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A review of Micro invasive Oral squamous Cell Carcinoma: A diagnosis Linked to Histopathology

[1]Dr. Beena George, Professor, Department of Oral and Maxillofacial Pathology, Sree Mookambika Institute of Dental Sciences, Kulasekharam, Kanyakumari , Tamil Nadu 629161

[2]Dr. Malarkodi Chitra M, Postgraduate Student, Department of Oral and Maxillofacial Pathology, Sree Mookambika Institute of Dental Sciences, Kulasekharam, Kanyakumari, Tamil Nadu 629161

[3]Dr. Prasanth T, Professor and Head, Department of Oral and Maxillofacial Pathology, Sree Mookambika Institute of Dental Sciences, Kulasekharam, Kanyakumari , Tamil Nadu 629161

[4]Dr. Angelin D, Reader, Department of Oral and Maxillofacial Pathology, Sree Mookambika Institute of Dental Sciences, Kulasekharam, Kanyakumari ,Tamil Nadu 629161

[5]Dr. Jeslin Mary S, Reader, Department of Oral and Maxillofacial Pathology, Sree Mookambika Institute of Dental Sciences, Kulasekharam, Kanyakumari District, Tamil Nadu 629161

[6]Dr. Franklin R, Senior Lecturer, Department of Oral and Maxillofacial Pathology, Sree Mookambika Institute of Dental Sciences, Kulasekharam, Kanyakumari , Tamil Nadu 629161

[7]Dr. Rajalekshmi M P, Senior Lecturer, Department of Oral and Maxillofacial Pathology, Sree Mookambika Institute of Dental Sciences, Kulasekharam, Kanyakumari , Tamil Nadu 629161

Corresponding Author: Dr. Prasanth T, Professor and Head, Department of Oral and Maxillofacial Pathology, Sree Mookambika Institute of Dental Sciences, Kulasekharam, Kanyakumari , Tamil Nadu 629161

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Abstract

One in ten cases of cancer worldwide is head and neck cancer, with the oral cavity accounting for the majority of these cases. Oral squamous cell carcinoma, which makes up almost 90% of all oral malignancies, is a serious public health concern. Micro invasive oral squamous cell carcinoma is a type of incipient stage of oral cancer that affects the superficial part of lamina propria through a breach in the basement membrane, without invading the deeper structures.

They are characterised by their varied clinical presentation, minimal lymphatic involvement and better prognosis. The local spread of the lesion is primarily characterized by two critical features: Depth of Invasion and Tumor Thickness. Histopathologic examination is the primary method used to diagnose micro invasion,

which usually shows varying degrees of epithelial dysplasia, a dense infiltrate of inflammatory cells and a rupture in the basement membrane.

Keywords: Head and Neck Cancer, Oral Squamous Cell Carcinoma, Micro invasive Oral Squamous Cell Carcinoma, Depth of Invasion, Tumor Thickness, Epithelial Dysplasia.

Introduction

Globally, head and neck cancer is the sixth most common malignancy, with the majority of cases occurring in the oral cavity. Oral squamous cell carcinoma (OSCC), which constitutes 90% of cases, ranks as the second most prevalent cancer type in India. It tends to occur more frequently in males during the 6th to 8th decades of life and is associated with a serious prognosis. Conventional risk factors for mouth cancer include alcohol and tobacco abuse [1, 20].

Microinvasive squamous cell carcinoma (MIOSCC) is an early-stage cancer affecting both males and females equally, with an average age of 67.2 years, ranging from 42 to 87 years and does not infiltrate into the deeper tissues[21].

Global Cancer Observatory (GLOBOCAN) has estimated that there were 19.3 million incident cancer cases worldwide in the year 2020. India ranked third globally, following China and the United States of America. GLOBOCAN predicts that cancer cases in India will rise to 2.08 million in the future, representing a 57.5% increase from 2020 to 2040[4]. According to the data in 2020 approximately 77,000 new cancer cases and 52,000 deaths were reported annually in India. This accounted for roughly one-fourth of the global cancer incidences [16].

