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RESEARCH ARTICLE

DIFFERENT GRADING SYSTEMS OF ORAL SQUAMOUS CELL CARCINOMA AND THEIR RELATION TO LYMPH NODE METASTASIS – A COMPARATIVE STUDY

***,[1]Aroonika S. Bedre and [2]Don, K. R.**

[1] Third Year BDS Undergraduate Student, Saveetha Dental College, Chennai-600077, Tamil Nadu, India
[2]Senior Lecturer, Department of Oral and maxillofacial Pathology, Saveetha Dental College, Chennai-600077, Tamil Nadu, India

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ABSTRACT

Background: Histological grading is an important diagnostic tool to predict the clinical and biological behaviour of cancer. Cervical lymph node metastasis indicate poor prognosis of oral cancer. Oral squamous cell carcinoma has a great predisposition to produce metastasis in lymph nodes. An analysis of the prognostic factors is important for predicting prognosis and reducing the mortality in these patients.

Aim: The aim of this study is to do a comparative study of different grading systems in oral squamous cell carcinoma and assess their relationship to Lymph node metastasis.

Materials and Methods: This study comprised of 20 excisional biopsy cases of OSCC with neck dissections retrieved from the archives of Department of Oral Pathology, Saveetha dental college, Chennai, India. The examiner was blinded to the clinical details and LN status of the patients. The slides were graded using 3 grading systems, namely, Broder's, Anneroth's and Bryne's invasive front grading. Chi - square test was applied to compare the proportion between grades and lymph node status trend. Binary logistic regression analysis was done to estimate the odds of grades with respect to positivity of lymph nodes.

Results: Bryne's grading system showed significant relation with lymph node metastasis, when compared with Broder's and Anneroth's. Chi - square results comparing the 3 grading systems, showed that whenever there is increase in grading from grade I to III, there is increase in positivity of lymph node metastasis. But statistically significant results were seen only in Bryne's. (P=.009) On comparing the 3 grading systems, the Odds ratio of all 3 showed an increase (>1), but it was not statistically significant.

Conclusion: In conclusion, we believe that Bryne's grading of the invasive parts of oral SCC could be taken as a valuable predictive factor in lymph node metastasis. The clinical value of this system can be increased if more number of samples were taken for the study.

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INTRODUCTION

In India, oral cavity is one of the five leading sites of cancer. (Newcomb and Carbone, 1992) Squamous cell carcinoma (SCC) of the buccal mucosa (BM), alveolus, and retromolar trigone together grouped as gingivo-buccal complex, aptly called as the "Indian Oral Cancer", constitute 60% of oral cancer in India. (Annual Report, 1988) Despite the therapeutic and diagnostic progresses in oncology, the clinical outcome of intraoral cancer has remained poor. (Bryne, 1998) Patients with oral squamous cell carcinoma (OSCC) can die from failure to control the primary lesion or regional lymph node (LN) and distant metastasis. (Kurokawa *et al*., 2005) Regional LN involvement is an important prognostic factor. The 5 year survival rate for patients with LN involvement is 20-36% after surgery as compared with 63-86% in patients without LN involvement. (Shingaki *et al*., 1988) Histological grading is an important diagnostic tool to predict the clinical and biological behaviour of cancer. Cervical lymph node metastasis indicates poor prognosis of cancer. (Jamadar *et al*., 2014) Oral squamous cell carcinoma has a great disposition to produce lymph node metastasis. (Akhter *et al*., 2011) Analysis of metastasis will help in predicting prognosis and reducing the mortality in these patients. (DoshiNeena *et al*.,) For many

Corresponding author:* **Aroonika S. Bedre,
Third Year BDS Undergraduate Student, Saveetha Dental College, Chennai-600077, Tamil Nadu, India.

