10.5005/jp-journals-10001-1171

REVIEW ARTICLE

Dilemmas in Grading Epidermoid Carcinoma

[1]Varun Rastogi, [2]Naveen Puri, [3]Satyaranjan Mishra, [4]Rachna Sharma, [5]Lalita Yadav, [6]Robin Sabharwal

ABSTRACT

Oral squamous cell carcinoma (OSCC) can be preceded by the appearance of lesions which have the potential either to develop into cancer or signal the development of cancer in the oral cavity. Oral squamous cell carcinoma is the 8th most common cancer worldwide and found particularly in low income communities and mainly a problem of older men, 90% being in the 45-year-age group. Histologic grading has been used as a prognostic factor and for clinical evaluation of OSCC for the past several decades. At the same time, the prognostic value of different grading classification remains controversial. So, in this article, we have reviewed the different grading system of oral squamous cell carcinoma and their prognostic value.

Keywords: Oral cancer, Grading systems, Clinical staging, Head and Neck, Prognosis.

How to cite this article: Rastogi V, Puri N, Mishra S, Sharma R, Yadav L, Sabharwal R. Dilemmas in Grading Epidermoid Carcinoma. Int J Head Neck Surg 2014;5(1):9-14.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Oral squamous cell carcinoma (OSCC) has a relatively unfavorable prognosis with a 35 to 50% of 5-year survival.[1] For many years, TNM staging system has been used to clinically estimate response to therapy and survival,[2] but this staging system is not sufficient for optimal prognostication and must be supplemented by other reliable methods.[2,27] The patients who die of oral squamous cell carcinoma, despite the fact that their neoplasms were considered clinically to be stages I and II, a combined assessment of clinical staging and cytomorphology of the neoplasms might serve as a more precise measure for predicting the outcome of the neoplasm and for determining their treatment in such patients.[2]

[1,3]Reader, [2]Professor and Head, [4-6]Senior Lecturer

[1,2,5]Department of Oral Pathology, Kalka Dental College, Meerut Uttar Pradesh, India

[3]Department of Oral Medicine and Radiology, Institute of Dental Sciences, Bhubaneswar, Odisha, India

[4]Department of Oral Pathology, Seema Dental College and Hospital, Rishikesh, Uttarakhand, India

[6]Department of Oral Pathology, DJ College of Dental Sciences and Research, Modinagar, Uttar Pradesh, India

Corresponding Author: Varun Rastogi, Reader, Department of Oral Pathology, Kalka Dental College, Meerut, Uttar Pradesh, India Phone: 917417864865, e-mail: drvarunrastogi@gmail.com

Many studies on OSCC correlating histologic malignancy grading with different clinical parameters, such as clinical staging, recurrences and prognosis, has been published,[2] and a close relationship between the degree of histologic differentiation and the incidence of lymph node metastasis has been reported by several investigators.[3]

GRADING SYSTEMS

Oral squamous cell carcinoma is a malignant neoplasm arising from mucosal epithelium of the oral cavity. It consists of heterogenous cell population with different biologic characters.[4] The histologic grading of tumors has been used for many decades in an attempt to predict the clinical behavior of OSCC. The various grading systems are as follows:

1. Broder's (1927) grading system
2. Jakobsson et al (1973)
3. Eneroth and Moberger (1973)
4. Fisher (1974) classification
5. Lund et al (1975) classification
6. Willen et al (1975) classification
7. Crissman et al (1980) classification
8. Yamamoto et al (1984) classification
9. Anneroth and Hansen (1987) classification
10. Bryne's (1989, 1992) invasive tumor front grading system.

Broder's (1927) Grading System[5-7]

According to this classification, tumors were graded on the basis of degree of differentiation or maturation of tumor cell population and keratinization of tumor cells into: grade I—well differentiated (75-100% of cells are differentiated), grade II—moderately differentiated (50-75% of the cells are differentiated), grade III—poorly differentiated (25-50% of the cells are differentiated) and grade IV—anaplastic tumor (0-25% of the cells are differentiated).

The lack of correlation between Broder's grades and the prognosis of OSCC has been explained by the fact that squamous cell carcinoma (SCC) usually exhibits a heterogenous cell population with difference in degree of differentiation.[2]

Broder's system is limited and in many instances form insufficient basis for prognosis and therapy. Arthur and Farr[8], in a study of SCC of the mouth and pharynx, found that the histologic grade reflected the aggressiveness of the individual neoplasm and there was a clear relationship between grade and cure rate, stage of disease and metastatic

involvement. McGavran et al[9] in a study of SCC of the larynx found a significant correlation between the frequency of metastasis and the type of invasive growth pattern.