Oral squamous cell carcinoma is defined as “a malignant epithelial neoplasm exhibiting squamous differentiation as characterized by the formation of keratin and/or the presence of intercellular bridges”[5].

Microinvasive squamous cell carcinoma on the other hand is a minimally invasive tumor invading the superficial part of lamina propria and is characterized by lichenoid type of dense inflammatory infiltrate and intracellular keratinization of tumor cells [17].

Numerous cases of oral squamous cell carcinoma (OSCC) go unnoticed in their early stages because of their diverse clinical presentation. Improved prognosis and increased survival rates for patients rely on the early detection of cancer. Oral submucous fibrosis, oral lichen planus, erythroleukoplakia, erythroplakia, leukoplakia, and proliferative verrucous leukoplakia are among the several potentially malignant disorders (PMDs) that have the potential to progress to OSCC. Several etiological factors may contribute to the progression of various potentially malignant disorders (PMDs) into oral squamous cell carcinoma (OSCC). There have been several documented etiological factors for OSCC in the literature.

The most typical are enumerated here

- Cigarette smoking
- Alcohol consumption
- Shammah
- Chewing of khat
- Shisha (water pipe) smoking
- High exposure to UV light
- Diet with low levels of vitamins A and C
- Genetic predisposition
- Immuno suppressed patients[5,6]

Genetic basis of oral cancer

Ras is activated when epidermal growth factor (EGF) binds to the EGF receptor (EGFr), stimulating normal oral keratinocyte division. Raf, MEK, and MAPK are the kinases that are activated by active ras, and they

cause an increase in c-myc levels in the nucleus. Cyclin D's transcription is stimulated by c-myc, and this in turn activates cyclin-dependent kinase (CDK).

The phosphorylation of the retinoblastoma tumor suppressor protein (pRb) is catalyzed by active CDK. The transcription factors E2F, which are necessary for the transcription of DNAreplication proteins like PCNA, are released by phosphorylated pRb. Cell division comes next in line after DNA replication. With every round of cell division, cyclin D and the majority of DNA replication proteins are broken down and they subsequently undergo new transcription.

P53 detects damage to DNA in oral keratinocytes. Consequently, there is a rise in p53 levels, which triggers the transcription of p21, a CDK inhibitor that prevents pRb from becoming phosphorylated. Moreover, p21 binds to and deactivates PCNA. The transcription of Bax is stimulated by p53, and this prevents the activity bcl-2 . This results in unchecked caspase 3 activity and the progression of apoptotic cell death[5].

Histomorphological variants of OSCC

During progression into frank malignancy, a lesion passes through multiple stages, from initial cell damage to the development of features of anaplasia. Simple, moderate, or severe dysplasia gives way to in situ carcinoma, which then becomes an invasive cancer of the mouth. According to histology, the tumors were categorized as follows:

1. Well-differentiated squamous cell carcinoma
2. Moderately differentiated
3. Poorly differentiated.

Well-differentiated squamous cell carcinomas: These cancers have a good amount of intracellular and extracellular keratinization, as well as round to polygonal squamous cells that are arranged in islands of varying sizes and shapes. They also exhibit mild pleomorphism. It is evident that the tumor cell islands are penetrating the stroma.

Moderately differentiated squamous cell carcinoma: Round or oval-shaped neoplastic atypical epithelial cells infiltrate the tumoral stroma. Carcinoma islands are separated at the periphery by inflammatory cells or fibrous stroma. Most neoplastic cells have nuclei that vary in size and shape. Neoplastic cells have nuclei of different sizes and shapes, with the majority having hypochromic nucleoli and mild nuclear pleomorphism. Although the nuclei of neoplastic cells vary in size and shape, most of them are hypochromic, have large nucleoli, and exhibit moderate nuclear pleomorphism. Tumor cells were seen under a microscope to be atypical, widely dispersed cells with a mitotic rate of 3/10 Hpf and few keratin pearls in the stroma.

