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Histologic Risk Assessment and its Relationship with Clinical Parameters in Oral Squamous Cell Carcinoma

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Abstract

Oral cancer is the sixth most common cancer in the world, and has the highest incidence in the South Asia. The TNM staging system cannot predict the biological behaviour and patient survival precisely. Therefore, histopathological grading system for oral squamous cell carcinoma (OSCC) in an attempt to provide additional information about biological behavior and prognosis of OSCC. The aim of this study is to assess the relationship between histologic risk assessment and clinical parameters of OSCC. This was a cross-sectional study. Histopathological examination of the surgical specimen was performed using the histological risk assessment grading system. The relationship between histologic risk assessment and clinical parameters were assessed by chi square test using SPSS v. 20.0. No significant association observed between the histologic risk assessment and tumor size, regional lymph node metastasis or clinical stage of the lesion. However, perineural invasion (PNI) was significantly associated with clinical stage of the lesion (P= 0.02), which indicates that PNI could be an important prognostic factor for understanding the biological behavior of OSCC patients. Therefore, we propose that every OSCC patient should be checked for perineural invasion.

Keywords: TMN staging, oral squamous cell carcinoma, histological grading system, and
perineural invasion.

Introduction

Oral cancers are malignant lesions occurring in the oral cavity that include squamous cell carcinomas (SCC), salivary gland and odontogenic neoplasms. The majority (84-97%) of oral cancers are SCCs arising from the stratified squamous epithelium of the oral cavity.[1] Tobacco exposure (smoking and smokeless tobacco), alcohol intake, and HPV infection are the most common risk factor for head and neck cancers (HNCs). HNC is the sixth most common cancer in the world. The incidence of oral cancer in South Asia is the highest in the world.[2,3] It is the most common cancer in male in the South Asia.[4]

The international standard to classify malignant tumors into stages is the TNM staging system. For purposes of simplification, the 32 possible T, N and M combinations can be reduced to clustered stages: I, II, III and IV (a, b, c), which are meant to reflect homogeneous survival and inter-stage discrimination.[5] In some cases, local recurrence and distant metastasis may occur even if the carcinoma is diagnosed at an early stage and treated accordingly. For this reason, a new histo-pathological grading system for oral squamous cell carcinoma (OSCC) has been proposed with an attempt to provide additional information about biological behaviour and prognosis of OSCC other than TNM system. Anneroth et al proposed the Multi parameter Grading System in 1987 that evaluates the tumor cells of surgical specimen such as degree of keratinization, nuclear pleomorphism, number of mitoses, pattern and depth of invasion and inflammatory infiltration.[6] Bryne et al advocated 'Invasive Front Grading System' in 1992 that examines exclusively the most invasive tumor cell front at the tumor host interface.[7] The World Health Organization (WHO) grading system for OSCC is based on microscopic differences between normal epithelium and tumoral tissue and divides the SCC into three categories: well-, moderately and poorly differentiated tumors.[5] In 2005, Brandwein Gensler et al proposed the Histologic Risk Assessment for grading of OSCC. This system evaluates the worst pattern of invasion, perineural invasion and lymphocytic response to tumors (complete, intermediate or little host response).[8] Perineural invasion (PNI) is the process of neoplastic invasion of nerves, which also might be a potential route for metastatic spread, well beyond the extent of any local invasion. This pathologic feature is commonly observed in many malignancies, including, pancreas, colon and rectum, prostate and head and neck. PNI is seen as a marker of poor survival outcome. According to the above-mentioned histopathological findings, patients are classified into low, intermediate and high-risk groups for prediction of local recurrence and overall survival probability. Generally, if the patient has a high risk score, adjuvant radiotherapy is indicated despite the size or resection margin of the primary tumor. Histologic Risk Assessment grading system was applied in this study to evaluate the system with clinical parameters in OSCC. The purpose of this study is to find out the relationship between histologic risks assessments grading system with the TNM staging system of OSCC, with the expectation that this study will help in different aspects of oral cancer management.

Materials and Methods

Study was conducted from September 2021 to August 2022. A total of 50 (Fifty) cases of histopathologically diagnosed oral squamous carcinoma patients were selected. A standardized structured data collection sheet was used to collect necessary information of the

subject group. Ethical clearance was obtained from the Ethics Committee. The procedure and outcome of the research were explained to the patients in detail and written consents were taken. The study was designed to assess the relationship of clinical parameters of OSCC with the parameters of Histologic Risk Assessment grading system. Patients were thoroughly examined and clinical staging of the lesion was performed using the TNM Staging system. After excision of the lesion, the specimens were marked properly and sent for histopathological examination. The specimen examined by an expert oral pathologist. The Histologic Risk Assessment grading system was used to score the lesion. Statistical analysis performed using SPSS v.20.0 to identify the relationship between the clinical parameters and histologic risk assessment grading system. In the histopathological grading system proposed by Brandwein-Gensler et al- the low, intermediate and high-risk tumors were compared with the TNM classification using the x2 test (Table 1). These tests were also used to evaluate possible associations between single morphological parameters (worst pattern of invasion, lymphocytic infiltrate and perineural invasion) and clinical characteristics. A level of significance was ($P < 0.05$) adopted for all tests.

