mitotic activity with cut off value of ≤ 13/10hpf (low mitotic activity) and ≥ 14/10hpf (high mitotic activity) [11]. In our study we compared the different grading systems with these prognostic markers.

CONCLUSION

Despite the small tumour size of oral squamous cell carcinomas prognosis is poor in significant percentage of cases [12] TNM staging system cannot assess aggressive clinical behaviour of oral squamous cell carcinoma. Broders histological grading system did not have prognostic significance. Brynes invasive front grading system which is multifactorial grading system can be used in predicting the prognosis of oral squamous cell carcinomas.

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