years TNM staging system has been used clinically in predicting prognosis. In early cases of oral squamous cell carcinoma, however, there are many patient who die despite the fact that their neoplasm were considered clinically to be stage I and II and were treated accordingly. In such patient a combined assessment of clinical staging and of cytomorphology of neoplasm might serve as more precise measure for predicting the outcome of neoplasm and for determining their treatment. (Chang, 2002) Many study of squamous cell carcinoma correlating histologic malignancy grading with different clinical parameter such as clinical staging, recurrence and prognosis has been published. Broder's initiated quantitative grading of cancer. His classification system has been used for many years in squamous cell carcinoma and based on proportion of neoplasm resembling normal squamous epithelium. A lack of correlation between Broder's degree of differentiation and prognosis, however, been reported. One of main reason being that squamous cell carcinoma usually exhibits a heterogenous cell population with differences in degree of differentiation. So, multifactorial malignancy grading system was developed to obtain a more precise morphologic evaluation of growth potential of squamous cell carcinoma in head and neck region. This malignancy grading system has been used during last few years in both its original form and modified version, especially for reterospective studies of squamous cell carcinoma. (Anneroth *et al*., 1984) Thus, in our study we reviewed three grading systems along with their prognostic value.

MATERIALS AND METHODS

This study comprised of 20 excisional biopsy cases of OSCC with neck dissections retrieved from the archives of Department of Oral Pathology, Saveetha dental college, Chennai, India. The examiner was blinded to the clinical details and LN status of the patients. The slides were graded using 3 grading systems, namely, Broder's, Anneroth's and Bryne's invasive front grading.

1. Broder's (1920) classification: (Table 1)

Accordingly, tumors were graded on the basis of degree of differentiation and keratinization of tumor cells into

Grade I: Well differentiated tumors – 75-100% of cells are differentiated
Grade II: Moderately differentiated tumors – 50- 75% of cells are differentiated
Grade III: Poorly differentiated tumors – 25-50% of cells are differentiated

2. Anneroth's *et al* (1987) multifactorial grading system: (table 2)

According to this system, three parameters reflecting tumor cell features including keratinization, nuclear pleomorphism, and mitoses were evaluated in the whole thickness of the tumor and each scored from 1-4. Pattern of invasion, stage of invasion, and lymphoplasmacytic infiltration representing tumor-host relationship were graded in the most invasive margins and scored from 1-4. Then the sum of scores were grouped as follows: 5-10 grade I, 11-15 grade II, 16-20 grade III, and the results were compared in the metastasizing and non-metastasizing groups.

3. Bryne's *et al* (1992) deep invasive cell grading system: (Table 3)

According to this system, stage of invasion was omitted from the Anneroth's grading system, while the rest of the 5 parameters mentioned above were measured in the deepest invasive margins, and not in the whole thickness of the tumor, and graded similarly. The sum of scores were grouped as follows: 4-8 grade I, 9-12 grade II, 13-16 grade III, and the results were compared in the metastasizing and non-metastasizing groups.

In cases where opinion of the two authors differed, the disagreement was resolved by consensus after joint review using a multiheaded microscope, and reviewed by the third author. Chi - square test was applied to compare the proportion between grades and lymph node status trend. Binary logistic regression analysis was done to estimate the odds of grades with respect to positivity of lymph nodes.

RESULTS

Broder's System

(Table 4, graph 1)
33.33% of cases (5 cases) were positive for lymph node metastatis and 66.67% (10 cases) were negative among 15 grade I cases.
33.33% of cases (1 case) were positive for lymph node metastatis and 66.67% (2 cases) were negative among 3 grade II cases.
50% of cases (1 case) were positive for lymph mode metastasis and 50% (1case) were negative among 2 grade III cases.

Anneroth's System
(Table 5, graph 2)
25% of cases (3 cases) were positive for lymph node metastatis and 75% (9 cases) were negative among 12 grade I cases.
50% of cases (3 cases) were positive for lymph node metastatis and 50% (3 cases) were negative among 6 grade II cases.
50% of cases (1 case) were positive for lymph node metastatis and 50% (1 case) was negative among 2 grade III cases.