Results

A. Clinicopathological Features

The mean age of the patients was 50 years with a range from 26 to 75 years with 34% male and 66% female (Figure 1). The most prevalent age range was 41 to 50 years, represented by 42% of the cases (21 patients). Only one patient was above 70 years of age (Table 3). Most of the patients suffered from squamous cell carcinoma of the mandibular alveolar mucosa (Figure 2). TNM staging of the patients suggested that more than half of the patients were presented with stage IV lesion.

B. Relationship of TNM Classification with Histologic Risk Assessment

Only 8% patient presented with small T1 lesion and 14% patient had low histologic risk assessment score (Table 4). 46% patient had T2 tumor and 72% patient fall in the intermediate risk group. No significant relationship observed between histologic risk assessment and tumor size (Table 4). However, 16% patient had N0 neck and 36% patient had N1 lymphnode metastasis (Table 5). The relationship between histologic risk assessment and lymphnode metastasis was not significant. Moreover, only 6% patient had Stage I lesion whereas 52% patient suffered from stage IV lesion. The association was non-significant (Table 6).

C. Relationship of Single Parameter of Histological Risk Assessment with TNM System

Pattern of invasion type 1, type 2 and type 3 were merged into a single group and type 4 and 5 were merged into a single group for comparison with the tumor size (Table 7). There was nearly same distribution (54% and 46% respectively) of type1-3 and type 4-5 cases (Table 7). Worst pattern of invasion was not associated with tumor size. No significant relationship observed among the lymphocytic infiltration with the clinical stage of lesion ($P > 0.05$) (Table 8). However, the histology of perinural invasion (PNI) (Figure 4) showed significant association with the clinical stage of the lesion ($P= 0.023$) (Table 9). Stage III lesions present maximum (12%) PNI whereas stage I lesions had no PNI.

Table 1: Morphological parameters and their respective scores in the Histologic Risk Assessment Grading System proposed by Brandwein-Gensler et al

Morphological Parameters / **Worst Pattern of Invasion**	**Definition**	**Score**
Type-1	Pushing border	0
Type-2	Finger-like growth	0
Type-3	Large separate islands (>15 cells per island)	0
Type-4	Small tumour islands (≤15 cells per island)	+1
Type-5	Tumour satellites, ≥1 mm away from main tumour or next closest satellite	+3
Lymphocytic Infiltrate		
Type-1	Dense complete host response rimming tumour (lymphoid nodules at advancing edge in each ×4 field)	0
Type-2	Intermediate host response (lymphoid nodules in some but not all ×4 fields)	+1
Type-3	Little or no host response (no lymphoid nodule)	+3
Perineural Invasion		
None	None	0
Small nerves	Tumour wrapping around nerves, <1 mm diameter	+1
Large nerves	Tumour wrapping around nerves, ≥1 mm diameter	+3

Table 2: Interpretation

Risk Score (sum of allpoints)	Risk for local Recurrence	Overall Survival Probability
Score = 0	Low	Good
1 or 2	Intermediate	Intermediate
3 to 9	High	Poor

Table 3: The age distribution of Patients

Age Range (years)	**Frequency**	**Percent (%)**	**Mean Age**
21-30	1	2	
31-40	8	16	
41-50	21	42	50.28
51-60	14	28	
61-70	5	10	
71-80	1	2	

Table 4: Histological Risk Assessment with Tumor Size

Histologic risk assessment	Tumor size				Total	P-value
	T1	**T2**	**T3**	**T4**	**n (%)**	
	n (%)	n (%)	n (%)	n (%)		
Low risk	0 (0.0)	3 (6)	4 (8)	0 (0.0)	7 (14)	
Intermediate risk	4 (8)	18 (36)	12 (24)	2 (4)	36 (72)	**0.493**
High risk	0 (0.0)	2 (4)	5(10)	0 (0.0)	7 (14)	
Total	4 (8)	23 (46)	21 (42)	2 (4)	50 (100)	

