Pattern of Invasion; a Reliable Prognostic Indicator for Oral Squamous Cell Carcinoma

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Abstract

Despite substantial advancements in both diagnostic and therapeutic fields in recent decades, theprognosis of oral squamous cell carcinoma remains poor. Extensive local invasion and frequent regional lymph node metastases are usually present even atinitial diagnosis, resulting in unpredictable prognosis of oral squamous cell carcinoma (OSCC). Clinical assessment by the tumour node metastasis (TNM) system is routinely used to define the extent of tumour load and determine treatment options for patients with OSCC. One of the major criticisms of the TNM system is that itignores individual histological characteristics of tumours. Therefore, many workers have developed different histological grading systems to predict the biological behaviour and recommended prognostic markers for OSCC. Multi-parameter scoring systems had been developed and modified over decades. This scoring systems were based on histological variables that include nuclear pleomorphism, mitotic index, lymphocytic response, tumour growth pattern, tumour thickness, degree of keratinization, depth ofinvasion, and pattern of invasion (POI). Among these parameters, pattern of invasion has got better prognostic value over the others. This article briefly describes the background of different histological grading systems and current state of knowledge about pattern of invasion as a histological prognostic indicator.

[Journal of Histopathology and Cytopathology, 2021 Jan; 5 (1):32-41]

Keywords: OSCC, POI, Anneroth grading, TNM staging, CAP protocol

Introduction

Oral cavity cancer is one of the most common malignancies worldwide. It causes substantial mortality and morbidity. India has the world's largest number of oral cancer patients. Statistics from National Cancer Registry Programme of Indian Council of Medical Research show that the annual age-standardized incidence in India is 12.5 per 100,000.[1] In Bangladesh around 7000 cases are diagnosed yearly. The incidence is predicted to increase over the next few decades.[2] Almost half of the cases worldwide are diagnosed in stage III and IV. Primary resection with elective nodal dissection is the usual treatment protocol for early stage of oral squamous carcinoma.[3] It is generally agreed upon that T1/2, N0, M0 tumors show afavorable outcome and are called early-stage cancers.[4] Margin status is the main factor that guide adjuvant treatment (postoperative radiotherapy and chemotherapy) decisions in case of early stage, node-negative patients.[5]

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Prognosis of OSCC depends on multiple factors. Clinically, tumorstage and lymph node (LN) status are the 2 most importantfactors that determine patients' treatment and outcome. However,prognosis of the patients with early-stage OSCC is unpredictable. While most of the patients have a prolongeddisease-free survival, some patients of early stage cancer show early relapse and death[6].Researchers have evaluateddifferent clinical and histological parameters for predicting therisk of LN metastasis and recurrencein early-stage tumors. Various histological parametersare associated with a higher incidence of nodal metastasis inoral cavity cancer. Of these, lymphovascular invasion (LVI) and perineural invasion (PNI) are well-known in case of OSCC and other malignanciesin all stages and are mandatory part of reporting format[7]. However, LVI and PNI aredifficult to evaluate, especially in small biopsies. In these circumstances, pattern of invasion of OSCC could be a very useful parameter for prediction of patients' prognosis. This review article summarizes the historical background of development of multiparameter grading systems and the recent concepts of pattern of invasion as apredictor of prognosis in OSCC patients.