Bryne's System
(Table 6, graph 3)
7.69% of cases (1 case) were positive for lymph node metastatis and 92.31% (12 cases) were negative among 13 grade I cases.
100% of cases (5 cases) were positive for lymph node metastatis and 0% (0 cases) were negative among 5 grade II cases.
50% of cases (1 case) were positive for lymph node metastatis and 50% (1 case) were negative among 2 grade III cases.

Chi - square results comparing the 3 grading systems, showed that whenever there is increase in grading from grade I to III, there is increase in positivity of lymph node metastasis.

But statistically significant results were seen only in Bryne's. (P=.009)

On comparing the 3 grading systems, the Odds ratio of all 3 showed an increase (>1), but it was not statistically significant.

Table 1. Broder's grading system

S. No	Grade	Differentiation of tumour	% of differentiated cells
1	I	well	75-100%
2	II	moderate	50-75%
3	III	poor	25-50%

Table 2. Anneroth's grading system

S.No	Morphological parameter	Score			
		1	2	3	4
1	Degree of keratinisation	>50% cells keratinised	20-50% cells keratinised	5-20% cells keratinised	0-5% cells keratinised
2	Nuclear pleomorphism	little	moderately abundant	abundant	extreme
3	No. of mitosis	0-1	2-3	4-5	>6
4	Pattern of invasion	Pushing, well delineated infiltrating borders	infiltrating, solid cords, bands and/or strands	small groups or cords of infiltrating cells	marked and wide spread cellular dissemination in small groups and/or in single cells
5	Stage of invasion	carcinoma in situ and/or questionable invasion	distinct invasion but involving lamina propria only	invasion below lamina propria adjacent to muscles, salivary gland tissues, and periosteum	extensive and deep invasion replacing most of the stromal tissue and infiltrating jaw bone
6	Lymphoplasmacytic infiltration	marked	moderate	slight	none

Table 3. Bryne's grading system

S. No.	Morphological parameter	Score			
		1	2	3	4
1	Degree of keratinisation	>50% cells keratinised	20-50% cells keratinised	5-20% cells keratinised	0-5% cells keratinised
2	Nuclear pleomorphism	little	moderately abundant	abundant	extreme
3	No. of mitosis	0-1	2-3	4-5	>6
4	Pattern of invasion	Pushing, well delineated infiltrating borders	infiltrating, solid cords, bands and/or strands	small groups or cords of infiltrating cells	marked and wide spread cellular dissemination in small groups and/or in single cells
5	Lymphoplasmacytic infiltration	marked	moderate	slight	none

Table 4. Broder's results

S. No.	Broder's Grade	Lymph node metastatis - positive	Lymph node metastasis - negative	Total
1	I (WDSCC)	5 (33.33%)	10 (66.67%)	15
2	II (MDSCC)	1 (33.33%)	2 (66.67%)	3
3	III (PDSCC)	1 (50%)	1 (50%)	2

Table 5. Anneroth's results

S. No	Anneroth's Grade (score)	Total no. of cases assessed	Lymph node metastasis - positive	Lymph node metastasis - negative
1	I (5-10)	12	3 (25%)	9 (75%)
2	II (11-15)	6	3 (50%)	3 (50%)
3	III (16-20)	2	1 (50%)	1(50%)

Table 6. Bryne's results

S.No	Bryne's Grade (score)	Total no. of cases assessed	Lymph node metastasis - positive	Lymph node metastasis - negative
1	I (4-8)	13	1 (7.69%)	12 (92.31%)
2	II (9-12)	5	5 (100%)	0 (0%)
3	III (13-16)	2	1 (50%)	1 (50%)

Table 7. Discussion comparing our results with previous literature

S. No	studies	Results
1	Our study	Bryne's grading system showed significant relation with lymph node metastasis, when compared with Broder's and Anneroth's
2	Jamadar et al	Bryne's grading system is more predictive for LNM as compared with the multifactorial grading systems that is, Jakobsson's and Anneroth and Hansen's. Broder's grading system is of no prognostic value.
3	Akhtar et al	Both Anneroth's and Broder's grading have been significant but Anneroth's one is more significant then Broder's.
4	Neena et al	Bryne's deep invasive cell score showed significant relation with lymph node metastasis, when compared with Anneroth's and Broder's.