Since Broder's initial classification, multifactorial grading systems were introduced which were mainly based on different parameters of tumor cell population as well as tumor-host relationship.

Jakobsson et al (1973) Classification[10]

Jakobsson et al gave importance to the histologic relationship of the neoplasm to the surrounding host tissue. This system (Tables 1A and B) not only includes the morphologic parameters, such as structure, tendency to keratinization, nuclear aberrations and number of mitoses, but also an evaluation of tumor-host relationship as estimated by parameters, such as mode, stage of invasion, vascular invasion and the degree of lymphocytic infiltration.

The multifactorial grading system developed by Jakobsson et al[10] has been used in studies of squamous cell carcinoma in the head and neck regions both in its original form[12,13] and in several modified versions. The study conducted by Jakobsson[11] in glottis carcinoma clearly demonstrated the validity of multifactorial malignancy grading system and the results showed a statistically significant correlation between malignancy grading and recurrence as well as survival rates.

Eneroth and Moberger (1973) Classification[12]

They used the grading system developed by Jakobsson et al[10] in a study of SCC of the palate. They found that the system gave a considerably more accurate assessment of the ultimate prognosis than those based on the degree of differentiation of the tumors. They also concluded that the correlation between the histologic grade of malignancy and number of patients who die of neoplastic disease was independent of other factors, such as clinical stage and therapy.

Fisher (1974) Classification[13]

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

Lund et al (1975) Classification[14-16]

Lund et al also the grading system modified by Jakobsson et al by presenting a more exact definition of each parameter and grade and introducing a histologic score, which is defined as the total sum of points divided by the number of parameters evaluated.

Lund et al found a statistically significant correlation between the microscopic score and death rate as well as frequency of local recurrences and regional lymph node metastasis in a series of 438 patients with squamous cell carcinoma of the lip (Table 3).

Helweg-Larsen et al[17] used the modified grading system by Lund et al in a study of 52 patients with carcinoma of larynx and found no significant correlation between histologic grade and clinical course of the disease.

Tables 1A and B: Jakobsson et al (1973) histologic grading system

A

Tumor cell population	*Based on 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 irregularly enlarged nuclei	Anaplastic immature enlarged nuclei
Mitoses	Single	Moderate number	Great number	Numerous

B

Tumor-host relationship	*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	Micro carcinoma (few cords)	Nodular into connective tissue	Massive
Vascular invasion	None	Possibly	Few	Numerous
Cellular response (plasma-lymphocytic infiltration)	Marked	Moderate	Slight	None

Willen et al (1975) Classification[18]

Willen et al also used the grading system modified by Jakobsson et al. Their modification consists of deletion of two morphologic parameters, such as structure and vascular invasion (Tables 4A and B) and their results showed no definite correlation between the clinical stage and histologic grade of malignancy.

In the group with no metastasis, the neoplasm were highly differentiated with low mitotic rates and nuclear pleomorphism sometimes prominent whereas in the group with metastasis, the neoplasm were less differentiated with increased mitotic rates and nuclear aberrations.

Holmes et al (1982)[19] applied a modified version of the malignancy grading system used by Willen et al in a study of 95 patients with SCC from the anterior 2/3rd of the tongue. The result showed that the expected 5-year survival was 85% for patient with neoplasm having total malignancy scores of fewer than 13 points and concluded that histologic grading of malignancy is a better method than the degree of differentiation for evaluating the biologic behavior of lingual SCC.

Crissman et al (1980) Classification[20,21]

They modified the criteria outlined by Jakobsson et al in two steps. They concluded a different point scale for vascular invasion, structure and mode of invasion into a single parameter 'pattern of invasion'. The new parameter was considered to reflect the capacity of tumor cells cohesiveness to keep the tumor cell population together as well as the association of the invading tumor cells and host stroma.

This modified system was applied on 73 patients with squamous cell carcinoma of floor of the mouth and the result showed that the 'frequency of mitoses' and 'stage or depth of invasion' correlated with the extent of the disease (Tables 5A and B). The result also showed that the parameter 'pattern of invasion' was the single most important histologic variable in predicting survival.

