

## Genetically altered fields in head and neck cancer and second field tumor

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## Abstract

The concept of field cancerization has been ever changing since its first description by Slaughter et al in 1953. Field cancerization explains the mechanisms by which second primary tumors (SPTs) develop. SPTs are the tumors, which develop in the oral cavity in succession to the primary malignant tumors, which might vary in duration ranging from few months to years. Conceivably, a population of daughter cells with early genetic changes (without histopathology) remains in the organ, demonstrating the concept of field cancerization. This review explains the concept of field cancerization and various field theories along with molecular basis of field formation.

**Key words:** Second primary tumor, head and neck squamous cell carcinoma, tumor adjacent mucosa, upper aerodigestive tract

## Introduction

In patients with head and neck cancer, investigators examined different pathological in an effort to understand the gross changes found in epithelia surrounding these tumors and explain their clinical behavior. It was discovered that all of the epithelium beyond the boundaries of tumor possessed histologic changes, and 88/783 (11%) of patients were found to have more than one independent area of malignancy. The conclusion drawn was that the mucosa of the head and neck had undergone a change, perhaps due to carcinogen exposure, and was therefore more susceptible to the development of many foci of malignant transformation.<sup>[1,2]</sup>

Survival of squamous cell carcinoma patients depends on tumor size, nodal stage, and success of initial treatment and has not improved very much during the last decades.<sup>[3]</sup> The prognosis of squamous cell carcinoma patients is adversely influenced by the development of new tumor, which may arise as a recurrence of an incompletely resected index tumor or may be a second field tumor (SFT) or a second primary tumor (SPT) that has arisen on a genetically altered premalignant field.<sup>[4]</sup>

The incidence rate of SPTs is 10-35%, depending on both the location of the first primary tumor and the age of the patient.<sup>[5]</sup>

These finding led to the field cancerization theory, which hypothesizes that the entire epithelial surface of the upper aerodigestive tract (UADT) has an increased risk for the development of (pre) malignant lesions because of multiple genetic abnormalities in the whole tissue region.

The concept of the field effect in cancer, also known as field defect/field carcinogenesis/condemned-mucosal syndrome or field cancerization.

Field cancerization is a well-known and well-documented process of malignant transformation. The term “field cancerization” was proposed by Slaughter *et al.*, in 1953, when studying oral cancer.<sup>[6]</sup>

On the basis of recent molecular findings, the following definition of field cancerization has been proposed: “The presence of one or more areas consisting of epithelial cells that

have genetic alterations. A field lesion (or shortly ‘field’) has a monoclonal origin, and does not show invasive growth and metastatic behavior, the hallmark criteria of cancer.”

A field lesion is preneoplastic; it may have histological aberrations characteristic for dysplasia. A detailed comparison between histology (dysplasia grading) and molecular pathology in oral fields shows:

- A relatively large interobserver variability of histopathological grading
- A genetically altered field can occur with normal histology
- All moderately and severely dysplastic lesions, and about two-thirds of the mildly dysplastic lesions show genetic alterations.

The term “lateral cancerization” was subsequently used to indicate that the lateral spread of tumors was due to progressive transformation of cells adjacent to a tumor, rather than the spread and destruction of the adjacent epithelium by preexisting cancer cells.<sup>[7,8]</sup>

Organ systems in which field cancerization has been described are: Head and neck squamous cell carcinoma (HNSCC) in oral cavity, oropharynx, and larynx; lung; esophagus; vulva; cervix; colon; breast; bladder; and skin.

## Field Theories

The mucosal changes in the entire UADT were generally considered to be the result of exposure to carcinogens that caused multiple genetic abnormalities in the whole tissue region.

The occurrence of multiple tumors can be explained by two competing hypotheses:<sup>[9]</sup>

- Monoclonal theory in which a single cell is transformed and through mucosal spread gives rise to genetically related multiple tumors
- Polyclonal theory in which multiple transforming events give rise to genetically unrelated multiple tumors
- An alternative theory for the occurrence of multiple (pre) malignant lesions has been proposed and is based on the premise that any transforming event is rare and that the multiple lesions arise due to widespread migration of transformed cells through the whole aerodigestive tract.

Two types of migration are involved in the concept of this theory:

- Migration of tumor cells by, for example, saliva (micrometastases)
- Intraepithelial migration of the progeny of the initially transformed cells.

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## Molecular and Genetic Basis of Field Formation

### Epigenetics and epigenetic alterations in cancers

Epigenetic information is defined as information other than the deoxyribonucleic acid (DNA) sequence that is faithfully replicated upon somatic cell replication. It is carried by DNA methylation at CpG sites, histone modifications, and polycomb complex formation.<sup>[10]</sup>

In cancer cells, “genome-overall hypomethylation and regional hypermethylation” are present. The hypomethylation can lead to genomic instability and is considered to be involved in tumor progression.