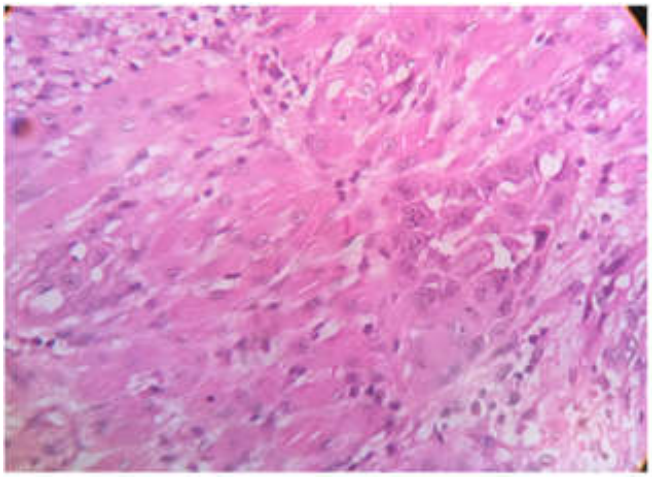


Figure 1. Invasion of epithelial cells into muscles

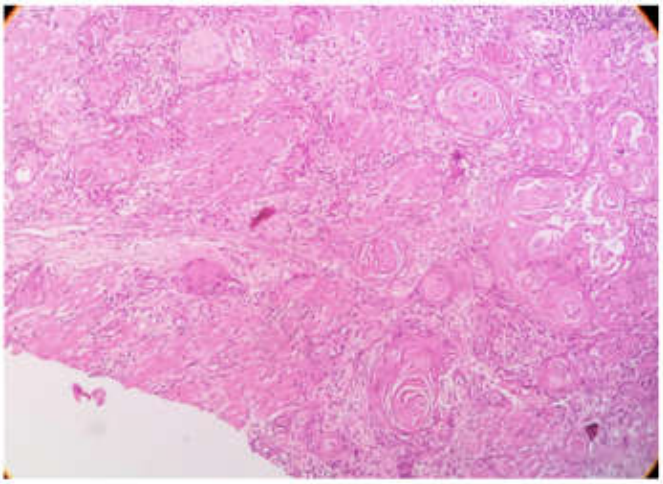


Figure 2. Keratin pearls

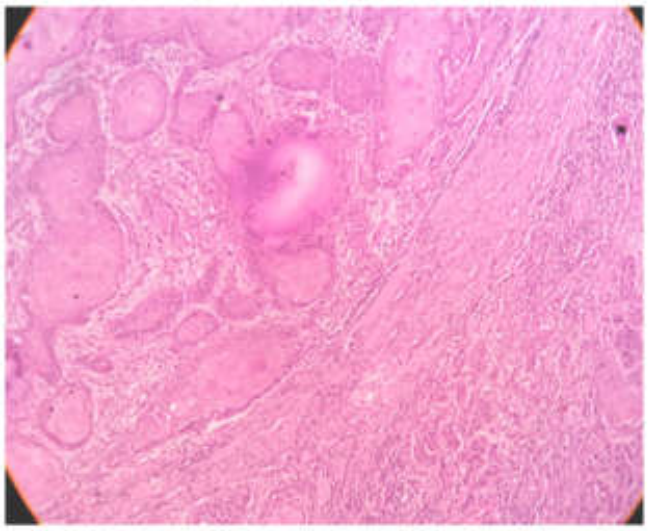


Figure 3. Infiltrating solid cords, bands

