J. Int Oral Health **2010**

Histopathological Grading Systems In Oral Squamous Cell Carcinoma: A Review

Ankur Bhargava* Sonal Saigal* Monali Chalishazar†

*M.D.S, Senior Lecturer, Department of oral & maxillofacial Pathology, Government Dental College, Raipur, Chhattisgarh, †M.D.S, Reader, Ahmedabad Dental College, Ahmedabad, India.
Contact: sonal_ankur@rediffmail.com

Abstract:

The prognostic value of histopathologic grading of oral squamous cell carcinomas (SCC) has varied from not any to highly significant. BRODERS' method of grading was compared with a modification of a recent malignancy grading system recommended by ANNEROTH *et al.* which was performed only within the histologically most invasive areas of the tumors. Cox's multivariate survival analyses showed that this grading in the invasive sites had highly significant prognostic value. BRODERS grade had no prognostic value. The stage of tumor had also prognostic value. Bryne M. presented a hypothesis suggesting that molecular and morphological characteristics at the invasive front area of various squamous cell carcinomas may reflect tumor prognosis better than other parts of the tumor. He further states that several molecular events of importance for tumor spread. These highly significant results indicate that the histologically invasive areas may be primarily responsible for the clinical behavior of the tumor, and this may be of importance for the choice of therapy for oral SCC.

Key words: Oral squamous cell carcinoma, Histopathological grading, Invasion.

P- ISSN
0976 – 7428

E- ISSN
0976 – 1799

Journal of International Oral Health

Oral & Maxillofacial Pathology

Review Article

Received: Aug, 2010
Accepted: Oct, 2010

Bibliographic listing:
EBSCO Publishing
Database, Index Copernicus, Genamics Journalseek Database

Introduction:

The oral cavity is the site where food is received and therefore an area of body where contact with exogenous material, microorganism and harmful agents is particularly intense. The oral mucosa functions as a mechanical as well as immunological barrier. Contact with exogenous material means the likelihood of attack from microorganism (parasite, fungi, bacteria, viruses) on the one hand and exposure to micro-trauma, irritants, toxins and carcinogens on the other. Hence the oral mucosa must be assessed for local condition. Inflamed lesion, keratosis as well as premalignant and malignant changes in mucosa may be diagnosed on macroscopic inspection and palpation[1].

Protective mechanisms are an increased capacity for epithelial regeneration, and increased keratinization which present, on inspection, as leukoplakia, a white discoloration of the mucosa. These epithelial changes are reactive and reversible, but with progressive lose of normal control mechanism they lead to precancerous states and oral carcinoma. Apart of the effect of contact with exogenous material, endogenous factor, such as genetic determination, hormonal factors, metabolic disease (eg. Iron deficiency, hepatic disease) also influence these changes[2]. Experience has shown that there is insufficient general awareness of the opportunity offered by oral examination to diagnose premalignant lesion and the early stage of oral cancer[1]. The early diagnosis and treatment of cancer are based on the concept that carcinomata developed over a long period of time, going through intermediate stages of different biological significance, and that treatment at this early or preinvasive stage offers the best prognosis and even the chance of cure[2].

Oral cancer is one of the ten most common cancer in the world. Its high frequency in Central and South East Asian countries (India, Bangladesh, Sri Lanka, Thailand, Indonesia, Pakistan) has been well documented[2-4]. Globally, the varied incidence rates of oral cancer (per 100,000 cases) are seen ranging from 2.0 (UK) to 9.4 (France); 4.4 in Colombia to 13.4 in Canada; 1.6 Japan to 13.5 India; and from 2.6 New Zealand to 7.5 in South Australia. Each year, about 5,75,000 new cases and 3,20,000 deaths occur world-wide. Oral cancer accounts for less than 3% off all cancer in United State, but is the sixth most common cancer in males and twelfth most common cancer in females. In some country, like India, it is the most common cancer[5].

The starting point of oral cancer is the mucosal epithelium. Approximately 94% of all oral malignancies are Squamous Cell Carcinoma[6]. It is because of environmental difference or life style or habit among certain population such as betel quid chewing, snuff dipping or habit of cancer of reverse smoking[7,8]. Oral cancer in younger person may be distinct disease entity, on the basis of different biological behavior and aetiological factor. With regard smoking and alcohol habit, it has been estimated that smoking and alcohol consumption account for 75% of all case of oral squamous cell carcinoma[9,10]. However the significance of these risk factors among young patient is still controversial. Smoking is strongly associated with development of oral cancer in older person but is not generally considered to be significant aetiological agent in younger patient. It suggest that oral cancer in younger and old patient is similar disease with similar outcome[10].