Poorly differentiated squamous cell carcinoma: Poorly differentiated squamous cell carcinoma cells exhibit increased mitosis >10/10 Hpf, lack of intracellular and extracellular keratinization, and moderate to marked pleomorphism[7].

TNM grading and staging

The two systems used to forecast tumor behavior and direct treatment following the detection of a malignant tumor are "grading" and "staging." Grading is largely based on 2 important histologic features: Degree of anaplasia and Rate of growth.

Cancer was first quantitatively graded by Broder's. His categorization scheme, which is based on the percentage of the tumor that resembles normal squamous epithelium, has been applied to squamous cell carcinoma for many years[23].

Other grading systems includes: Jakobbson et al (1973), Fisher (1975), Lund et al (1975), Willen et al (1975), Crissman et al (1980), Anneroth et al (1987), Bryne's

(1989, 1992) (ITF) Invasive Tumor Front Grading System[15].

Broders' grading (1927):

Grade I: Well-differentiated (less than 25% anaplastic cells)

Grade II: Moderately-differentiated (25-50% anaplastic cells)

Grade III: Moderately-differentiated (50-75% anaplastic cells)

Grade IV: Poorly-differentiated or anaplastic (more than 75% anaplastic cells) [23]

The TNM system of cancer staging is based on an evaluation of the size of the primary tumor

(T), the involvement of locoregional lymph nodes (N), and distant metastases (M). It represents the extent of tumor growth throughout the body. Treatment planning, recurrence risk estimation, and overall survival assessment all depend on this classification. But this classification ignores other prognostic factors like co-morbidity or treatment, and only takes the disease's anatomic extent into account[2]

Table 1: TNM clinical staging

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Carcinoma in situ.
T1	Tumor 2 cm or less in the greatest dimension.
T2	Tumor more than 2cm but not more than 4 cm in the greatest dimension.
T3	Tumormorethan4cminthegreatestdimension.
T4	**Lip**: Tumor invades adjacent structures, e.g. through cortical bone, tongue, skin of neck. **Oral cavity:** Tumor invades adjacent structures e.g., through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, skin.

Table 2: N- Regional lymph nodes

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph no demetastasis.
N1	Metastasis in a single ipsilateral lymph node, 3cm or less in the greatest dimension.
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6cminthegreatestdimension,orinmultipleipsilaterallymphnodes,nonemorethan6 cm in the greatest dimension, or in bilateral or contra lateral lymph nodes, none more than 6 cm in the greatest dimension. ✓ N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in the greatest. ✓ N2b: Metastasis in multiple ipsilateral lymph nodes, dimension none more than 6 cm in the greatest dimension. ✓ N2c: Metastasis in bilateral orcontralateral lymph nodes, none more than 6cm in the greatest.
	✓ N3- Metastasis in a lymph node, more than 6 cm in dimension the greatest dimension.

Table 3: M-Distant metastasis

MX	Presence of distant metastasis cannot be assessed.
M0	No distant metastasis
M1	Distant metastasis

The first staging manual was published in 1977 by the American Joint Committee on Cancer (AJCC), while the International Union Against Cancer (UICC) released the first edition of the TNM staging in 1968. The eighth edition of the UICC and AJCC staging manual (AJCC 8) was released in 2017. Two major changes for OSCC

were the incorporation of tumor depth of invasion (DOI) and extra capsular spread (ECS) in the N stage and their consolidation in the T stage[2].

Discussion

Micro invasive cancer is defined by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) as a lesion that is predominantly intraepithelial with a focus of invasion. Barnes defines micro invasive carcinoma as invasive squamous cell carcinoma that extends into the stroma by <0.5mm as measured from the adjacent (non- neoplastic) epithelial basement membrane[22].

Micro invasive oral squamous cell carcinoma (MIOSCC), is an early-stage tumor that is relatively thin and does not invade the deeper tissues. The hallmark of micro invasive oral squamous cell carcinoma is its ability to invade the superficial lamina propria with a breach in the basement membrane[9].