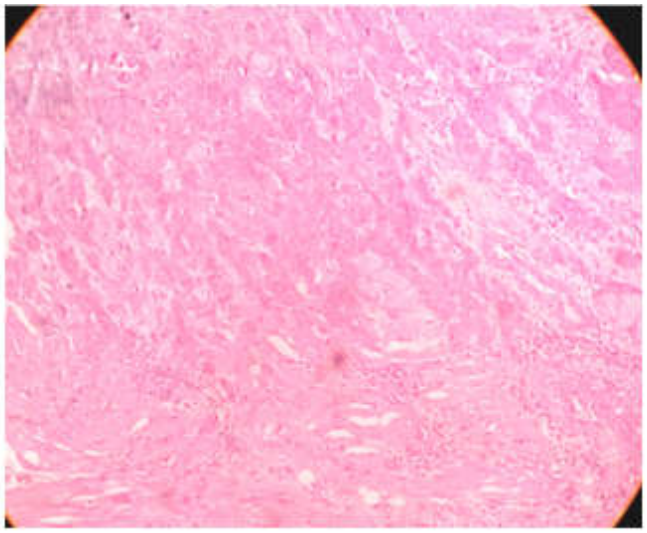


Figure 4. Small groups of infiltrating cells

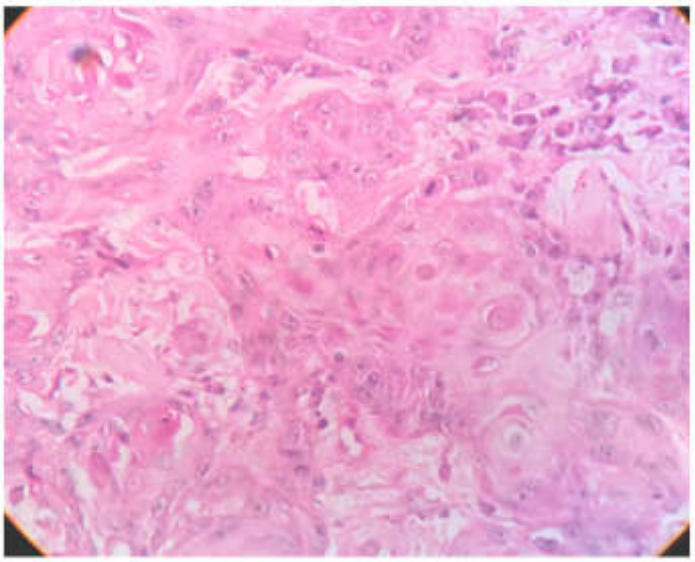
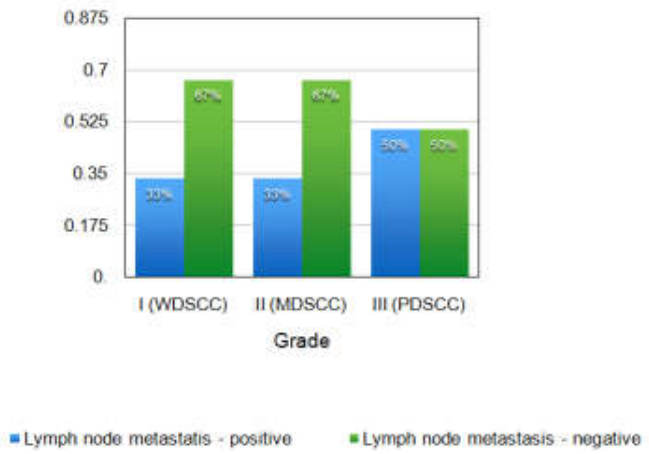
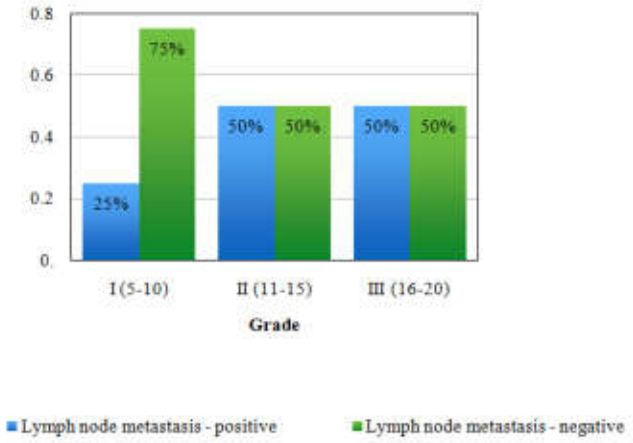


