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Review Article

PLETHORA OF ORAL FIELD CANCERIZATION: A REVIEW

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ABSTRACT

Oral cavity is one of the predominant and prevalent sites of development of oral cancer, since many carcinogens comes into its direct contact. Squamous cell carcinoma is one of the most common malignancies developed in the oral cavity with an average 5 years survival rate. Recurrences and second primary tumors develops, even when surgical margins are histopathologically tumor-free corroborates the field cancerization concept. *Field Defect or Field Effect*, terms also known for Field cancerization is a well-known process of malignant transformation of an existing precancerous lesion.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the worldwide most prevalent oral malignant tumor of head and neck region. It is the sixth most common malignancy in men and accounts for approximately 5% of malignant tumors in the population of developed countries.[1] In 1953, Slaughter *et al*. proposed this concept of "field cancerization" in patients diagnosed with squamous cell carcinomas of head and neck, and questioned its clinical significance for the development of second primary, either synchronous or metachronous, tumors in the same territory, or local recurrence.[2] This term was used to describe the presence of histologically abnormal tissue surrounding primary cancerous lesions and was proposed to be the reason for the occurrence of multifocal tumors and for the development of locally recurrent cancer. Field cancerization was much later proposed for other organ systems, including prostate.[3-8] Accordingly, the original intention by Slaughter and colleagues was to describe: *"The presence of histologically abnormal tissue surrounding cancerous lesions."* Hockel and Dornhofer extended this definition by using the term "hydra phenomenon of cancer" : *"The monoclonal or multiclonal displacement of normal epithelium by a genetically altered but microscopically undistinguishable homologue"*[9] Hence the prognosis of treatment of primary malignancy depends on occurrence of secondary primary tumors(SPTs) or Multiple primary tumors(MPT) the incidence of which is about 30-35%.[10]

This article aims to describe and explain the theories of field cancerization. The article also highlights in brief, about the molecular methods, therapeutic implications and chemoprevention for SPTs.

Second Primary Tumors

To define SPT, criteria of Warren and Gates is used which was published in 1932.it is as follows:

1. Each of the tumor must present a definite picture of malignancy.
2. Each must be distinct.
3. The probability of one being a metastasis of other must be excluded.[11]

A new classification of SPT was recently proposed.

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The tumors were also classified by time to recurrence:

If a tumor recurred at the same anatomic site, it is to be considered a SPT, atleast a gap of 3 years should be there between the detection of the tumors.[11]
SPTs are divided into 2 groups:

- Synchronous, which develop with or within 6 months after the index tumor
- Metachronous, which develop more than 6 months after the initial tumor.

Most of the SPTs are metachronous which develop during the follow up period. When the second tumor arises from the same field in which the first tumor has developed, it was called as Second Field Tumor (SFTs).[12]

Oral field cancerization theories

According to Slaughter *et al*. The entire epithelial surface of the upper aerodigestive tract (UADT) has an increased risk for the development of premalignant lesions. He gave this hypothesis based on the fact that multiple genetic abnormalities occur in the whole tissue region due to the result of exposure to carcinogens.[1] The occurrence of multiple tumors can be explained by these 2 hypotheses:

1. Monoclonal theory is in which single cell is transformed, and through the mucosal spread, give rise to multiple genetically related tumors.
2. Polyclonal theory in which multiple transforming events give rise to genetically unrelated multiple tumors.

An alternative theory for the occurrence of multiple malignant lesions has been proposed and is based on the premise that any transforming events is rare and that multiple lesion arise due to widespread migration of transformed cells through the whole aerodigestive tract.[13]

The alternative theory was further elaborated by Monique GCT van Oijen *et al* in 2000 which explained the basis of 2 types of migration of already genetically transformed cells.