Few studies have analyzed the pathology of these lesion to confirm whether or not, lesion are histologically similar. Oral squamous cell carcinoma is malignant neoplasm arising from mucosal epithelium of oral cavity. It consist of heterogeneous cell population with different biologic characters[11]. For many years TNM staging system has been used clinically estimated response to therapy and survival. The T-designated has been found to be especially reliable prognostic factor. 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 andII 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[11]. 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[12].

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 year in both its original form and modified version, especially for reterospective studies of squamous cell carcinoma[12]. So, in our study we reviewed all the grading systems along with their prognostic value.

Malignancy grading systems

Oral squamous cell carcinoma is a malignant neoplasm arising from the mucosal epithelia of the oral cavity. It consists of heterogeneous cell populations with different biologic characteristics. For many years, TNM staging system has been used to clinically estimate response to therapy and survival. Broder first initiated histological quantitative grading of cancer based on the proportion of the neoplasm resembling normal squamous epithelium. Many workers have devised histological grading systems to predict the biologic behavior of oral carcinoma.

I. BRODER'S SYSTEM (1927)

Broder's suggested a system of grading tumors in which a grade I lesion was highly differentiated (its cell were producing much keratin) while grade IV was poorly differentiated (the cells were highly anaplastic and showed practically no keratin formation) [12].

Broder's initiated quantitative grading in cancer. His classification has been used for many year 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 has been reported. One of main reason being that squamous cell carcinoma usually exhibits a heterogenous cell population with difference in degree of differentiation.

Thus in study of squamous cell carcinoma they found that the histologic grade reflected the aggressiveness of the individual neoplasm and that there was a clear relationship between grade and cure rate, stage of disease and metstatic involvement[12].

II. JAKOBBSON ET AL (1973)

This system not only includes the morphologic parameters "structure", "tendency to keratinization", "nuclear aberrations", and "number of mitosis", but also an evaluation of tumor-host relationship as estimated by parameters such as "mode," "stage of invasion", "vascular invasion" and "degree of lymphoplasmocytic infiltration"[13] (Table 1).

III. FISHER (1975)

They modified slightly the grading system developed by Jakobsson et al. and indicated the malignancy grade of biopsy tissue tended to be lower than the grade of definitive section obtained from surgical specimen[12] (Table 2).

IV. LUND et al (1975)

They also modified grading system of Jakobsson et al. by presenting a more exact definition of each parameter and grade and by introducing a

histologic score, defined a total sum of points divided by the number of parameters evaluated.

They found a statistically significant correlation between microscopic score and death rate as well as the frequency of local recurrence and regional lymph node metastases in a series of 438 patient with squamous cell carcinoma of the tongue[14] (Table 3).

V. WILLEN et al (1975)

They also used modified system of Jakobsson et al.. They consisted of the deletion of two morphological parameter "structure" and "vascular invasion". The results showed no definitive correlation between the clinical stage and histologic grading of malignancy.

In the group with no metastases the neoplasm were highly differentiated and mitotic rates were low, but nuclear polymorphism was sometime prominent. In the group with metastases the neoplasm were less differentiated and advanced nuclear aberrations with increase mitotic rates[12] (Table 4).

VI. CRISSMAN et al (1980)

They modified the criteria outlined by Jakobsson et al. in two steps. They included a different point scale for vascular invasion and structure and mode of invasion into a single parameter "pattern of invasion".

The new parameter was considered to reflect the capacity of the tumor cells cohesiveness to keep the tumor cell population together as well as the association of the invading tumor cell and host stroma. "Differentiated" cohesive neoplasm infiltrated with well delineated pushing margins, whereas "less differentiated" noncohesive neoplasm infiltrated as small, irregular neoplastic cell aggregates or single cells.

This modified system applied on 73 oral squamous cell carcinoma patient. This result shows only the "frequency of mitosis"[15] (Table 5).

VII. ANNEROTH et al (1987)

They also use Jakobsson et al. system for application to squamous cell carcinoma in the tongue and floor of mouth. One of the parameters, "vascular invasion" was omitted. Statistical analysis revealed that the reproducibility of the system was good for all morphologic variables. Mean total malignancy, tumor population and tumor-host relationship scores showed statistically significant correlation with mean rating for all the different morphologic parameters with certain specified exceptions.

