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Review Article

Histological Malignancy Grading Systems –Review

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***ABSTRACT*:**
Oral Squamous Cell Carcinoma (OSCC) has a relatively unfavorable prognosis with a 35% to 50% of 5 year survival. The TNM (Tumor, Node, Metastasis) classification is a commonly used staging system for the Prognostic evaluation for OSCC is mainly based on clinical features, but this staging system supplemented by grading system is required for correct prognostic evaluation. In an attempt to predict the clinical behavior of SCC, the histologic grading of tumors has been used for many decades. SCC's usually reveal a heterogenous cell population with potential differences in invasiveness and metastatic behavior , therefore the initial grading systems like Broder's that classified OSCC into well, moderate and poorly differentiated based on the histologic parameters alone showed a lack of correlation with the prognosis. Therefore, multifactorial grading systems which were mainly based on different parameters of tumor cells as well as tumor-host relationship were introduced.
Our article is an attempt to analyze the historical evolution of these grading systems, summarize and compare each of them and finally determine the most predictive grading systems for the clinical behavior and outcome of Oral Squamous Cell Carcinoma.
Key words: Oral Squamous Cell Carcinoma, staging system, heterogenous cell, multifactorial, parameters, tumor-host relationship.

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INTRODUCTION

Oral squamous cell carcinoma, developed from the mucosal epithelia of the oral cavity with multifactorial causes, both intrinsic and extrinsic, is a malignant neoplasm. It is made up of heterogeneous cell populations with different biologic characteristics. OSCC has a relatively unfavorable prognosis with a 35% to 50% of 5 year survival. The Union for International Cancer Control (UICC) TNM staging system has been used for many years to clinically estimate response to therapy and survival. Broder first commenced with histological quantitative grading of cancer based on the proportion of the neoplasm resembling normal squamous epithelium. Following Broader many workers have devised different histological grading systems to predict the biologic behavior of oral carcinoma. Various grading systems have been put forth and each one has its own advantage over the other. Various evaluative studies have compared these grading systems in order to standardize the one which is less expensive, more informative and has a better co-relationship with lymph node metastasis.

I BRODER'S SYSTEM (1927)

In 1920; Dr. Broders' study of 537 cases of squamous cell carcinoma of lip was the beginning of an index of malignancy that hospitals worldwide have adopted since then(1). Followed by this grading was also done on skin in 1921, then Gastro Urinary tract in 1922, Head and neck in 1925 a Soft tissues in 1939. Accordingly, tumors were classified based on the 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
Grade IV: Anaplastic tumors – 0-25% of cells are differentiated

In a literature review discussed by Anneroth G et al, they found that the lack of correlation between Broders' grades and the prediction of Oral Squamous Cell Carcinoma has been described by the fact that SCC's usually exhibit a heterogeneous cell population with probable differences in invasiveness and metastasis behaviour.[2] Studies done by I. Yazdi[3] et al and Doshi Neena[4] et al also failed to observe any relationship between Broders' system of grading and lymph node metastasis.

II. JAKOBSSON et al (1973)

This system not only takes into account the morphological characteristics such as structure, tendency to keratinization, nuclear aberrations, and number of mitosis, but also an evaluation of tumour-host relationship as estimated by factors such as mode, stage of invasion, vascular invasion and degree of lymphoplasmocytic infiltration[3] (TABLE 1). After Jakobsson, many other researchers modified or developed new system based on the Jakobsson grading system. This includes Fisher (1975), Willen (1975), Lund (1975), Anneroth and Hansen (1984) and Crissman (1980 & 1984).