The thickness of the tumor and the depth of invasion are the two most crucial features of any epithelial malignancy for determining its degree of local invasion[3]. These lesions show a variation in their clinical presentations and exhibit minimal lymphatic involvement and usually have better prognosis than OSCC[9]. The predominant risk factor could be tobacco chewing alone which was in the form of gutkha and arecanut[10]. Distinctive clinical characteristics of MIOSCC may be discovered by accident during routine dental visits or follow-up visits for evaluation of premalignant disorders[14]. These lesions presented more frequently as patches, plaques, or erosions rather than ulcers or veracious lesions. Even though most lesions with micro invasion have a better prognosis than frank OSCC, it is still important to determine how deep the invasion is because proximity to lymphatic and blood vessels raises the risk of nodal metastasis[19].

Depth of invasion (DOI)

According to the 8th edition of the AJCC, DOI was the fact taken into consideration as invasion of tumor could precisely predict the aggressiveness of the tumor [12]. 'Depth of invasion' refers to the extent of cancer's penetration into the tissue beneath an epithelial surface[9]. MIOSCC typically invades at a depth of 0.5 to 2 mm, which is comparatively less. The measurement is typically taken from the basement membrane of the neighbouring non-neoplastic surface epithelium due to the larger variations in epithelial thickness[3]. The tumor has spread to adjacent tissues, at least 5 mm in depth and measured both histologically and clinically[8].

Analysis of the histological study of micro invasive OSCC by Kanno.N. (1990) has resulted in the identification of two types of invasion:

1) Primary invasion

2) Secondary invasion

Primary invasion: characterized by the dysplastic epithelium growing downward and exhibiting structural atypia; indistinct basement membrane; round cell infiltration; proliferation of blood vessels; and loose connective tissue surrounding the early invasion. It is observed as microinvasion from the basal layer as budding, drop, and diffuses infiltration of atypical cells from the dysplastic epithelium or carcinoma-in-situ.

Secondary invasion: This type of infiltration is observed in the vicinity of the muscle layer or periosteum as a drop and diffuse infiltration, morphologically resembling the invasive patterns of developmental carcinoma[11].

Microinvasion is purely a histopathological diagnosis, the hallmark being the breach in basement membrane along with the presence of dense inflammatory cell infiltrate[9,10].

The primary characteristic Histopathologic feature of an invasive tumor is the loss of the basement membrane.

This process of invasion is aided by migration, proteolysis, and adhesion.

Some of the initial histologic features are isolated cells, tiny, bounded groups of cells, or irregularly shaped finger-like processes. Small cytoplasmic protrusions of tumor cells into the adjacent stroma can be seen in sites where the membrane is absent, seemingly representing cancer invasion. When compared to the intraepithelial section of the lesion, the invasive peg in MISCC is distinguished by a larger and more distinct nucleus and richer cytoplasm.

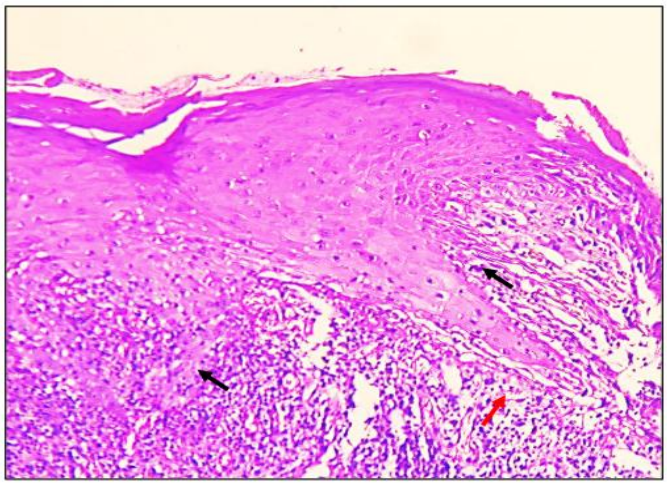

Figure 1: Histopathological section of the tissue specimen showing breach in the basement membrane and invasion of tumor cells into lamina propria under 10X magnification. Black arrow indicates breach in the basement membrane; Red arrow indicates Invasion of tumor cells into lamina propria.

