

EDITORIAL



Tumor Budding in Oral Squamous Cell Carcinoma

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INTRODUCTION

Tumor budding is defined as the presence of a single tumor cell or a small cluster of up to five cells in the tumor stroma, linking it to the epithelial-mesenchymal transition (EMT).¹ Imai² illustrated that tumors with this trait have more aggressive qualities and allocated the term "sprouting" instead of "budding." The term "tumor budding" was coined by Morodomi et al in 1989.³ Tumor budding *in vitro* or in experiments has been addressed by many names, depending on the researcher's background, few of which are tumor cell dissociation, focal dedifferentiation, or EMT.⁴

Tumor budding is the sequestration and deployment of cancer cells from a primary tumor through the initial stages of tumor invasion and is known to depict an effective cancerous invasion. Tumor cells undergoing EMT are an indication of tumor budding. Tumor budding can be considered as a histological prognostic marker as it predicts lymph node metastasis, lymphatic or vascular invasion, resistance to chemotherapy-radiotherapy, local recurrence, distant spread, and prognosis. Several human solid cancers associated with a poorer prognosis

show more areas of tumor budding as seen in esophageal squamous cell carcinoma (SCC), nasopharyngeal carcinoma, and laryngeal carcinoma.⁵ Tumor budding has also been detected in the tumor front in most of the oral squamous cell carcinomas (OSCCs), and a higher frequency of it recurring has been shown to be associated with an elevated number of budding.⁶

Interestingly, assessment of tumor budding can be done using hematoxylin and eosin-stained specimens, and thus can be easily done with routine histopathological examination. Moreover, the results achieved are reproducible.⁷ This assessment can be used as a significant prognostic marker and aid in a better treatment planning for the patient.

Tumor budding has received recent attention, particularly in the setting of colorectal carcinoma. Even though it is documented in several publications throughout the last few years, tumor budding as a histopathological predictive marker in head and neck SCC has been explored only recently.

ORAL SQUAMOUS CELL CARCINOMA

Oral cancer is among the top 10 cancers in the body. The survival of the patients has not enhanced significantly despite the progress in research and therapy. Thus, it represents a continuing challenge in the field of biomedical sciences and cancer researchers.⁸

The tumor microenvironment consists of cancer-associated fibroblasts (CAFs), immune cells, and other auxiliary cells. Changes in genetic profiles provide microenvironmental alterations, such as overproduction of cytokines, reactive oxygen species accretion, and EMT.⁸ Some markers for elements in OSCC tumor microenvironment include cytokeratin, E-cadherin, programmed death (PD)-ligand 1, FasL, CD33, CD144, cancer stem cell markers like aldehyde dehydrogenase, N-cadherin, vimentin (EMT), integrin $\alpha 6$ (CAFs), CD4+CD25+FoxP3+ (T regulatory cells), CD8+, T-cell receptor, Fas, PD-1 (cytotoxic T cells), CD4+ (cytotoxic Th2 cells), CD34+ (myeloid precursor cells), etc.⁹

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TUMOR BUDDING IN OSCC: LESSONS LEARNED

Marangon Junior et al¹⁰ found a convincing association between high level of tumor budding and amplified concentration of stromal alpha smooth muscle actin +ve myofibroblasts. Increased activity of tumor budding was found to be associated with high expression of laminin-5 gamma 2, suggesting that tumor budding plays a pivotal role in OSCC development.

Wang et al¹¹ studied 230 patients with tongue SCC (TSCC) to examine tumor budding by investigating E-cadherin and vimentin expression. They detected tumor budding in 165 cases (71.7%), with a mean tumor bud count of 7.5 ranging from 1 to 48 buds. Statistical analysis showed that tumor budding was linked with tumor size, clinical stage, differentiation, and lymph node metastasis and was concurrent with reduced survival. They also observed noteworthy correlation among tumor budding and deregulation of E-cadherin and vimentin. Hence, they concluded that tumor budding seems to be a self-determining prognostic factor in TSCC.

Xie et al¹² retrospectively studied 195 patients with T1/T2 stage SCC of tongue. They reviewed tumor invasive depth, the concentration of tumor budding, and other clinicopathological characteristics and discovered that the incidence of tumor buds in tongue OSCC was about 85.6% in their study. They also noticed that the intensity of tumor budding showed strong correlations with occult lymph node metastasis, worse invasive pattern, invasive depth, and local relapse. They concluded that tumor budding which is a frequent event in TSCC can be used for routine pathological diagnosis and grading and while making the decision of elective lymph node dissection. It can also be applied independently to predict the prognosis of patients with T1/T2 stage TSCC.

Seki et al¹³ examined 91 cases of OSCC for conventional histopathologic assessment and tumor budding, and their association with lymph node metastasis. From the study they concluded that tumor budding should be added to routine histologic evaluation as a new measure of factoring into the decision as to whether neck dissection should be indicated or not.

FUTURE DIRECTIONS

The presence of tumor budding can be used as a promising prognosticator in OSCC. It can also be directed toward

grading of OSCCs and help the surgeon to devise a better treatment plan regarding lymph node dissection.

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