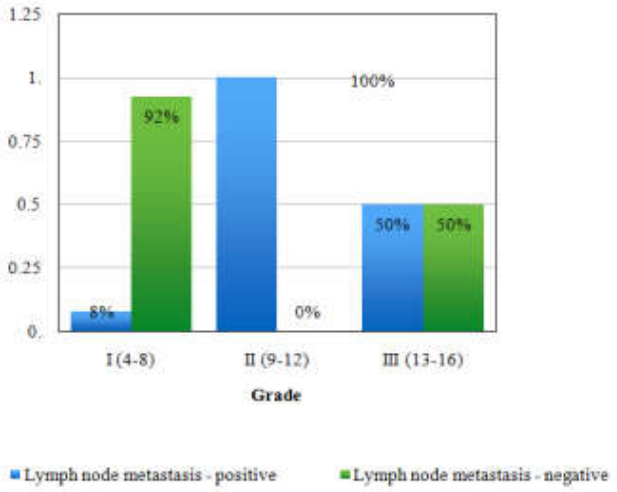
Figure 5. Mitotic figures



Graph 1. Broder's results



Graph 2. Anneroth's results



Graph 3. Bryne's results

DISCUSSION

Oral squamous cell carcinoma (OSCC) is the sixth most common malignancy in the world. Approximately, 405,000 cases of OSCC are diagnosed each year, with a rising incidence in many countries. Due to its relative high mortality and low cure rate, OSCC represents a major public health problem. The WHO acknowledged that the 5 years survival rate of these patients has not improved over the past few decades despite treatment advances. Early detection of OSCC and reliable prognostic parameters is important to reduce mortality rates and to help provide successful cancer treatment. (Don *et al*., 2014) Oral cancer is the commonest cancer in India, accounting for 50-70% of total cancer mortality. (Yazdi and Khalili, 2006) In our study on 20 oral SCC's, males comprised of 80% of cases. According to a study by Akhtar *et al*, among 57 oral SCC's, males comprised of 73.7% of cases. Khandekar *et al*. (DoshiNeena) in their study on 80 cases of oral cancer, showed a prevalence of cancer in 61.25% of males and I. Yazdi *et al* in their study on 48 cases of tongue SCC showed male prevalence of 60.4% (Yazdi and Khalili). High proportion of cases among males may be due to high prevalence of tobacco consumption habits in them, coupled with smoking whereas in our society females less commonly indulge in tobacco smoking. The current TNM classification is the widely used system for predicting the clinical result of oral SCC. In a study by Akhtar *et al*, T1 tumors lacking metastasis, showed statistical significance. (DoshiNeena) However, a significant percentage (35%) of patients with early stages of SCC (T1-T2) had shown a poor prognosis despite the small size of the tumor. Bundgaard *et al* demonstrated that up to 25% of patients with T1 could show poor prognosis at follow-up (Muñoz-Guerra, 2006). Thus, the TNM system includes acceptable prognostic parameters but the biological properties of the tumor cannot be predicted.

According to our study, Bryne's grading system showed significant relation with lymph node metastasis, when compared with Broder's and Anneroth's. Similar results were obtained by two other studies. (Table 7) According to Jamadar *et al*, Bryne's grading system is more predictive for LNM as compared with the multifactorial grading systems that is, Jakobsson's and Anneroth and Hansen's. They also reported that Broder's grading system is of no prognostic value. (Jamadar *et al*., 2014) According to Neena *et al*, Bryne's deep invasive cell score showed significant relation with lymph node metastasis, when compared with Anneroth's and Broder's. (Akhter *et al*., 2011) According to Akhtar *et al*, both Anneroth's and Broder's grading have been significant but Anneroth's one is more significant than Broder's. (DoshiNeena) AC Broders' in 1920 initiated a quantitative grading system for the cancer of the lip. (Figure 2). Despite the widespread use of this system, or slight modifications of it, there has generally only been a limited relationship with the grading and the outcome of treatment and survival of the patient. The suggested reason for such a poor correlation with the grading and prognosis, is the relative heterogeneity of the cell population present in the tumors. Similar to studies by Akhtar *et al* and Yazdi *et al* (2011) we failed to observe any relationship between Broders' system of grading and lymph node metastasis. Due to poor relationship between Broders' grading and patient survival, need for new system of grading was felt. It was recognized by many authors including Jakobsson, Eneroth, Moberger etc., that observing a number of factors in the biopsy along with cellular differentiation might give a better prognostic indicator of oral SCC. They also recognized that not only tumor cells, but also the reaction of the host to the tumor, needs to be graded to give more prognostic information.

