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Original Research Paper

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GETTING INTO THE PROGNOSTICATION OF ORAL SQUAMOUS CELL CARCINOMA BASED ON TUMOR BUDDING

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ABSTRACT Oral squamous cell carcinoma is one of the most common cancers in India. Oral cancer is linked to the habit of tobacco intake either as betel, gutkha, bidi, hookah, or cigarette; which is widespread in India. In India, most of the oral cancer patients present in locally advanced stage, and only a small proportion present in early stage. According to the published literature these cancers should have better outcomes with modern day treatment. Although, the outcome in early stages is better but still around 12-14% patients got recurrent disease and die eventually. There are many suggested clinical-pathological and histological models for prognostication of the oral cancers. These models are not very common everywhere but are in developing stage. Some of the suggested models include the Brandwein Gensler model and Almangush et al and others. These models consider depth of invasion, perineural invasion, lymphocytic host response, worst pattern of invasion and tumor budding. These models are predictive of locoregional recurrence, disease free survival, lymph node metastasis and mortality. The various suggested models have some positive and some negative points. This article focusses on tumor budding as a prognostic marker in early oral cancers.

KEYWORDS : Recurrence, death, oral, bud, predictive

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is eighth cancer globally. Even with the modern treatment, 3.5 lakhs patients die per year due to HNSCC. [1] Early stage oral tongue cancer (OTC) is associated with 20-40% occult metastasis at the time of presentation. [2] The tongue has high muscle bundle content; plus, rich lymphatic drainage affect tumor spread. Published literature suggests that histopathological parameters might be used as prognostic markers and patients may be stratified into low and high-risk categories. [2] The high rate of occult metastasis at presentation raises the concern to explore more effective treatments and of course, heavily reliable prognostic markers. [1,3] The main prognostic markers are stage and location of HNSCC. HNSCC has the propensity to show variable prognosis for the same subsite. Some of the prognostic markers for HNSCC are grade, post-op margin, perineural invasion, depth of invasion and worst pattern of invasion. [1]

Tumor budding (TB) is a histopathological marker, which was first described by Imai et al at Japan in 1949. First it was described for cancer stomach, but, later on, it was also studied for tongue, larynx, colon, cervix, breast and rectum. [4] TB is defined as the presence of a single cancer cell or a cluster of less than 5 cancer cells at the invasive front. [1,3] TB is associated with nodal involvement, distant metastasis and poor survival. [1] Now, TB is a proven poor prognostic factor for carcinoma lung, larynx, esophagus, rectum, colon, gastrointestinal tract, tongue, breast, pancreas and anus. [1,5-9] This study focuses on tumor budding and its role in the prognostication of early oral cancers.

MATERIAL AND METHODS

The articles were searched on Google Scholar, PubMed, Scopus and Web of Science. The articles were searched with terms oral cancer, oral squamous cell cancer, early stage, prognostic markers, tumor bud and depth of invasion. All the relevant articles were studied and included in the present study.

DISCUSSION

Invasion is one of the important signs of malignancy which further detects progression and metastasis. [1] TB as a marker of invasion was first described in 2010 for HNSCC. [10] TB may be intratumoral TB if within main tumor body or peritumoral TB if at peritumoral invasive front. [1] The scoring of TB has been performed on Hematoxylin and Eosin stain. [10] But, when tumor buds are small, or present as a single cell or a small cluster; then, it becomes very difficult to detect TB on H & E stain as the invasive front of the tumor may be usually marked by stromal cells, fibroblasts and reactive lymphocytes. Hence, IHC (immunohistochemistry) using pan-cytokeratin is a good tool to examine TB in such cases. [1,11]

Tumor budding is the outcome of two main characteristics i.e. loss of cellular cohesion plus active invasion. [2] A histologic risk evaluation score model was proposed by Brandwein-Gensler et al that predicted the survival of patients with T1-T4 OTC and divided the patients into high-risk and low-risk (Table 1). [12]

Table 1. Brandwein-Gensler model [12]

Variable	Definition	Point assignment
WPOI	Pushing border	0
Type 1	Finger-like growth	0
Type 2	Large separate islands, more than	
Type 3	15 cells per island	0
Type 4	Small tumor islands, 15 cells or	
Type 5	fewer, per island	1
	Tumor satellites, C1 mm from main	
	tumor or next closest satellite	3
LHR	Dense complete host response	
Type 1	rimming tumor	
Strong	Lymphoid nodules at advancing	
Type 2	edge in each 4X field	0
Intermed	Intermediate host response	
iate	Lymphoid nodules in some but not	
Type 3	all 4X fields	1
Weak	Little or no host response	
	No lymphoid nodule	3

PNI	None	0
None	Tumor wrapping around nerves,	
Small	<1 mm diameter	1
nerves	Tumor wrapping around nerves,	
Large	≥1 mm diameter (20X)	3
nerves		

The total points are added from each of the variable for each patient. If total point score comes 0, then it is classified as low risk; if the score is 1 or 2, then it is termed as intermediate risk; and, if score is 3 or more, then it is classified as high risk. [12] Other comparative models were reported by Anneroth et al [13], Jakobsson et al, [14] Martınez-Gimeno et al [15], and Bryne et al [16]. Majority of the models are either very hard to use or have no prognostic significance for OTC. [2]