1. Migration of tumor cells by saliva(micrometastasis)
2. Intraepithelial migration of progeny of initially transformed cells.[10]

Therefore, the patients with head and neck squamous cell carcinoma are exposed to the risk of developing local recurrences or second primary tumors due to field cancerization, which is considered to be a bad prognostic sign. According to the concept of the field cancerization, normal mucosa adjacent to oral cancer has suffered certain histopathological changes, as well as molecular, which can be the cause for the development of multiple premalignant lesions.[1]

Model of field cancerization

The carcinogenesis process begins with a stem cell that develops one or more genetic and epigenetic alterations. Gradually a clone of genetically altered cells gives rise to a patch or a cluster. Further genetic alterations result in the stem cell to escape normal growth control pattern and gains advantage by developing into an expanding clone. As the lesions progress it displaces laterally the normal epithelium. This genetically altered field has enhanced proliferative activity which is the driving force of the entire process. As the lesions progress it gives rise to various sub-clones within the field. Eventually this process ends up in the formation of an invasive cancer. The probability of developing cancer from a genetically altered stem cell depends on the nature of the affected stem cell itself and additional hits. The carcinogenesis model proposed is based on a monoclonal origin and includes three main steps (Fig-1):

- First phase (patch formation): conversion of a single stem cell (patch) into a group of cells (clone) which carry the genetic alterations without a proper growth control pattern.
- Second phase (clonal expansion): additional genetic alterations develop and the patch proliferates taking advantage of its enhanced growth potential and forms a field which displaces the normal epithelium.
- Third phase (transition to tumor): the clone or field eventually turns into an overt carcinoma with invasive growth and metastasis.[14]

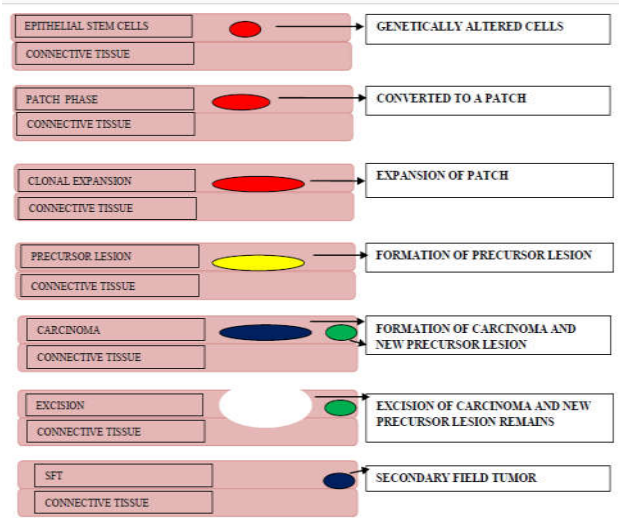

Figure 1 Model of Field Cancerization

Field cancerization molecular concepts

Findings at molecular level show the existence of cytokeratin 7, 8, 13, 16 and 19 at abnormal sites and abnormal levels within the epithelium.[14] Bonger *et al*. In their study found fourfold lower expression of type 2 chain ABH antigen in exfoliated cells from macroscopically normal mucosa from six different places far from head and neck squamous cell carcinoma compared with healthy individuals, which they assumed could be a promising negative marker for field change.[15] Bartkova *et al*. also observed the defined foci of cyclin D1 expression in the sections of the normal mucosa adjacent to head and neck squamous cell carcinoma which were not observed in the sections of the normal mucosa of healthy individuals.[16] amplified expression of epidermal growth factor receptor (EGFR) in tumor-associated normal mucosa have been studied in various research. EGFR expression in nonsmoking/ nondrinking head and neck squamous cell carcinoma patients and smoking/drinking head and neck squamous cell carcinoma patients were equally elevated. EGFR expression in the mucosa from head and neck squamous cell carcinoma patients was less

elevated when the epithelium was located more distant to the tumor.[17]

Five-fold elevation of mRNA level of TGF-α in normal tumor-associated mucosa is evident as compared to levels in control normal mucosa. By using proliferating cell nuclear antigen (PCNA) and argyrophilic nucleolar organizer region (AgNOR) it was seen that there was enlarged number of proliferating epithelial cells in normal tumor-associated mucosa in head and neck squamous cell carcinoma patients. Micronuclei assay in cytosmears of buccal mucosa showed increased micronuclei in strong tobacco and alcohol consumers as compared to controls without habits.[18,19] Gazzar *et al*. studied vascular markers (VwF, CD31, αVβ3, and α-SMA) and found significantly higher vascularity index in normal oral mucosa taken from cancer patients as compared to that of normal mucosa not concurrent with oral cancer.[17]