TNM staging of OSCC

In pretherapeutic clinical-diagnostic staging there are basically two classification systems that have been used during the last years: *Union Internationale Centre le Cancer (UICC)*and *The American Joint Committee for Cancer Staging (AJCC).*Staging protocols, such as those of CAP (College of American Pathologists), are to document surgical procedure, tumor site, tumor laterality, tumor focality, tumor size, histologic type, histologic grade where applicable, margin status, lymphovascular invasion, perineural invasion, regional lymph node findings and summarize these pathologic findings using TNM system. TNM staging for oral squamous cell carcinomas (OSCCs) is not sufficient for optimal prognostication.[8] AJCC 7th edition staging was sunset on December 31, 2017.Significant alterations were made in the 8th edition of AJCC for lip and oral cavity cancer staging. These include the incorporation of depth of invasion (DOI) into T stage and extranodal extension (ENE) into N stage. To simplify prognostication, the current edition of AJCC staging protocol recommends the assessment of WPOI-5. It should be reported whether WPOI-5 is present or not. WPOI-5 is defined as tumor dispersion of ≥ 1 mm between tumor satellites. Tumor dispersion is assessed at the advancing tumor edge. To some, WPOI-5 can be viewed as redundant and only optional for reporting purposes, as extratumoral perineural invasion or extratumoral lymphovascular invasion also count as WPOI-5.[9]

Current Histological Grading of OSCC

Current histologic grading system of OSCC is based on WHO (1971) defined morphologic criteria of the tumour. A.C. Broder primarily described the grading system of OSCC in 1925.[10] World Health Organization adopted this grading system later in 1971.[11] According to this system, tumors are graded into three groups: well-differentiated or grade I, moderately differentiated or grade II, poorly differentiated or grade III.

Well differentiated or Grade I squamous cell carcinoma is composed of relatively mature tumor cells with few nuclear aberrations. These tumors show presence of keratin pearls and/or individual cell keratinization. Moderately differentiated or Grade II tumor cells exhibit a wide range of differentiation. Keratinization is occasionally present and nuclear aberrations are moderately abundant. Poorly differentiated or Grade III tumors show no tendency towards keratinization.

Nuclear aberrations are abundant in this group.

Current grading system has been shown to be of limited value in prediction of prognosis and therapy. The reason behind this lacking may be that this system evaluates only the tumor cell population. It does not consider the biologic activity of the tumor in relationship to the surrounding host tissue.

Overview on Different Multifactorial Grading Systems

In order to include both the tumor cell population and the tumor-host relationship, Jakobbson introduced a multifactorial histological malignancy grading system in 1973.[12] They used seven histological parameters. Subsequently, several modifications followed in order to search for a better prognosticator of the outcome of patients of OSCC. Some of these modified grading systems are histologic malignancy grading by Eneroth (1973), Fisher (1975), Lund (1975), Willen (1975), Crissman (1980) et al etc.[13-17] Few years laer in 1984, Anneroth described a new grading system based on six morphological parameters.[18] Several independent workers have found that Anneroth's described morphologic parameters have a better prognostic value than the conventional Broders' (1925)/ WHO grading system (1971) in predicting nodal metastasis, local recurrence, and survival. In 2011 Akhter et al stated that Anneroth grading was more significantly associated with patients' prognosis over WHO grading.[19] Similarly, In 2012, Lindenblatt et al showed in their study that multiparameter Grading System was statistically associated with pathologic staging and lymph node involvement. At the same time, they stated that poorly differentiated tumors showed a statistically significant relationship with recurrence of cancer.[20]

It is generally accepted that most human neoplasms consist of heterogeneous cell populations with variable biological behaviour. Cells at the deep, invasive marginsof OSCCs and other cancers often show characteristicsother than those of superficial parts of the tumour. The histological features of OSCC may differ widely fromarea to area within the same tumour due to tumour heterogeneity and is subject to inter- and intraobserverdisagreement[21].In search for a better prognosticator, Bryne et al in 1972 introduced a multifactorial malignancy grading system of only the deep invasive margins of OSCC-'invasive cell grading' (1CG)-which proved to be of high prognostic value.[22] They used five morphological parameters omitting the stage of invasion.