Yamamoto et al (1984) Classification[22]

They modified Jakobsson et al grading system for application to SCC of the oral cavity. In a study on 102 patients with SCC, Yamamoto et al modified Jakobsson et al criteria for 'mode of invasion'. Grade 4 was subdivided into two

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	Micro invasion	Connective tissue	Deep
Vascular	None	Possible	Few	Many
Inflammatory response	Marked	Moderate	Slight	None

Table 3: Lund et al (1975) histologic grading system

	Microscopic grading points			
	1	*2*	*3*	*4*
Appearance	Exophytic papillomatous	Inverted papillomatous	Small cords and group of cells	Marked cellular dissociation
Cytoplasmic differentiation (keratinization)	High keratinization (>50%)	Moderate keratinization (20-50%)	Poor (5-20%) keratinization	None (0-5%) keratinization
Nuclear differentiation (Broder's)	High mature (>75%)	Moderate mature (50-75%)	Poor mature (25-50%)	None (0-25%) mature
Mitoses/high power field	Single (0-1)	Moderate number (0-3)	Great number (0-5)	Numerous (>5)
Mode of invasion (modus)	Well-defined borderline	Cords, less marked borderline	Groups of cells; no distinct borderline	Diffuse growth
Stage of invasion (depth)	Possible invasion	Micro carcinoma (few cords)	Nodular into submucosa	Invasion deeper than submucosa
Vascular invasion	None	Possible	Lymph vessels	Blood vessels
Cellular response (plasmalymphocytic)	Marked (continuous rim)	Moderate (many large patches)	Slight (a few small patches)	None

Tables 4A and B: Willen et al (1975) histologic grading system

A

Tumor cell population	*Based on tumor cell population*			
	1	*2*	*3*	*4*
Differentiation	Highly; keratinization	Moderately; some keratinization	Poorly; minimum keratinization	Poorly; no keratinization
Nuclear polymorphism	Few enlarged nuclei	Moderate number of enlarged nuclei	Numerous irregularly enlarged nuclei	Anaplastic immature enlarged nuclei
Mitoses	Single	Moderate number	Great number	Numerous

B

Tumor-host relationship	*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 invasion
Stage of invasion	Suspicious	Micro carcinoma (few cords)	Nodular into connective tissue	Massive invasion
Cellular response	Marked	Moderate	Slight	None

Tables 5A and B: Crissman et al (1980) histologic grading system

A

Histologic criteria	*Tumor scores*			
	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, variable-sized nuclei; 50-75% mature	Numerous enlarged pleomorphic nuclei; 25-50% mature	Anaplastic nuclei; 0-25% mature
Frequency of mitoses/high power field	0-1	2-3	4-5	>5

B

Histologic criteria	*Stroma of tumor-host interface*			
	1	*2*	*3*	*4*
Inflammatory cell response	Marked (continuous rim)	Moderate (many large patches)	Slight (a few small patches)	None
Tumor growth pattern	Carcinoma *in situ*; probable invasion	Early or micro invasion	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

grades—4C and 4D (Table 6). Grade 4C described a cord like type of invasion, while grade 4D involved a widespread type of diffuse infiltration of single and/or small groups of neoplastic cells.

Anneroth and Hansen (1987) Classification[23-25]

They modified the grading system developed by Jakobsson et al for application to squamous cell carcinoma in the tongue and floor of the mouth. In this grading system, one of the parameter 'vascular invasion' was omitted.

Table 6: Yamamoto et al (1984) histologic grading system

Histologic grading of 'mode of invasion' using modified Jakobsson criteria	
Grade	*Criteria*
1	Well-defined borderline
2	Cords, less marked borderline
3	Group of cells, no distinct borderline, diffuse invasion
4C	Cord like type
4D	Widespread type

Tables 7A and B: Anneroth et al (1987) histologic grading system

A

Morphological parameter	*Based on tumor cell population*			
	1	*2*	*3*	*4*
Structure	Solid sheets and/or papillary configuration	Bands and strands	Small group of cells	Marked cell dissociation
Tendency to keratinization	Highly keratinization	Moderate keratinization	Minimal keratinization	No keratinization
Nuclear aberrations	Few	Moderately abundant	Abundant and a few large anaplastic nuclei	Abundant and many large anaplastic nuclei
Number of mitoses above basal cell layer/high power field	Few (0-2)	Moderate number (3-4)	Numerous (5-6)	Extremely numerous (>than 6)