With regard to leucocytic infiltration, some of the cells might be in different stages of degeneration. The development of narrow cell columns, the appearance of cell groups that appear to be invading the stroma, and the small tongues of tapering or branching epithelial cells were also thought to be indicators of invasion[22].

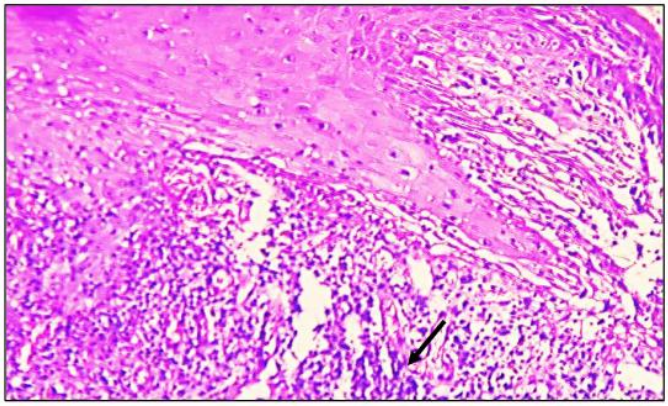

Figure 2: Black arrow indicates histopathological section of the tissue specimen showing dense leucocytic infiltration under 10X magnification.

Microinvasive carcinoma can develop in two distinct phases according to histology[10].

Histological measurement of depth of invasion (DOI) Determining the closest normal mucosa's basement membrane level and lowering a "plumb line" to the point of invasion that is the deepest[8].

Table 4: Categorization of T- stage by AJCC staging manual (Depth of Invasion DOI and not tumor thickness TT)

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm with depth of invasion (DOI)≤5 mm
T2	Tumor ≤2 cm with DOI > 5mmor Tumor > 2cm and ≤4 cm with DOI ≤10mm
T3	Tumor >2 cm and ≤4 cm with DOI >10mmor Tumor > 4cm with DOI ≤10 mm

T4	Moderately advanced or very advanced local disease T4a – Moderately advanced local disease Tumor >4 cm with DOI>10mm or Tumor invades adjacent structures only (e.g., through cortical bone of mandible or maxilla, or involves the maxillary sinus or skin of the face) T4b-Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/ or encases the internal carotid artery

Tumor thickness (TT)

Tumor thickness (TT) is measured perpendicularly between the tumour's deepest point and its highest point. The degree of tumor invasiveness that TT overestimates or underestimates depends on the tumour's morphology [12]. The tumor thickness (TT) of MIOSCC ranges from 4-10 mm[18].

Understanding the meanings of DI and TT in TSCC is crucial because these measurements have an impact on prognosis. It should be noted that these two terms have been used interchangeably. TT refers to the whole tumor volume, whereas DI is the extent to which the tumor cells can be histopathologically identified beneath the epithelium. The risk of nodal metastases is raised when a tumor with the capacity to grow spreads to adjacent blood vessels and lymphatics[22].

Diagnosis and management

Early cancer detection is essential for improved prognoses and higher patient survival rates.

Despite the ease of direct oral cavity examination, many cases of OSCC (oral squamous cell carcinoma) remain undetected in their early stages. For these patients, the 5-year survival rate has not increased and is still less than 50%. Early detection and treatment of cancers typically maximize long-term recovery and survival[14].