There is general agreement that the most useful prognostic information can be deducedfrom the invasive front of the tumour, where the deepest and presumably most aggressive cellsreside.[23] The invasive tumor front has been defined earlier in 2013 by Sharma et al as "the most progressed, three to six tumor cell layers or detached tumor cell groups at the advancing edge of the OSCC".[24]

Anneroth's Grading System (1984)

This histologic grading of malignancy is made using six morphological criteria according to this system[18]. Three of these represents the tumor cell population itself including tendency to keratinization, nuclear aberrations or pleomorphism, and number of mitoses. The three additional criteria signifies the tumor-hostrelationship. These are pattern of invasion, stage of invasion and inflammatory response. Each of the parameters are scored as 1 to 4 points based on microscopic findings (Table I). If different scores of the same parameter wereobserved in the same specimen the highest score was considered as representative for that

parameter.The total point value in the individual patientreflects the degree of malignancy, the higher thescore, the greater the malignancy. The sum of the scores are grouped as follows: 6-12: grade I, 13-18: grade II, 19-24: grade III.[25] A brief description on each of the parameters is as follows:

Keratinization -The grading of keratinization is dependent on individual cell keratinization or keratin pearl formation within the tumor cell population. Score 1 corresponds to tumors with large amounts of keratin (>50% cells). Score 2 represents a moderate amount of keratinization (20-50% cells) and score 3 denotes a poorly keratinized tumor cell (5-20%) population. Score 4 represents keratinization of very few (0-5%) cells.

Nuclear pleomorphism - Evaluation of nuclear pleomorphism includes variations in size and shape of tumor cell nuclei, increased nuclear-cytoplasmic ratio, and the presence of hyperchromatic and multiple nuclei as well as atypical mitoses. Score 1 represents a tumor cell population with few nuclear aberrations or pleomorphism in a relatively homogenous cell population. Score 2 exhibits moderately abundant nuclear pleomorphism. Score 3 shows abundant nuclear pleomorphism with few large anaplastic nuclei. Score 4 is characterized by tumor populations having extreme nuclear pleomorphism and numerous large immature anaplastic nuclei rich in chromatin.

Mitoses - The number of mitotic figures per high power field is estimated as follows:- 0-1: score 1, 2-3: score2, 4-5: score3 and >5: score 4.

Pattern of invasion - The cells at the deep, invasive fronts are assessed in the evaluation of pattern of invasion. Score 1 represents pushing, well-delineated infiltrating border. Score 2 describes pattern of invasion as solid, infiltrating bands, cords and/or strands. Score 3 denotes the pattern of invasion as small groups or nests of cells. Here, the nests or groups are composed of more than 15 cells. Score 4 describes marked and widespread cellular dissociation in small groups and/or in single cells. The number of cells of these groups are less than 15. (Figure 1-4)

Stage of invasion - Tumors with superficial, borderline, or microinvasion are considered as score 1. Distinct but moderate invasion involving only the lamina propria is recognized as score2. Invasion below the lamina propria involving muscle and/or salivary gland tissue is graded as score 3. And score 4 describes extensive and deep invasion replacing most of the stromaltissue and infiltrating jaw bone.

Inflammatory or lymphoplasmacytic response -Infiltrate of plasma cells and lymphocytes in close relation to invasive tumor cells is evaluated as follows: marked inflammatory response is scored 1, moderate inflammatory response is scored 2, slight inflammatory response is scored 3 and no inflammatory response is scored 4. The evaluation of the degree of inflammatory reaction is to be made in the stroma close to the tumor tissue and not adjacent to any ulceration.

Table I: Anneroth et al (1987) multifactorial grading/scoring system for OSCC

Morphologic parameter	Points/Scores			
	1	2	3	4
1.Degree of keratinization	>50% cells keratinized	20-50% cells keratinized	5-20% cells keratinized	0-5% cells keratinized
2.Nuclear pleomorphism	Little nuclear pleomorphism	Moderately abundant nuclear pleomorphism	Abundant nuclear pleomorphism	Extreme nuclear pleomorphism
3.Number of mitoses/HPF	0-1	2-3	4-5	>5
4.Pattern of invasion	Pushing, well-delineatedinfiltrating borders	Infiltrating, solid cords, bands and/or strands	Small groups or cords of infiltrating cells (n>15)	Marked and wide-spread cellulardissemination in small groups and/or in single cells (n<15)
5.Stage of invasion	Carcinoma-in-situand/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