B

Morphological parameter	*Based on tumor-host relationship*			
	1	*2*	*3*	*4*
Mode of invasion	Well-defined basement membrane	Less distinct basement membrane	No distinct basement membrane	No distinct basement membrane and diffuse invasion
Stage of invasion	Borderline or micro invasion	Distinct invasion but involving lamina propria	Invasion below lamina propria	Massive wide and deep invasion
Inflammatory response	Marked	Moderate	Slight	None

Table 8: Bryne's (1989, 1992) tumor invasive front grading system

Morphological parameter	*Based on tumor cell population*			
	1	*2*	*3*	*4*
Tendency to keratinization	Highly keratinization	Moderate keratinization	Minimal keratinization	No keratinization
Nuclear polymorphism	Few	Moderately abundant	Abundant nuclear polymorphism	Extreme nuclear polymorphism
Pattern of invasion	Pushing, well delineated infiltrating borders	Infiltrating, solid cords, bands and or strands	Small groups or cords of infiltrating cells	Marked and widespread cellular dissociation in small groups of cells and/ or in single cells
Host response (lympho-plasmacytic infiltrate)	Marked	Moderate	Slight	None

Statistical analysis revealed that the reproducibility of the system was good for all morphological variables (mean total malignancy, tumor cell population and tumor host relationship). This modified grading system was tested in a study of 89 patients with SCC in the floor of the mouth and the result showed a significant correlation between the mean total malignancy scores and clinical staging, frequency of recurrences, and death from first oral primary carcinoma (Tables 7A and B).

Bryne's (1989, 1992) Invasive Tumor Front Grading System[26,27]

Recently, Bryne et al introduced a multifactorial grading of only the deep invasive margins of oral SCC which proved to be of high prognostic value. Bryne et al (1989) recognized the fact that there are heterogenous tumor cell population in malignancies and observed that the cells in deep invasive margins tend to be less differentiated than the cells in the superficial part of the tumor.[28]

Bryne M (1998) presented a hypothesis suggesting that molecular and morphological characteristics at the invasive front area of various SCC may reflect tumor prognosis better than other parts of the tumor. According to this system, number of mitoses and stage of invasion was omitted from the Anneroth's grading system, while the rest of the four parameters, such as keratinization, nuclear pleomorphism, pattern of invasion and lymphoplasmacytic infiltration, were measured in the deepest invasive margins,

and not in the whole thickness of the tumor (Table 8) and graded similarly. The sum of the scores was grouped as follows: grade I—4-8, grade II—9-12, grade III—13-16, and the results were compared in the metastasizing and nonmetastasizing groups.

CONCLUSION

Squamous cell carcinoma is one of the challenges for oral surgeons. A significant percentage of patients with early stages of SCC have a poor prognosis despite the small size of the tumor. The various grading systems have emerged throughout the century, the 1st grading system being proposed by Broders till it was replaced by multifactorial grading system developed by Jakobsson and Anneroth which was used by different authors and it was recently even further replaced by invasive tumor front grading system developed by Bryne M, which is most reproducible and most popularly used throughout the world. With the recent advances in molecular biology techniques and introduction of immunohistochemical markers, there could be scope of further improving the clinical value of histological grading system which may also take into account the biological behavior of the tumor.