Table 5: Techniques for the diagnosis of oral cancer

Vital Staining	✓ 5%Aceticacid ✓ Toluidine Blue ✓ Methylene Blue ✓ Lugol's Iodine ✓ Rose Bengal ✓ Iodine staining ✓ Tolonium chloride
Light-Based detection systems	✓ Tissue fluorescence imaging (Velscope, identify 3000) ✓ Chemiluminiscence (Vizi Liteplus, Microlux /DL) ✓ Tissue fluorescence spectroscopy(NBI)
Cytological techniques	✓ Oral Brush biopsy(Oral CDX) ✓ Liquid Based Cytology ✓ Laser Microdisection (LCMd)
Molecular analyses	✓ Gene alterations ✓ Epigenetic alterations, loss of Heterozygosity and Microsatellite instability ✓ Viral genome studies ✓ Proliferation index and AgNOR Analysis ✓ Immunohistochemical identificationof tumor markers.
Histological techniques	✓ Incisional biopsy ✓ Excisional biopsy
Imaging techniques	✓ FDG-PET ✓ Optical Coherence Tomography(OCT)
Other technique	✓ Onco- chips

The most effective diagnostic method is one for which we have enough training and experience.

The gold standard for diagnosing oral cancer should unquestionably continue to be tissue biopsy and histopathological analysis[14].

The pathologist to locate the breach in the basement membrane, which may not always be achievable in standard H and E stained sections. Periodic acid schiff (PAS) stain was used to confirm the basement membrane breach and evaluate the basement membrane's integrity. Under such circumstances, the application of histochemical techniques can serve as helpful corroborators of the diagnosis.

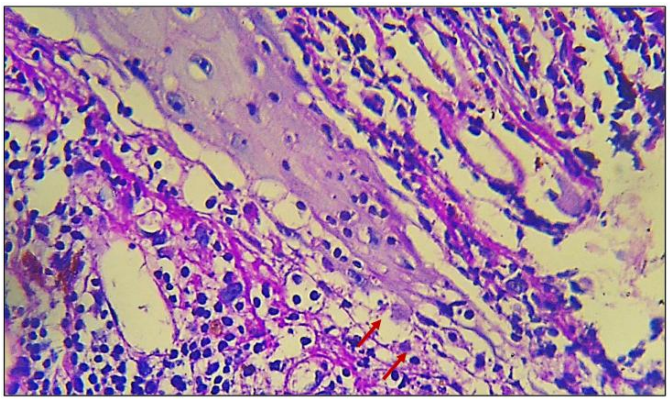

Figure 3: Periodic acid schiff (PAS) stained tissue section showing breach in the basement membrane under 40X magnification. Red arrow indicates breach in the basement membrane.

IHC staining was performed using the anti-cytokeratin, Pan (C11) antibody to highlight the 'invaded' epithelial cells. This antibody targets cytokeratin's 4, 5, 6, 10, and 13, which are prominently expressed in basal and supra-basal cells. It assists in distinguishing positively stained invaded epithelial cells from mesenchymal cells and facilitates the measurement of the depth of invasion.

To prevent irresponsible radical therapy, microinvasive OSCC must be diagnosed and treated as a distinct entity. Advances in molecular techniques should help the diagnostic process by enabling the prediction of the behavior of all tumors classified as microinvasive OSCC, which have the potential to progress to advanced grades of carcinoma[9].

Conclusion

Microinvasive squamous cell carcinoma is a tumor that invades the superficial part of the lamina propria with minimal spread. It is distinguished by intracellular keratinization of the tumor cells and a lichenoid type of dense inflammatory infiltrate. The purpose of characterizing micro invasive OSCC is to identify subsets of lesions with low risk of lymph node metastases and recurrence. Since diagnosis at an early stage of the disease is associated with better prognosis, a proper histopathological profile that assigns specific objective measures such as Tumor thickness (TT) and Depth of invasion (DOI) is essential. Early diagnosis can help the doctors to institute proper treatment modality and also provide appropriate care to the patients before the disease progresses further. Microscopic examination and assessment of formalin- fixed biopsy tissue specimen still remains the gold standard for pathological staging and cancer diagnosis in clinical practice. Thus, Histopathologic examination is even now the routine diagnostic tool.

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