Total Anneroth grade: Score 6-12: Grade I, Score 13-18: Grade II, Score 19-24: Grade III

The morphologic features, however, are notnecessarily equivalent in importance despitethe fact that they are given the same numericalpoint values.[26] Few investigators have quantitatively analyzed the relative importance of different morphologic parameter. Notable of these are the study done by Jakobsson et al in 1973 and Crissman et al in 1984.[27,28] Crissman et al noted that a single component might have a more clinical value over the combined score of multiple histologic parameters.[28]

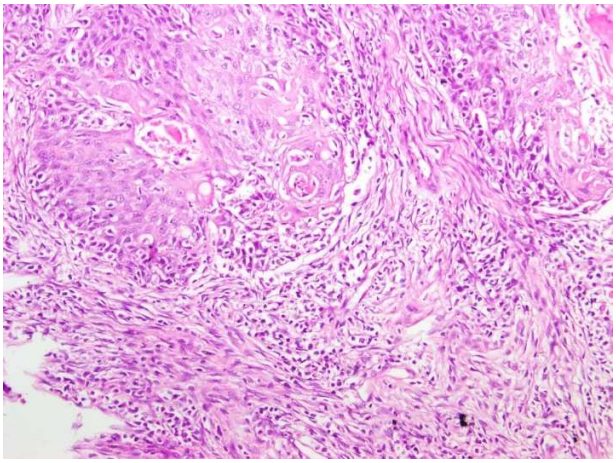

Figure1: POI 1 is represented bypushing, well-delineatedinfiltrating borders (H&E x400)

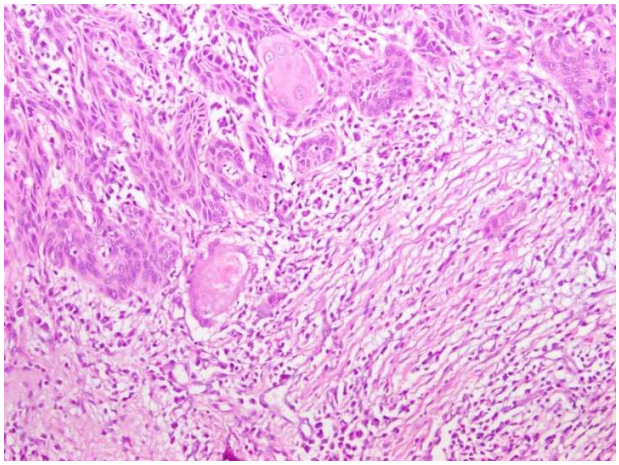

Figure 2: POI 2 is represented by solid, infiltrating bands, cords and/or strands (H&E x400)

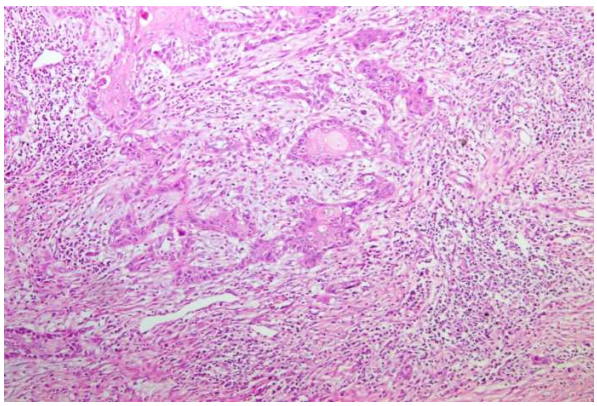

Figure 3: POI 3 is represented by Small groups or nestsof infiltrating cells (n>15) (H&E x400)