REFERENCES

1. Bundgaard T, Bentzen SM, Wildt J, et al. Histopathologic, stereologic, epidemiologic, and clinical parameters in the prognostic evaluation of squamous cell carcinoma of the oral cavity. Head Neck 1996;18:142-152.
2. Anneroth G, Batsakis J, Luna M. Review of the literature and a recommended system of malignancy grading in oral squamous cell carcinomas. Scan J Dent Res 1987;95:229-249.
3. Yazdi I, Khalili M. Oral cancer: An epidemiological study of squamous cell carcinoma in Iran. Iran J Med Sci 1993;18:171-174.
4. Bhargava A, Saigal S, Chalishazar. Histopathological grading systems in oral squamous cell carcinoma: a review. JIOH 2010;2(4): 1-10.
5. Broders AC. Squamous cell epithelioma of the lip. J Am Med Assoc 1920;74:656-664.
6. Broders AC. Carcinoma of the mouth: types and degree of malignancy. Ann J Roentgenol Rad Ther Nucl Med 1927;17:90-93.
7. Broders AC. The microscopic grading of cancer. Surg Clin North Am 1941;21:947-962.
8. Arthur K, Farr HW. Prognostic significance of histologic grade in epidermoid carcinoma of the mouth and pharynx. Am J Surg 1972;124:489-492.
9. McGavran MH, Bauer WC, Ogura JH. The incidence of cervical lymph node metastasis from epidermoid carcinoma of larynx and their relationship to certain characteristics of the primary tumor. Cancer 1961;14:55-56.
10. Jakobsson PA, Eneroth CM, Killander D, Moberger G, Martensson B. Histologic classification and grading of malignancy in carcinoma of larynx (a pilot study). Acta Radiol Ther Phys Biol 1973;12:1-8.
11. Jakobsson PA. Glottic carcinoma of the larynx. Factors influencing prognosis following radiotherapy. Thesis, Uppsala: Printlab AB 1973.
12. Eneroth CM, Moberger G. Histologic malignancy of grading of squamous cell carcinoma of the palate. Acta Otolaryngol 1973; 75:293-295.
13. Fisher HR. Grading of biopsies of laryngeal carcinomas by multiple criteria. Can J Otolaryngol 1975;4:881-884.
14. Lund C, Sogaard H, Elbrond O, Jorgensen K, Pedersen AP. Epidermoid carcinoma of the lip. Histologic grading in the clinical evaluation. Acta Radiol Ther Phys Biol 1975;14:465-474.
15. Lund C, Sogaard H, Jorgensen K, Hjelm-Hansen M. Epidermoid carcinoma of the larynx. Histologic grading in the clinical evaluation. Acta Radiol Ther Phys Biol 1976;15:294-304.
16. Lund C, Sogaard H, Elbrond O, Jorgensen K, Pedersen AP. Epidermoid carcinoma of the tongue. Histologic grading in the clinical evaluation. Acta Radiol Ther Phys Biol 1975;14: 513-521.
17. Helweg LK, Graem N, Meistrup-Larsen KJ, Meistrup-Larsen U. Clinical relevance of histological grading of cancer of larynx. Acta Pathol Microbiol Scand 1978;86:499-504.
18. Willen R, Nathanson A, Moberger G, Anneroth G. Squamous cell carcinoma of the gingiva. Histological classification and grading of malignancy. Acta Otolaryngol 1975;79:146-154.
19. Holm LE, Lundquist PG, Silversvard C, Sobin A. Histological grading of malignancy in squamous cell carcinoma of the tongue. Acta Otolaryngol 1982;94:185-192.
20. Crissman JD, Liu WY, Gluckman JL, Cummings G. Prognostic value of histopathologic parameters in squamous cell carcinoma of the oropharynx. Cancer 1984;54:2995-3001.
21. Crissman JD, Gluckman J, Whitley J, Quanelle O. Squamous cell carcinoma of the floor of the mouth. Head Neck Surg 1980;3:2-7.
22. Yamamoto E, Miyakawa A, Kohama GI. Mode of invasion and lymph node metastasis in squamous cell carcinoma of the oral cavity. Head Neck Surg 1984;6:983-987.
23. Anneroth G, Hansen LS. A methodologic study of histologic classification and grading of malignancy in oral squamous cell carcinoma. Scand J Dent Res 1984;92:448-468.
24. Anneroth G, Hansen LS, Silverman Jr S. Malignancy grading in oral squamous cell carcinoma of the tongue and floor of the mouth: histologic grading in the clinical evaluation. J Oral Pathol 1986;15:162-168.
25. Anneroth G, Batsakis JG, Luna M. Malignancy grading in oral squamous cell carcinoma in the floor of the mouth to clinical evaluation. Scand J Dent Res 1986;94:513-521.
26. Bryne M, Stromme H, Lileng R, Stene T, Bang G, Dabelsteen E. New malignancy grading is a better prognostic indicator than Broder's grading in oral squamous cell carcinoma. J Oral Pathol Med 1989;18:432-437.
27. Bryne M, Koppang HS, Lilleng R, et al. Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognostic value. J Pathol 1992;166:375-381.
28. Doshi NP, Shah SA, Patel KB, Jhabuwala MF. Histological grading of oral cancer: A comparison of different systems and their relation to lymph node metastasis. National J Commun Med 2011;2(1):136-142.