TABLE 1:

Histologic grading of malignancy based on tumour cell population				
Tumor Cell Population	1	2	3	4
Structure	Papillary and solid	Strands	Small cords and groups of cells	Marked cellular dissociation
Differentiation	Highly; Keratinization	Moderately; some keratinization	Poorly; minimum keratinization	Poorly; no keratinization
Nuclear polymorphism	Few enlarged nuclei	Moderate number of enlarged nuclei	Numerous	Anaplastic immature enlarged nuclei
Mitoses	Single	Moderate number	Great number	Numerous
Histologic grading of malignancy based on tumor-host relationship				
	1	2	3	4
Mode of invasion	Well-defined borderline	Cords, less marked borderline	Groups of cells, no distinct borderline	Diffuse growth
Stage of invasion	Possibly	Microcarcinoma (few cords)	Nodular, into connective tissue	Massive
Vascular invasion	None	Possibly	Few	Numerous
Cellular response (plasma-lymphocytic infiltration)	Marked	Moderate	Slight	None

III. FISHER (1975)

Fisher and his team did grading of biopsies of laryngeal carcinoma in 1975. They modified the grading system that was developed by Jakobsson et al as they found that the earlier grading systems indicated the malignancy grade of biopsy tissue to be lower than the grade determined in the sections from surgical specimens.[6](TABLE 2)

TABLE 2

	TUMOR SCORES			
	1	2	3	4
Differentiation	Much keratin	Some keratin	Squamous	Anaplastic
Nuclear polymorphism	Few aniso	Moderate aniso	Many aniso	Bizarre
Mitoses	Occasional	Few	Moderate	Many
Stroma	Abundant	Dense	Delicate	None
Mode	Pushing	Bands	Cords	Diffuse
Stage	No invasion	Microinvasion	In connective tissue	Deep
Vascular	None	Possible	Few	Many
Inflammatory response	Marked	Moderate	Slight	None

IV. LUND ET AL (1975)

They also modified the grading system of Jakobsson et al.by proposing a more exact definition of each parameter and grade and by introducing a specific histologic score, defined as a total mathematical sum of points divided by the number of parameters involved, hence their grading table was far more elaborate than the earlier grading systems. They found a statistically significant correlation between the microscopic score and the death rate as well as the frequency of local recurrence and regional lymph node metastases.[7](TABLE 3)

TABLE 3:

Appearance	Microscopic Grading			
	POINTS			
	1	2	3	4
	Exophytic Papillomatous	Inverted Papillomatous	Small cords and groups of cells	Marked cellular dissociation
Cytoplasmic differentiation	High: >50% keratinized	Moderate: 20-50% keratinized	Poor: 5-20% keratinized	None: 0-5%
Nuclear differentiation (Broder's)	High: >75% Mature	Moderate: 50-75% mature	Poor: 25-50% Mature	None: 0-25% Mature
Mitoses*	Single 0-1	Moderate number 0-3cords	total Great number 0-5	Numerous >5
Mode of invasion (modus)	Well-defined borderline	Microinvasion (few cords)	Groups of cells. No distinct borderline	Diffuse growth
Stage of invasion (depth)	Possible invasion	Less marked borderline	Lymph vessels	Invasion deeper than submucosa
Vascular invasion	None	Possible	Nodular, into submucosa	Blood vessels
Cellular response (plasmalymphocytic)	Marked (continuous rim)	Moderate (many large patches)	Slight (a few patches)	None

* per HPF: High power field

V. WILLEN et al (1975)

Willen et al. used revised system of Jakobsson et al. which is composed by the deletion of morphology parameter "structure" and "vascular invasion" (TABLE 4). The results showed no definitive correlation between the clinical stage and histology grading of malignancy. In the group that did not have any metastases, the neoplasm was found to be highly differentiated with low mitotic rates, but nuclear polymorphism was sometimes prominent. In this group with metastases, the neoplasm were less differentiated and mitotic rates are increased with advanced nuclear aberration.[8]

TABLE 4:

Histologic grading of malignancy				
I. Tumor Cell Population				
	1	2	3	4
Differentiation	High, keratinization	Moderate, some keratinization	Poor, minimal keratinization	Poor, no keratinization
Nuclear polymorphism	Few enlarged nuclei	Moderate enlarged nuclei	Numerous irregular enlarged nuclei	Anaplastic immature nuclei
Mitoses	Single	Moderate number	Great number	Numerous
Histologic grading of malignancy				
II. Tumor-host relationship				
	1	2	3	4
Mode of invasion	Well defined borderline	Cords, less marked borderline	Groups of cells, no distinct borderline	Diffuse invasion
Stage of invasion	Suspicious	Microcarcinoma few cords	Nodular invasion connective tissue	Massive invasion
Cellular response	Marked	Moderate	Slight	None

VI CRISSMAN ET AL (1980)

They modified the criteria outlined by Jakobsson et all. in two steps. A single parameter "pattern of invasion" was included as a different point scale for vascular invasion and structure, and mode of invasion.[6] The new parameter was taken into consideration to calculate the capacity of the tumour cells cohesiveness to keep the tumour cell population together as well as the association of the in-varying tumour cell and host stroma[9]. (TABLE 5)

TABLE 5:

Histologic Criterion	1	2	3	4
Tumor cytology	High degree	Moderate degree	Low degree	None identified
Cytoplasmic keratinization	(>50% of cells) well-formed keratin pearls	(20%-50% of cells), attempts at pearl formation	(5-20% of cells)	
Nuclear differentiation	Few enlarged nuclei, 75% mature	Moderate number enlarged, variably sized nuclei, 50-70% mature	Numerous enlarged pleomorphic nuclei, 25-50% mature	Anaplastic nuclei, 0-25% mature
Frequency of mitosis[#]	0-1	2-3	4-5	>5
Stroma of tumor –host interface				
Inflammatory cell response	Marked continuous rim	Moderate, patchy	Slight, few small patches	None
Tumor growth Pattern	CIS*, probable invasion	Early or microinvasion	Nodular infiltration into submucosa	Submucosa
Pattern of invasion	Verrucous or exophytic	Exophytic with infiltrating cords	Sessile with infiltrating cords	Infiltrating in small groups and dissociated cells
Vascular invasion	Not identified			Identified

* CIS (carcinoma in situ)
# per high power field

VII. ANNEROTH et al (1987)

According to this system, three parameters reflecting tumor cell features were evaluated in the whole thickness of the tumor including keratinization, nuclear pleomorphism, and mitoses and each scored from 1-4. Stage of invasion, Pattern of invasion, and lymphoplasmacytic infiltration representing tumor-host relationship scored from 1-4 and were graded in the most invasive margins. The sum of scores were classified as: 6-12 grade I, 13-18 grade II, 19-24 grade III[2] (TABLE:6)

Akther et al. in a study of 50 patients with squamous cell carcinoma compared the grading of histological malignancy. This is based on Anneroth's classification of biopsy specimens in relation to metastasis in the cervical lymph nodes to two recognized classifications. They concluded that Anneroth's classification can be taken as a standard diagnostic factor and predictive factor of lymph node metastasis.[10]

TABLE 6:

Histologic grading of malignancy of tumor cell population				
Morphologic Parameters	1	2	3	4
Degree of keratinization	Highly keratinized (>50% of the cells)	Moderately keratinized (5-20% of the cells)	Minimal keratinization (5-20% of the cells)	No keratinization (0-5%)
Nuclear polymorphism	Little nuclear polymorphism (>75% mature cells)	Moderately abundant nuclear polymorphism (50-75% mature cells)	Abundant nuclear polymorphism (25-50% mature cells)	Extreme nuclear polymorphism (0-25% mature cells
Number of mitoses/HPF*	0-1	2-3	4-5	>5
Histologic grading of malignancy of tumor-host relationship				
Morphologic parameters	1	2	3	4
Pattern of invasion	Pushing, well delineated infiltrating borders	Infiltrating, solid cords, bands and or strands	Small groups or cords of infiltrating cells (n>15)	Marked and widespread cellular dissociation in small groups of cells (n<15) and/or in single cells
Stage of invasion (Depth)	Carcinoma in situ /or Questionable invasion	Distinct invasion, 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
Lympho-plasmacytic infiltrate	Marked	Moderate	Slight	None