Jacobsson *et al*. (1973) multifactorial grading system was based on structure, differentiation, nuclear pleomorphism, mitosis, mode of invasion, stage of invasion, vascular invasion,

and lymphoplasmacytic infiltration. (Figure 1, 3, 4, 5) After Jacobsson, many other researchers modified or developed new system based on the Jacobssons' grading system. These include Fisher (1975), Lund (1975), Willen (1975), Anneroth and Hansen (1984), Crissman (1980 & 1984). (Jamadar *et al*., 2014) In a comprehensive review of the above mentioned grading systems used in oral SCC's, Anneroth *et al*. (1987) modified the existing multifactorial grading systems in use and proposed a new grading system. Unlike the previous systems where a number of parameters overlapped each other, this system reduced the number of parameters to be studied to keratinization, nuclear pleomorphism, mitoses, pattern of invasion, stage of invasion, and lymphoplasmacytic infiltration.

Dilana Duarte Lima Dantas *et al*. (2003) in their study on 16 cases of squamous cell carcinoma of the tongue, and Yazdi *et al*. in their study found no correlation between the Anneroth's histological scores of malignancy and the prognosis. In our study also, we failed to observe any relationship between Anneroth's multifactorial grading system and lymph node metastasis. Anneroth and other multifactorial grading systems used the entire tumor cell population in a biopsy, to obtain a final grading of the tumor. Bryne *et al* (1989) recognized the fact that there are heterogeneous tumor cell populations in malignancies, and observed that the cells in the deep invasive margin tend to be less differentiated than the cells in the superficial part of the tumor. Bryne *et al* in 1992 modified the grading system used by Anneroth. In Bryne's system, only the cells at the deep invasive margin of the tumor were graded. They also omitted stage of invasion and mitotic count from Anneroth's grading system, since their omission increased the reproducibility of the grading system. Also the validity of the mitotic count as a marker of prognosis remains controversial due to tumor heterogeneity, interobserver disagreement, variations in the size of the high power field in different microscopes and a too low mitotic count in the deep invasive parts of the tumor as compared with more solid tumor areas of tumors (Yazdi and Khalili). In our study, the statistical relationship between Bryne's deep invasive cell grading system with lymph node metastasis was significant, similar to a study by Jamadar *et al*. (2014) I. Yazdi *et al*. in their study showed significant statistical differences (p=0.05) between Bryne's grading system and lymph node metastasis.

Conclusion

The first and most widely practiced grading system for oral SCC was developed by AC Broder. Since then a multitude of multifactorial grading systems have developed. Jacobsson and Anneroth grading system, are still sometimes used and studied (Muñoz-Guerra, 2006; Vijay R Tumuluri, 1998; Squamous Cell Carcinoma, 2001; Okada and Mataga, 2003; Kazunari Karakida, 2002). However, the most recent of these multifactorial grading systems developed by Bryne *et al*. (1992), which analyses four factors of the carcinoma in its invasive front is most reproducible but less popularly used. We found a significant positive trend between Bryne's deep invasive cell grading system with lymph node metastasis. In conclusion, we believe that Bryne's grading of the invasive parts of oral SCC could be taken as a valuable predictive factor in lymph node metastasis. The clinical value of this system can be increased if more number of biopsy samples were included in the study (Yazdi and Khalili). There could be scope of further improving the clinical value of this histological grading system by including new immunohistochemical markers that take into account the biological behavior of the tumor. (Vijay R Tumuluri, 1998)

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