Table 5: Histological Risk Assessment with Nodal Metastasis

Histologic risk assessment	Nodal Metastasis				Total	P-value
	N0	**N1**	**N2**	**N3**	**n (%)**	
	n (%)	n (%)	n (%)	n (%)		
Low risk	0 (0.0)	1(2)	4 (8)	2 (4)	7 (14)	
Intermediate risk	8 (16)	14 (28)	7 (14)	7 (14)	36 (72)	**0.098**
High risk	0 (0.0)	3(6)	4 (8)	0(0.0)	7 (14)	
Total	8 (16)	18(36)	15(30)	9 (18)	50 (100)	

Table 6: Clinical stage with Histological Risk Assessment

Histologic risk assessment	Clinical Stage				Total	P-value
	Stage I	**Stage II**	**Stage III**	**Stage IV**	**n (%)**	
	n (%)	n (%)	n (%)	n (%)		
Low risk	0 (0.0)	0 (0.0)	2 (4)	5 (10)	7 (14)	
Intermediate risk	3 (6)	8 (16)	10 (20)	15 (30)	36 (72)	0.278
High risk	0 (0.0)	0 (0.0)	1 (2)	6 (12)	7 (14)	
Total	3 (6)	8 (16)	13 (26)	26 (52)	50 (100)	

Table 7: Relationship of tumor size with worst pattern of invasion

Pattern of invasion	Tumor size				Total	P-value
	T1	**T2**	**T3**	**T4**	**n (%)**	
	n (%)	n (%)	n (%)	n (%)		
Types 1-3	0 (0.0)	13 (26)	12 (24)	2 (4)	27 (54)	0.088
Types 4-5	4 (8)	10 (20)	9 (18)	0 (0.0)	23 (46)	
Total	4 (8)	23 (46)	21 (42)	2 (4)	50 (100)	

Table 8: Relationship of Lymphocytic Infiltration with Clinical Stage

Lymphocytic infiltration	Clinical Stage				Total **n (%)**	P-value
	Stage I n (%)	**Stage II** n (%)	**Stage III** n (%)	**Stage IV** n (%)		0.163
Types 1-2	3(6)	8 (16)	13 (26)	21 (42)	45 (90)	
Type 3	0 (0.0)	0 (0.0)	0 (0.0)	5 (10)	5 (10)	
Total	3 (6)	8 (16)	13 (26)	26 (52)	50 (100)	

Table 9: Relationship of Perinural Invasion with Clinical Stage

Perinural invasion	Clinical Stage				Total n (%)	P-value
	Stage I n (%)	Stage II n (%)	Stage III n (%)	Stage IV n (%)		
Absent	3(6)	5 (10)	7 (14)	24 (48)	39 (78)	**0.023**
Present	0 (0.0)	3 (6)	6 (12)	2 (4)	11(22)	
Total	3 (6)	8 (16)	13 (26)	26 (52)	50 (100)	

Figure 1: Gender distribution of patients. The figure demonstrates the distribution of sex among the patients. Out of 50 patients 17 (34%) were male and 33 (66%) were female with a male to female ratio 1:2

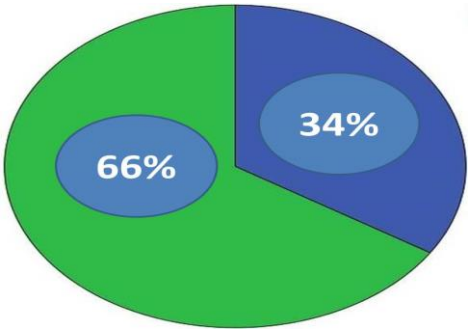
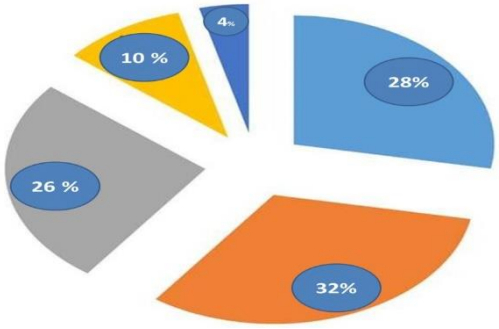


Figure 2: Site of oral squamous cell carcinoma. Most of the patients (32%) suffered from the squamous cell carcinoma of mandibular alveolar mucosa followed by a descending order of cheek (28%), maxillary alveolar mucosa (26%) and tongue (10%)