VIII BRYNE'S et al (1992)

Bryne M. in his study of the invasive margins of Oral Squamous Cell Carcinoma in 1992 presented a hypothesis suggesting that molecular and morphological characteristics displayed in other parts of the tumor has lesser tumor prognosis than at the invasive front area of various squamous cell carcinomas. He further states that several molecular events of importance for tumor spread occur at the host interface like gains and losses of adhesion molecules, production of proteolytic enzymes, increased cell growth and initiation of angiogenesis. As a result, they developed a simple grading system on morphological malignancy that restricted the assessment to the deep invasive front of the tumor[11](TABLE:7)

From the Anneroth's grading system, number of mitosis and stage of invasion was omitted, while the rest of the 4 parameters mentioned above were measured in the deepest invasive margins, and not in the whole thickness of the tumor, and graded similarly in this system. The summed up 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. The disagreement on opinions between the two authors was resolved by an agreement after collective review using a multiheaded microscope, and reviewed by the third author. The final results of the three grading systems from the two groups: i) metastatic and ii) non-metastatic were analyzed by logistic regression. Several studies have shown that Bryne's et al. system does significantly better prognosis. All studies performed suggests that invasive front grading should be introduced into the clinic as it is a valuable supplement to clinical staging.

These results that are of high significance obtained from studies indicate that the histologically invasive areas may be basically responsible for the clinical behaviour of the tumour. This might be of importance in choosing the therapy for oral SCC.[10,11]

Doshi Neena et al. in their 3 year retrospectively studied 57 cases with squamous cell carcinoma (metastasizing and non metastasizing tumor). Each of the cases were graded based on the whole thickness of tumours in Broders' classification, Anneroth's multifactorial grading system and Bryne's deep invasive cell grading system.

They concluded that Bryne's deep invasive cell score showed significant relation with lymph node metastasis. Other grading methods were unsuccessful to show any relation with metastasis. And they also concluded that Bryne's deep invasive cell grading system would be of great value in predicting lymph node metastasis in appropriate biopsy specimens and in the treatment of oral squamous cell carcinoma.[4]

TABLE 7:

Morphologic Feature	1	2	3	4
Degree of keratinization	Highly keratinized (>50% of the cells)	Moderately keratinized (5-20% of the cells)	Minimal keratinization (5-20% of the cells)	No keratinization (0-5%)
Nuclear polymorphism	Little nuclear polymorphism (>75% mature cells)	Moderately abundant nuclear polymorphism (50-75%mature cells)	Abundant nuclear polymorphism (25-50% mature cells)	Extreme nuclear polymorphism (0-25% mature cells
Number of mitoses (high power field)	0-1	2-3	4-5	>5
Pattern of invasion	Pushing, well delineated infiltrating borders	Infiltrating, solid cords, bands and or strands	Small groups or cords of infiltrating cells (n > 15)	Marked and widespread Cellular dissociation in small groups of cells(n<15) and or in single cells
Host response (lympho-plasmacytic infiltrate)	Marked	Moderate	Slight	None

IX.THE WORLD HEALTH ORGANIZATION (WHO) GRADING SYSTEM (2005)

This amended grading system was based on Broders' classification and it focuses on microscopic differences between normal epithelium and tumoral tissue because of the absence of cellular differentiation. This classification has applications in routine anatomic pathology for analysis of biopsy surgical specimens. This is also based on the degree of cell differentiation. SCC is classified into 3 categories: well, moderately, and poorly differentiated tumours.[13]

X.BRANDWEIN-GENSLER et al (2005)

They proposed Histologic Risk Assessment in 2005. It analyses the worst pattern of invasion, perineural invasion, and the lymphocytic response to tumors, assigning different scores for each characteristic and categorizing patients into low, intermediate and high risk groups according to local recurrence and overall survival probability.[14]

Rhayany de Castro Ribeiro Lindenblatt et al in their study applied the Multiparameter Grading System, Malignancy Grading of the Deep Invasive Margins, the WHO grading system,and Histologic Risk Assessment to primary OSCC and to analyze the association of these results with prognostic factors and survival.[15]

They inferred that of all the grading systems assessed, Histologic Risk Assessment demonstrated the best results for survival prediction in oral squamous cell carcinoma.