Almangush et al proposed scoring criteria for tumor budding. [17] For the assessment of tumor buds in H&E stained and pan-cytokeratin stained areas; scoring models were similar. For scoring 'B' type of tumor bud, the entire cancer region is to scanned at low magnification (4X) then, at that point, the biggest number of tumor bud is counted at a higher magnification (20X) and is used as the score for tumor bud. The cut-off point for tumor bud is set at 5 buds (low <5; high ≥5). Depth of invasion 'D' is estimated from the cancer surface to the deepest point of the invasion. The cut-off point for 'D' is 4 mm (low <4 mm; high ≥4 mm). By combining the both tumor bud 'B' and depth of invasion 'D'; BD model was formed and BD score was formulated (Table 2). [17]

Table 2. BD scores description as per Almangush et al [17]

BD score	Histopathological description
Score 0	D <4mm and B <5 buds
Score 1	D ≥4mm and B <5 buds OR D <4mm (superficial tumor) and B ≥5 buds
Score 2	D ≥4 mm and B ≥5 buds

BD= tumor budding (B) and depth of invasion (D)

Thus, according to this BD model, each patient is given a score between 0 and 2. Three categories were formulated based on this core – low risk with a score of 0, intermediate risk with a score of 1, and high risk with a score of 2. [17]

TB has a strong association with unfavorable clinico-pathological features, poor disease-free survival and poor overall survival. [1] TB represents that tumor cells have undergone epithelia-mesenchymal transition, which is a way for cancer progression. During this transition, there is loss of epithelial markers and attainment of mesenchymal markers. [18] There are a few published pieces of literature assessing the role of TB in HNSCC (Table 3). [1,2,10,19,20,21,22,23,24,25] Evidence revealed that TB is an independent poor prognostic factor and is a strong predictor of nodal metastasis, distant metastasis, loco-regional recurrence, poor disease-free survival, and worse overall survival. Even, TB has been recognized by UICC (International Union against Cancer) as a highly relevant prognostic cancer marker. [26] Using IHC with anti-cytokeratin antibodies, Shinto et al demonstrated cytoplasmic pseudo fragmentation in tumor buds which were associated with aggressive high-grade tumor budding. [27]

Table 3. Various studies including histologic risk model

Author	Almangush et al [2]	Li et al [21]	Chen et al [22]	Chatterjee et al [23]	Sinha et al [24]	Lindenblatt et al [25]
Year	2015	2013	2017	2019	2017	2012
Number of patients	311	299	180	126	64	53
Region	Finland, Brazil	USA	USA	India	Canada	Brazil
Risk model	BD model	Brandwein-Gensler model	HN-CCI	Tumor budding, WPOI	PNI, WPOI, LHR	Multiparameter grading system
DFS	Poor with high score	Predictive of DSS	Predictive of DFS	-	Predictive of DFS	Predictive of DFS
Death	More with high risk	-	-	Predictor of LN mets and outcome	-	Predictive of LN mets and death
LRR	More with high risk	Predictive of LRR	Predictive of LRR	-	Predictive of recurrence	Predictive of LRR

DFS-disease free survival, LRR-locoregional recurrence rate, BD-tumor bud and depth of invasion, USA-United states of America, DSS-disease specific survival, HN-CCI- Head and Neck Charlson Comorbidity Index, WPOI-worst pattern of invasion, LN-lymph node, PNI-perineural invasion, LHR-lymphocytic host response

Early OTC is associated with more mortality than early stages of other sites of HNSCC. [17] Early OTC is associated with LRR rate of 23% and an occult metastasis rate of 30%. So, multimodality treatment becomes the only hope but it is quite important to avoid over-treatment also. [17] Thus, BD scoring criteria help in prognosticating the patients of early OTC and it further enhances the optimum treatment plan. From the biological perspective, this BD model considers the depth of tumor invasion, which shows the efficacy of the tissue penetration, and it also takes into account the tumor budding, which depicts EMT and tumor dissociation at the tumor invasive front. Tumor budding is also reported to have a heavy association with stromal myofibroblasts density in OTC. [28] In nutshell, the BD model provides a snapshot of tumor invasiveness and its ability to metastasize. [17]

According to a biological perspective, the BD model consider the depth of tumor invasion, which shows the viability of tissue invasion, and it likewise gauges tumor budding, which reflects EMT and dissociation of tumor at the invasive front. TB has been shown to associate with stromal myofibroblast density in oral SCC. [12]

CONCLUSION

Earl stage oral squamous cell cancers recur in 12-14% cases even after best treatment. With tumor budding as a prognostic marker, BD model predicts loco-regional recurrence, disease-free survival, disease-specific survival, lymph nodal metastasis, mortality and overall survival. On the basis of this model, adjuvant treatment may be modified according to the scoring criteria. But, this marker should be extensively studied in future prospective trials, and that too, on a large scale including large sample data so that conclusive evidence may be drawn and treatment guidelines may be amended accordingly.

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