### Characteristics of a genetically altered field

A field of precancerization in the oral cavity can be defined as an area of clinically normal looking epithelium which is either microscopically normal or shows dysplasia, but in which some keratinocytes have undergone cytogenetic alterations. The process of progressive cytogenetic alteration (transformation) can confer upon the keratinocytes in such an epithelial field a growth advantage in relation to the normal surrounding keratinocytes so that within an apparently clinically normal stretch of oral mucosa there can be a pathobiological continuum from normal epithelium to precancerized epithelium where carcinoma can arise. When these progenitor cells divide asymmetrically, one daughter cell is completely identical and retains proliferation capacity, whereas the other undergoes a limited number of cell divisions to produce, in the first three suprabasal layers of the oral epithelium, a ‘transitory amplifying’ cell population that undergoes terminal differentiation. Progenitor cells and their daughters form a clonal unit and it has been estimated that an average of five oncogenic events are necessary for the cancerization of a normal cell.<sup>[11]</sup>

### Polyclonality of MPTS in the head and neck

Most studies that used clonal markers to investigate the relationship between MPTs or to investigate dysplastic lesions occurring in the UADT and that were remote from each other showed polyclonality between these lesions. Only a limited amount of MPTs showed the same genetic alterations as evidenced by showing identical microsatellite alterations, LOH patterns, or cytogenetic features. However, the overwhelming majority of remote MPTs shows no clonal relationships and can therefore be assumed to have developed independently.

HNSCC or adjacent premalignant lesions that are located very close to each other more often show identical genetic changes.<sup>[12]</sup>

### Field precursor lesions: Patches

In various epithelia, clusters of cells with cancer-associated genetic alterations can be found that are much smaller than the fields described above. With respect to tumor-adjacent oral mucosa, clusters (<200 cells diameter) can be observed with a TP53 immunostaining. These clusters, known as “patches”, are defined as a group of cells that share a common genotype, contiguous at the moment of consideration.<sup>[13]</sup>

### Risk Factors

In chronic inflammatory diseases like oral lichen planus (OLP), there is chronic inflammation and immune activation. Activated inflammatory cells and cytokine network promote squamous tumorigenesis, influence clonal spreading, and thus support process of field cancerization.<sup>[14]</sup> Tobacco can cause morphological changes in cells of normal buccal mucosa in

patients with malignant disease. The changes include increase in nuclear size, discontinuous nuclear membrane, numerous Feulgen-negative areas, increase in associated chromatin surrounding clear areas, absence of a single large nucleolus and altered nuclear-cytoplasmic ratio.<sup>[15]</sup>

### Investigations

Field cancerization can be demonstrated by supravital staining by toluidine blue or by electron microscopic study of random biopsies taken from apparently normal mucosa.<sup>[16]</sup>

### Current Clinical Definition of Locally Recurrent Cancer, SFT, and SPT

For a definition of SPT, most clinicians currently use the criteria of Warren and Gates,<sup>[17]</sup> which were published in 1932:

- Each of the tumors must present a definite picture of malignancy
- Each of the tumors must be distinct
- The probability of one being a metastasis of the other must be excluded.

Histological examination will often find that a tumor is malignant, but with this method, it is difficult to prove that the lesions are distinct. To exclude the possibility of a local recurrence, most studies use a distance of at least 2 cm between the first tumor and the SPT.

An additional criterion of an SPT at the same or an adjacent anatomical site is that it should occur at least 3 years after the diagnosis of the primary tumor. SPTs can be divided into two groups: Synchronous SPTs, which develop simultaneously with or within 6 months after the index tumor and metachronous SPTs, which develop >6 months after the initial tumor. Most SPTs are metachronous and develop during follow-up of HNSCC patients after curative treatment of the first tumor. The term SPT suggests that these tumors and the index tumors have developed independently. Recently, however, genetic studies have shown that, in a proportion of cases, the first and second tumors have originated from the same precursor cell.

A new classification method of SPTs has been proposed, to account for the information gained from molecular studies.<sup>[17]</sup>

In the past, these lesions were distinguished as being distinct simply by an arbitrary distance, often 1.5 or 2.0 cm apart. The tumors were also classified by the time to recurrence: If a tumor recurred at the same anatomic site, then some investigators believed that, for it to be considered a SPT, at least 3 years had to have elapsed between detection of the tumors. These somewhat arbitrary distinctions have been refined by molecular techniques that can identify relationships between lesions. Therefore, the authors suggest a different designation—“second field tumors” (SFT)—for those lesions that are anatomically distinct but demonstrate genetic similarities.

For those tumors that arise in the same anatomic location postresection, SFTs can be identified as well. Thus, true second primaries would be those lesions that did not share any genetic similarity and therefore likely arose as a result of independent events.

### Conclusion

The presence of a field with genetically altered cells is a risk factor for cancer. The large number of preneoplastic cells in the

proliferating fields is likely to increase cancer risk dramatically. The finding that field changes frequently occur in TAM of HNSCC patients creates a different view on tumor excision margins that contain molecularly altered cells. Early detection and monitoring of field may have profound implications for cancer prevention.

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## Announcements

**32nd ICON Meeting 2014**  
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**For further details please contact:**  
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## Announcements

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