Discussion

The most common etiological factors are chewing tobacco, smoking, viral infection and poor oral hygiene. Oral cancer is generally a disease of elderly people. Sree Vidya Krishna Rao and his co-workers found that the mean age of the patients from Asian countries with cancer in different parts of oral cavity was between 51-55 years. About 17% of the younger patients were below 40 years of age, whereas our study found 18% of our patients were below 40 years of age described the epidemiology of oral cancer in Asia for last decade in 2014.[9] In our study the mean age of the patients was ~ 50 years ranging from 26 to 75 years. Usually, men are more likely to be affected by OSCC than women. The male to female ratio was found to be 1:1.45 in Japan, and the highest in Taiwan with 1:10.5.[10,11] However, our results show the male to female ratio was 1:2. Similar ratio was observed in a study from Bangaluru, India[12] This could be due to the fact that more use of smokeless tobacco (betel quid, pan) by rural women as part of their social culture. The site of occurrence of oral cancer depends on the predominant risk factors in that particular geographical region. In Japan, India, and Iran, the oral tongue is the foremost among all sites contributing up to 42% of all oral sites in adults of all ages. In our study, the most common site for OSCC was the mandibular alveolar mucosa with 32% cases, and only 10% cases involved the oral tongue. This is because betel quid chewing is a very common habit in our country and most of the people are used to keep the chewed betel quid in the buccal vestibule for a long time. Carcinoma of lip found to be less common in our country. Prognosis of oral cancer depends upon many factors, among which, clinical stage of the lesion at diagnosis is very important. Although there has been advancement in oral cancer treatment, the prognosis of the disease remains poor.[14,15] In fact, if the disease is diagnosed at a late stage, the prognosis tends to be poor. Moreover, patients with advanced stage of the disease have a higher mortality rate than those at the initial stages. Margaret Brandwein-Gensler et al studied 292 patients of OSCC among which stage I and stage IV lesion were 17% and 47%, respectively.[8] Another study from Brazil evaluated 38 cases in which stage I and stage IV cases were 18% and 38%, respectively.[17] The clinical stages in our study from Stage I to stage IV were 6%, 16%, 26% and 52%, respectively. In fact, most of the patients in our study presented with late stage of the disease due to illiteracy, lack of awareness, poor socioeconomic condition and lack of proper treatment facilities. The TNM system has been used as an international standard to help establish therapeutic protocols for malignant tumors and to estimate patient survival. However, this system often unable to determine the clinical outcome OSCC patients, a fact that has encouraged this study to design to identify factors that could complement the TNM system in determining the prognosis of patients. In this context, histopathological grading systems are historically important. The relationship of clinical parameters (tumor size, nodal metastasis and clinical stage) with the histologic risk assessment grading system proposed by Brandwein-Gensler et al were assessed in this study.[8] No significant relationship observed between histologic risk assessment and tumor size, nodal metastasis or clinical stage of the lesion ($P > 0.05$). However, H. B. de P. Santos et al. evaluated the histopathological grade of malignancy in a series of lower lip squamous cell carcinomas (LLSCCs) using three histopathological grading systems (invasive front grading system, World Health Organization (WHO) grading system, and histological risk assessment),and found that grading of the invasive tumour front had a significant association between low grade of malignancy and the absence of regional lymph node metastasis ($P = 0.030$) and initial clinical stage ($P = 0.043$).[22] No significant associations were observed between the clinical parameters analyzed and the WHO system ($P>0.05$).

Furthermore, using the risk assessment, a highly significant association was observed between the risk score and regional lymph node metastasis (P = 0.004) and clinical stage (P = 0.002). No significant association was observed between tumour size/extent and risk score.[19] Bibi Rahima et al. examined 101 patients of SCC of the oral cavity and oropharynx for the evaluation of the occurrence and prognostic significance of PNI, and found that PNI was present in 25.7% (26/101) of patients, and was significantly associated with tumor differentiation, lymphnode metastasis, and depth of invasion.[20] Perineural spaces are well recognized routes for the extension of tumors of various histologic types arising in the head and neck region. Literature suggests, the occurrence of PNI from OSCCis reported to be ranged from 6% to 30%, which is similar to the PNI rate of 22% found in our study.[20] Fagan and co-workers noted that carcinomas that invade the perineural space had a higher metastatic rate (73%) than those without PNI (46%).[20] Our study shows that metastatic rate was 21.43% (9/42) in patients with PNI, whereas it was 25% (2/8) in patients without PNI. It does not match with the previous studies. Tumors that invade the perineural space are biologically more aggressive. The incidence and extent of PNI are greater at the periphery and deeper portion of the tumor than at the proximal or distal margins. This suggests that PNI less likely to develop via the lymphatic-vascular network but is a continuous extension from the primary tumors. Although previous studies showed a significant association of risk scores with the regional lymph node metastasis and clinical stage of the lesion, such relationship was not established in this study.

Conclusions

The results of the present study indicate that perinural invasion is significantly associated with the clinical stage of the OSCC. Therefore, the presence of PNI should be checked in every surgical specimen with SCC of the oral cavity as it is a potential prognostic factor for OSCC. A more extensive clinical study is recommended in different centres of Bangladesh with a larger sample size to better evaluate the relationship of histologic risk assessment grading system with the TNM system. This will assist us to better understand the clinical behaviour of oral squamous cell carcinoma.

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