The clinical validity of the this system was tested in a comprehensive study was tested in 89 patient of squamous cell carcinoma in the floor of mouth. A statically significant correlation was found between mean total malignancy scores and clinical staging, frequency of recurrence, and death from first oral primary carcinoma[12] (Table 6).

VIII. BRYNE'S (1989, 1992) (ITF) Invasive Tumor Front Grading System

Bryne M. (1998) presented a hypothesis suggesting that molecular and morphological characteristics at the invasive front area of various squamous cell carcinomas may reflect tumor prognosis better than other parts of the tumor. He further states that several molecular events of importance for tumor spread like gains and losses of adhesion molecules, secretion of proteolytic enzymes, increased cell proliferation and initiation of angiogenesis occur at the tumor host interface; consequently they have developed a simple morphological malignancy grading system that restricts the evaluation to the deep invasive front of the tumor. Several studies have shown that this system is a significantly better predictor of prognosis. All studies performed so far show that invasive front grading is a valuable supplement to clinical staging, suggesting that it should be introduced into the clinic[16] (Table 7).

Discussion:

Carcinomas are suggested to be composed of diverse cell populations that are heterogenous for a wide variety of characteristics. Some cells within a given tumor probably have the ability to metastasize, and it is expected that changes in the metastatic cell subpopulations determine one of the most important biologic characteristics of tumors.

Hitherto, it has not been possible to identify the metastatic cell subpopulations with accuracy[16], but the histologic pattern of tumors is often related to the metastatic behavior of tumor cells.

Table 1: Jakobbson et al (1973) histologic grading system

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 nucle	Moderate number o enlarged nuclei	Numerous	Anaplastic immatur 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-lymphocyt infiltration)	Marked	Moderate	Slight	None

Table 2: Fisher (1975) histologic grading system

	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 respons	Marked	Moderate	Slight	None

Table 3: Lund et al (1975) grading system

Appearance	Microscopic Grading			
	POINTS			
	1	2	3	4
	Exophytic Papillomatous	Inverted Papillomatous	Small cords and group of cells	Marked cellular dissociation
Cytoplasmic differentiation	High: >50% keratinize	Moderate: 20-50% keratinized	Poor: 5-20% keratinize	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	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 borderlin	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

Table 4: Willen et al (1975) grading system

Histologic grading of malignancy				
I. Tumour Cell Population				
	1	2	3	4
Differentiation	High, Keratinization	Moderate, some Keratinization	Poor, minimal keratinization	Poor,no keratinization
Nuclear polymorphism	Few enlarged nucle	Moderate enlarged nuclei	Numerous irregula 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 invasior	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

Table 5: Crissman et al (1980) grading system

Histologic Criterion	1	2	3	4
Tumor cytology	High degree	Moderate degree	Low degree	None identified
Cytoplasmic keratinization	(>50% of cells) well-formed kerati pearls	(20%-50% of cells), attempts at pearl formation	(5-20% of cells)	
Nuclear differentiation	Few enlarged nuclei, 75% matur	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

Table 6: Anneroth et al (1987) histologic grading system

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 polymorphisı	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 delineate infiltrating borders	Infiltrating, solid corc 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-plasmacyti infiltrate	Marked	Moderate	Slight	None

Table 7: Bryne's (1989, 1992) (ITF) Invasive Tumor Front Grading System

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

Thus, poorly differentiated cells are believed to demonstrate a higher probability to metastasize than highly differentiated cells. As the presence of metastases is highly correlated with survival, histopathologic grading of tumors has therefore been used for many years to predict the outcome of a tumor, although with varying prognostic value[12]. In the present study we have compared the prognostic value of different grading. The new malignancy grading ANNEROTH *et al.* was a highly significant prognostic factor (P=0.001) in a multivariate survival analysis. The stage of tumor, which is previously accepted as a highly predictive factor for the prognosis[16,17], was also a significant prognostic factor (P<0,015). The Broders' grade was not a prognostic factor (P=0.17). A main difference between these two grading systems is that Broders' grade considers features within the tumor only, whereas in Anneroth's new system tumor cell features in addition to the relationship between the tumor and underlying connective tissue are graded[12]. Since the histologically most invasive parts of the tumor may contain the cells which most probably metastasize the new grading system was slightly modified; only the histologically most invasive areas of the tumors were registered. The present multivariate survival analysis may support this view since morphologic features within the most invasive sites of the tumor could predict the prognosis with high significance,