The most promising marker for field cancerization has been p53. It has been found that frequency of p53-positive cells gradually increases as oral epithelium progresses from normal to hyperplasia to dysplasia to carcinoma.[20,21] The determination of clonality was moderately successful by techniques like karyotype analysis, p53 mutations ,X chromosome inactivation. Ultimately "microsatellite alteration" has been concluded as overall effective method for demonstrating clonality. These are the tandem repeat sequences found typically in non coding regions. Loss of allelic material adjacent to micro satellite markers, known as loss of hetrozygosity, is a marker that can be used to characterize lesions by using PCR.[10] Summing up the data on these molecular markers, it appears that normal mucosa associated with carcinoma shows a range of alteration and genetic abnormalities.

Table 1 Potential end point markers for the detection of Field Cancerization.[17]

Histology	Dysplasia
	Carcinoma in situ
Differentiation antigens	Cytokeratins
	Secretory products
	Telomerase
	Retinoic acid receptor
Proliferation indices	PCNA
	Ki-67
Indices for genomic instability	Aneuploidy
	Microsatellite markers
	DNA adducts
	Micronuclei
Tumor suppressor/oncogenes or cell cycle control genes	p53
	p16
	Cyclin D1
	Fhit
	Ras
	C-jun
Growth factors/receptors	EGF
	EGFR
	VEGF
	CD34
	TGF-α
Genetic studies	Chromosomal anomalies/ aberrations
	Loss of heterozygosity (LOH)
	DNA sequence analysis
	Gene profiling
	Mitochondrial genome changes

Clinical relevance

The take away memorandum from the above review of the literature is that using histologically normal appearing samples as the control tissue in cancer research is probably inappropriate.[22] SPTs are the cancers that are not linked by neoplastic epithelial changes from primary cancer; they can be either synchronous, or metachronous. Such lesions may alter the line of treatment to original tumors and can affect the prognosis. By changing the field a different view on tumor excision margins can be created that contains molecularly altered cells. Even if the primary tumor is removed completely, recurrence may develop from the field of preconditioned epithelium, because of the remnants.[23] Multistep field cancerization indicates two levels of cancer progression: first, molecular progression where histologically normal looking cells undergo chronological cumulative attainment of genomic damage, and phenotypic progression where a neoplastic cell accumulates genetic alterations and undergoes further phenotypic changes. Functionally relevant pathways alterations at the molecular progression will be useful for early detection and monitoring of cancer.[22] Histologically benign mucosa often can progress to further pre-malignant or malignant diseases.[24] Patients which are at risk could be identified and treated to prevent the progress of disease, and patients amid pre-malignant lesions could have them reversed or halted. And finally, chemoprevention could be used to prevent the recurrence of cancer after surgery. So the recognition of tumor specific biomarkers for field cancerization will have outstanding usefulness in monitoring the tumor progression and in preventing transformation of pre-malignant lesions into invasive cancer.

CONCLUSION

Chemoprevention and cessation of unfavourable habits of smoking and chewing tobacco may prevent the development of second primary tumors if they arise independently. But in few cases they are of no benefit if multiple primary tumors have metastasised to other locations different compounds such as 13-cis-retinoic acid and COX-2 inhibitors are under trial.[17] information of genetic alteration may provide basis for gene-based therapy for preneoplastic lesions. Upcoming researches should concentrate on several unanswered issues like how important is the affected mucosa in respect to risk of malignancy, do synchronous and metachronous lesions act differently over time, and how much noteworthy is the termination of tobacco and alcohol use in disease progression? Furthermore, the hunt for a pertinent molecular marker that maps field lesions should continue, and the potential role of stroma in should be evaluated. A protocol for managing high-risk patients is essential to be developed and tested. This can be accomplished by performing longitudinal studies with large population groups having both single and multiple oral tumors.

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