CONCLUSION

The TNM (Tumour, Node, Metastasis) classification failed to signify any information related to the actual histological condition of lesion since it is based on tumour size. It is widely accepted that patients with similar stages of oral cancer may have diverse clinical courses and responses to similar treatment regimes. A high recurrence rate is observed in Stage I and Stage II squamous cell carcinomas in spite of their size and relative amenability to the surgical excision.

However, pathologists have observed for decades that tumour cells in the most invasive parts of a malignant tumor differ substantially from those in the central and/or superficial parts. One of the most promising recent findings in this respect has been the identification of the importance of structural and functional features of the most advanced parts of a carcinoma. It is called the invasive tumor front (ITF) which is used in determining the biological aggressiveness of oral cancer. It has been postulated that the invasive front of the tumors consists of the most aggressive cells, which have the ability to invade surrounding tissues, structures including vessels, and thereby metastasize[8,15,16].

The World Health Organization (WHO) grading system[13], amended in 2005 is based on the classification of Broders' and looks for microscopic differences between normal epithelium and tumoral tissue, because of a absence of cellular differentiation. This classification has utilization in routine anatomic pathology for analysis of biopsy and surgical specimens. Currently, it is also established on the degree of cell differentiation, grouping SCC into three categories: well-, moderately, and poorly differentiated tumors.[11]

Brandwein-Gensler et al. proposed Histologic Risk Assessment in 2005. It analysed the worst pattern of invasion, perineural invasion, and the lymphocytic response to tumors, assigning different scores for each attribute and classifying patients into low-, intermediate and high-risk groups according to local recurrence and overall survival probability.[14]

The Surveillance, Epidemiology, and End Results (SEER) Program, a branch of the National Cancer Institute (NCI) works on collecting and publishing the incidence and prevalence of cancer as well as survival data from population-based cancer registries.

The SEER (Surveillance Epidemiology and End Results) grade assigned by individual pathologists from 9 SEER sites was analyzed. The method of grading was left to the discretion of the individual pathologist. The SEER review team concluded that, i) for all sites studied, the overall 5-year survival rates decreases with higher tumor grade; ii) relationship exists between stage and grade; iii) relationship between grade and survival is often maintained within a given grade; iv) grading is most useful for estimating prognosis in localized disease.

The main recommendations of the SEER review were i) A uniform grading system with defined criteria should be developed in a manner similar to that for cancer patient staging; ii) The criteria should vary for the individual sites and the different histologic types; iii) The establishment of a uniform system of grading will increase the frequency of grading by the pathologists, significantly reduce observer variation, and strenghten the predictive value of histologic grade.

Since Oral Squamous Cell Carcinomas (OSCCs) are majorly made up of heterogenous cell populations,[15] a small biopsy may not include the metastatic phenotype within a tumor. This is substantiated by the fact that grading of larger specimens of surgically removed tumors gives better prognostic indications than the corresponding biopsy.[6,12,15,16]

In conclusion, we consider that Bryne's grading of the invasive front of Oral Squamous Cell Carcinoma is indeed a valuable prognostic factor in lymph node metastasis. Brandwein-Gensler et al. proposed Histologic Risk Assessment Classification in 2005 which analysed the worst pattern of invasion, perineural invasion, and the lymphocytic response to tumors also is a valuable system.

The clinical value of these systems can be increased if larger more representative pieces of biopsies are taken from the tumour.

At present, the established factors that we use to study the biological behaviour of an individual tumour still need firm substantiation. With further study into the molecular genetics of tumors, there still is scope of enhancing the clinical value of this histological grading system by including new immunohistochemical and genetic markers like studying expression of growth factors, genes and proteins that account for the biological behavior of the tumour.

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