while Broders' grading of the whole tumor could not. Because SCCs are most often composed of heterogenous cell populations[18], a small biopsy may not include the metastatic phenotype within a tumor. This is supported by the fact that grading of larger specimens of surgically removed tumors gives better prognostic indications than the corresponding biopsy. Also, the total malignancy score was higher in the surgical specimens than in the biopsies on an average. Non-representativity of the biopsies is of clinical importance because the treatment of SCC may partly be based on the malignancy grading of the biopsy[12]. Unfortunately, the 'stage of invasion', i.e. the depth of tumor cell infiltration, had to be excluded in the malignancy grading because of the inadequate amount of underlying connective tissue infiltrated by tumor in many specimens. This variable alone has been reported to be an important prognostic factor, indicating the importance of removing larger biopsies which more probably include some of the underlying tumor infiltrated connective tissue.

In conclusion: A new malignancy grading system which only considers the histologically invasive parts of the SCCs was superior to Broders' system for predicting the prognosis of oral SCCs. The results indicate that features regarding the histologically invasive cells of the tumors may be most crucial for metastases and prognosis. Further this study shows that most, but not all, biopsy specimens submitted for histopathologic diagnosis can be graded according to the method described here. Biopsies only including tumor tissue cannot be assessed by this method. 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.

References:

1. Greenberg MS, Glick M. Burket's Oral Medicine, 10th ed. India: Elsevier 2003;
2. Park K. Preventive and social medicine, 18th ed. India:Bhanot 2005;
3. Hiremath SS. Textbook of preventive and community dentistry, 1st ed. India:Elsevier 2007;
4. Reinberg S. Cancer to suppress heart diseases as a world killer. Oral cancer 2008; 1: 24-8.
5. Sapp JP. Maxillofacial Pathology, 2nd ed. India:Mosby 2004;
6. Neville, Damm, Allen, Bouqupt. Oral and Maxillofacial Pathol 2nd ed. India:Elsevier 2005;
7. Rajendran R, Shivapathasundharam B. Shafer's text book of Oral Pathology, 5th ed. India:Elsevier 2006;
8. Schildt EB, Mikael E, Lennart H, Anders M. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a swedish case-control study. Int. J. Cancer 1998; 77: 341-6.
9. Mia H, Paul B, Simone B, Xavier C, Chu C, Maria PC et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the international head and neck cancer epidemiology consortium. JNCI 2010; 99: 779-89.
10. Sasaki T, Moles DR, Imai Y, Speight PM. Clinico-pathological features of squamous cell carcinoma of the oral cavity in patients <40 years of age. J Oral Pathol Med 2005; 34:129-33.
11. Chang SS. American joint committee on cancer. 6th ed. New York: Springer 2002;
12. Anneroth G, Batsakis J, Luna M. Review of literature and recommended system of malignancy grading in oral squamous cell carcinoma. Scand J Dent Res 1984; 92:229-49.
13. Jakobsson PA, Eneroth CM, Killander D, Moberger G, Martensson B. Histological classification & grading of malignancy in carcinoma of larynx. Acta Radiologica Therapy Physics Biol 1973; 2: 1-7.
14. Lund C, Sogaard H, Elbrond O, Jorgensen K, Anderson AP. Epidermoid carcinoma of lip. Histologic grading in clinical evaluation. Acta Radiologica Therapy Physics Biol 1975; 14: 465-74.

15. Crissman JD, Liu WY, Gluckman JL, Cummings G. Prognostic value of histopathological parameters in squamous cell carcinoma of the oropharynx. Cancer 1984; 54: 2995-3001.
16. Bryne M, Stromme H, Lilleng R, Stene T, Bang G, Dabelsteen E, Bryne M. New malignancy grading is a better prognostic indicator than Broder's grading in oral squamous cell carcinoma. J Oral Pathol Med 1989; 18: 432-7.
17. Piffka J, Nkfalvi A, Ofner D, Bryne M, Rasch D, Joos U et al. Prognostic value of histobiological factors (malignancy grading and AgNOR content) assessed at the invasive tumour front of oral squamous cell carcinomas. Br J Cancer 1997; 75: 1543-6.
18. Nicolson GL. Tumor cell instability, diversification, and progression to the metastatic phenotype: from oncogene to oncofetal expression. Cancer Res 1987; 47: 1473-87.

Source of Support: Nil

Conflict of Interest: Not Declared