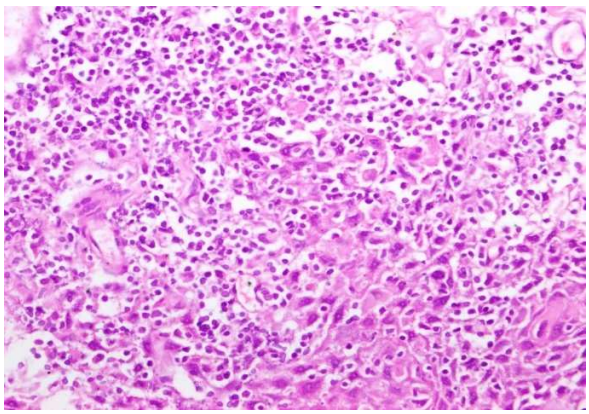

Figure 4: POI 4 is represented bymarked and widespread cellular dissociation in small groups and/or in single cells (n<15) (H&E x800)

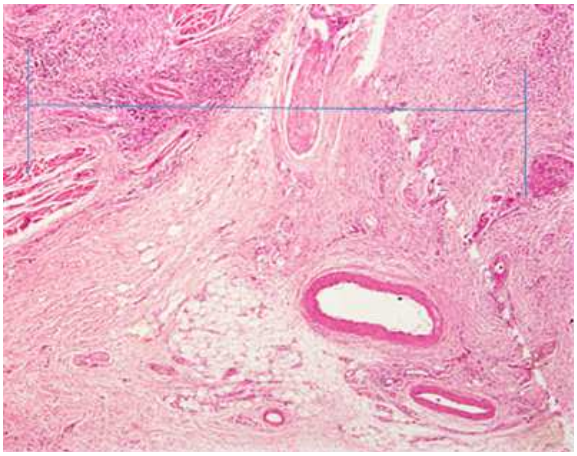

Figure 5: Pattern 5 was defined by presence of tumor island outside the main tumor at a distance of >1 mm (H&E x200)

Crissmanet al described pattern of invasion as the single most important histologic variable in predicting patient survival.[28] Pattern of invasion is the parameter which was most frequently studied in oral squamous cell carcinoma patients in relation to prognosis or patient outcome and also in association with prognostic markers like E-cadherin etc. This is one of the most important prognostic parameter of Anneroth grading system. Odell et al also demonstrated pattern of invasion as a significant prognostic parameter in their study in 1994.[29] The significance of pattern of invasion as a prognostic indicator was enhanced because it was the most accurately scored parameter among observers and the scores were relatively evenly distributed among tumors.[18,22]

In the recent years, pattern of invasion of OSCC was studied by several researchers and classified as 5 patterns.According to the study done by Parekhet al (2020) Pattern 1 was defined as broad, pushing margin oftumor with a smooth outline. Pattern 2 was defined as broad, pushing finger-like projection. Pattern 3 represents invasivetumor islands with >15 cells per island. Pattern 4 representsinvasive tumor islands with less than 15 cells per island. Pattern5 was defined by the presence of tumor island outside the maintumor at a distance of >1 mm (Figure 5).[30] In a given case showing multiple patterns of invasion, the score was determined by the highest pattern present, even if present focally (WPOI). Among these 5 patterns, POI 4 and 5 wereclassifiedas invasive pattern, whereas POI 1 to 3 as cohesive pattern in some literatures.[31,32] They found strong association of worst pattern of tumor invasion (pattern 4 and 5)with LN metastasis. Hiratsuka et al also investigated previously in 1997 about pattern of invasion and stated that Invasive POI is able to predict the risk of occult LN metastasis efficiently.[33] Taking this facts in consideration, worstpattern of invasion has been included very recently as a required criteria for reporting of oral cavitymalignancies according to College of American Pathologistguideline.[34] So, worst pattern of invasionmust be included in the histopathology reporting guidelines in our routine practice.

Conclusion

It can be concluded that the prognosis of OSCC is predicted by various histological parameters that are easy to assess on routine hematoxylinand eosin–stained sections. POI is easy and reliable predictive factors in early-stage OSCC. Based on the findings of previous studies, we recommend that this parameter should be routinely evaluated both in resection and in preoperative biopsy specimens and should be a part of standard reporting format for OSCC. It will be beneficial forindividualization of treatment modalities in these patients.

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