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Detection of micrometastasis in oral cancer: A comprehensive review

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Abstract

Oral squamous cell carcinoma (OSCC) presents a significant global incidence and equally challenging mortality rates. Despite advances in diagnosis and treatment, mortality and morbidity rates among oral cancer patients remain constant. The most critical prognostic factor for patients with OSCC is the spread of cancer to cervical lymph nodes or distant organs. Micrometastasis refers to the microscopic deposits of malignant cells distinct from the primary tumour. Various methods, such as Immunohistochemistry (IHC), Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), and serial sectioning, are employed for detecting micrometastasis. Early detection of micrometastasis in oral squamous cell carcinoma (OSCC), particularly after surgery, is undeniably beneficial for the patient and can help guide treatment modifications. Micrometastasis is a crucial adverse factor in the prognosis of oral and oropharyngeal SCC. This article comprehensively reviews the detection of micrometastasis in oral cancer.

Keywords: Micrometastasis, Oral Cancer, Head and Neck Cancer

Introduction

Oral cancer is a significant global public health issue, leading to over 7.6 million deaths annually. In India, the estimated incidence of oral cancer is 73.6 cases per 100,000 population. Despite the presence of modern medical facilities, the overall mortality rate for oral cancer remains high at around 50%. It is the sixth most common cancer worldwide, with a high prevalence in South Asia. The annual mortality rate from head and neck carcinoma (HNSCC) exceeds 11,000, accounting

for 2% of all cancer deaths. HNSCC commonly spreads to the regional lymph nodes, which serve as the initial site of blockage for tumour cells that have invaded the peritumoral lymphatics. This spread appears to be the most significant predictor of disease prognosis and outcome. [1-5]

Metastasis is the spread of cancer cells from the place where they first formed to another part of the body. In metastasis, cancer cells break away from the original (primary) tumour, travel through the blood or lymph system, and form a new tumour in other organs or tissues of the body.

Metastasis involves a series of distinct stages: proliferation, angiogenesis induction, detachment, motility, invasion into circulation, aggregation, survival in the bloodstream, cell arrest in distant capillary beds, and extravasation into organ parenchyma. The progression of metastasis depends on the interplay between host factors and the inherent traits of cancer cells. [6-8]

Micrometastasis refers to the microscopic deposits of malignant cells discrete from the primary lesion. Lymph node metastasis decreases the survival rate by 50%.

Metastasis can be classified as isolated tumour cells (ITC) (size $\leq$ 0.2 mm), micrometastasis (size > 0.2 mm and $\leq$ 2 mm) and macrometastasis (size > 2 mm).[9]

Sentinal lymph node biopsy

This technique entails the usage of injecting a radiolabelled colloid around the primary tumour that drains into the first level lymph nodes, and this can be detected by the use of gamma probes. [10]

Immunohistochemistry

Cytokeratin (CK) proteins are essential components of the epithelial cytoskeleton and serve as dependable markers for detecting micrometastasis. Specific anti-cytokeratin antibodies can be used to identify epithelial cells in the lymph nodes. CKs are highly expressed in epithelial tumours, with CK19 and CK20 being commonly assessed.

Molecular detection

Molecular assays are extremely sensitive as compared to standard histopathological methods. Brenan et al. originally used PCR-based assays with the p53 gene for detection of micrometastasis in head and neck cancer. They found that the number of nodes that showed evidence of micrometastasis was much higher in molecular studies as compared to light microscopic study.[11]

PCR is an in vitro process of amplification of specific DNA sequences with the help of oligonucleotide primers (short DNA sequences) and therefore define the region of interest in the target DNA. The methods reliably assess relapse and death and would have a major influence on the treatment of solid tumours. They can also improve the preoperative staging of patients with malignancies and monitor the efficiency of adjuvant therapy.[12]

There are specific special stains such as Modified Papanicolaou and Toluidine blue that are easily accessible and can be applied to serially sectioned lymph node samples to identify micrometastases, which are often overlooked in single-section Hematoxylin and Eosin staining. [3]

Conclusion

Micrometastasis is a major cause of death in oral squamous cell carcinoma patients, with metastatic rates of up to 30% even in early stages. Understanding the molecular mechanisms driving metastasis is crucial for developing precise clinical models and improving outcomes. Identifying micrometastasis as a critical adverse prognostic factor underscores the importance of

integrating detection methods into clinical trials and management strategies.

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