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## RESEARCH ARTICLE

# FIELD OF CANCERIZATION

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**ABSTRACT**

The oral cavity is one of the predominant and prevalent sites of development of potential malignancies, since it comes into direct contact with many carcinogens. Despite monitoring the original tumour site following an advanced surgical and non-surgical therapy, the overall mortality rate remains unchanged probably due to the recurrence of the tumour either locally or at a remote site. Field Cancerization also called field defect or field effect is a well-known process of transformation of an existing precancerous lesion into a malignancy. This definition is often used to describe the development of abnormal tissues around a tumorigenic area, resulting into an oral multifocal cancer in individual sites, which later coalesce and create atypical areas, even after complete surgical removal of the tumour. Early detection and monitoring of the field may have profound implications for Cancer Prevention.



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# INTRODUCTION

The oral cavity is one of the predominant and prevalent sites of development of potential malignancies, since it comes into direct contact with many carcinogens. The squamous cell carcinoma is one of the most common malignancies developed in the oral cavity with an average survival rate of about 5 years.[1] Despite monitoring the original tumor site following an advanced surgical and non-surgical therapy, the overall mortality rate remains unchanged probably due to the recurrence of the tumor either locally or at a remote site. [2]The development of recurrences and second primary tumors, even when surgical margins are histopathologically tumor-free corroborates the concept of field cancerization.[3]Field cancerization also called field defect or field effect is a well-known process of transformation of an existing precancerous lesion into a malignancy.[4] Oral field cancerization implies that oral cancer does not arise as an isolated cellular phenomenon, but rather as an anaplastic tendency involving many cells at once that results into a multifocal development process of cancer at various rates within the entire field in response to a carcinogen, such as in particular tobacco.[5]This definition is often used to describe the development of abnormal tissues around a tumorigenic area, resulting into an oral multifocal cancer in individual sites, which later coalesce and create atypical areas, even after complete surgical removal. This may explain the cause for second primary tumours and recurrences. [6] Prolonged exposure to carcinogens alters the state of the epithelium, making it susceptible to developing a multifocal carcinoma, which can also derive from independent mutations in the absence of any genetic influence. Multifocal areas of precancerous alterations may trigger this process without involving in particular an individual cell which becomes malignant.[7]

## HISTORY OF FILED CANCERIZATION

The concept and the definition of field cancerization was first introduced by Slaughter et al. in 1953, when he analyzed the tissues adjacent to squamous cell carcinoma. [8] The concept was first examined in the aero digestive tract, where multiple primary tumors and local recurrent tumors originate from the anaplastic tendency of multiple cells. The term lateral cancerization was coined later to suggest the lateral spread of tumors, which occurs due to a progressive transformation of the tissue adjacent to the tumor rather than the expansion of pre-existing cancer cells into the adjacent tissue.[9] On the basis of a broad analysis of 783 carcinoma patients, Slaughter et al. observed that the entire epithelium adjacent to the tumor exhibited more than one independent area of malignancy Later,

the expression of field cancerization was adopted, as these findings suggested that the exposure to carcinogen-induced mucosal changes makes the adjacent area susceptible to multiple malignant foci. The concept of field cancerization was extended to other organs, including oropharynx, oesophagus, lungs, stomach, colon, cervix, anus, skin and bladder. [10] The oral cavity was proven to be most susceptible to this process, as it is exposed to a wide range of environmental carcinogens which affect the entire mucosa and result into the simultaneous occurrence of premalignant states. This led to various molecular analyses to investigate the genetic mutations and clonality to validate this carcinogenesis model. [10] In particular these findings were reported in 1950's when the Watson and Crick model was first described. Later numerous molecular techniques provided unequivocal evidence supporting the concepts proposed by Slaughter et al.

**SECOND PRIMARY TUMOR:** Second primary tumours in patients with head and neck cancer. These patients have a high risk of developing other cancers simultaneously or subsequently. The incidence of multiple primary tumors in this population can be as high as 27%. Recurrences are the most common cause of treatment failure within the first 2 years of follow-up. After the third year the diagnosis of a second primary tumor becomes the most important cause of morbimortality in head and neck cancer patients, especially in those treated for cancers early diagnosed. Most second primary tumors occur in the upper aero digestive tract (40%-59%), lung (31%-37.5%), and oesophagus (9%-44%). Patients who develop second primary tumor have a significant reduction of survival expectancy.

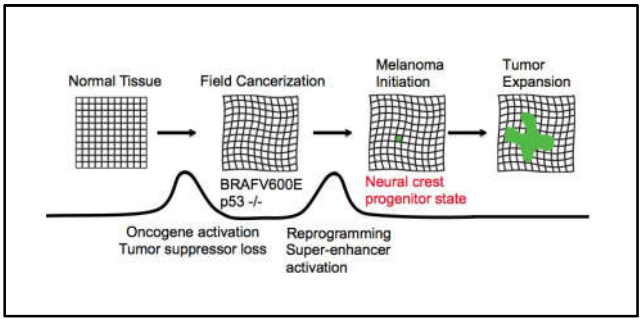
**For SPT, most clinicians currently use the criteria given by Warren and Gates, [11]which were published in 1932:**

- Each of the tumors must present a definite picture of malignancy,
- Each must be distinct, and
- The probability of one being a metastasis of the other must be excluded. [11, 12]

Histological examination will often find that the tumor is malignant, but with this method, it is difficult to prove whether 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. [11, 13] .Another criterion for SPT, at the same or an anatomical adjacent sites, is that it should be classified by the time of recurrence. For a tumor to be considered a SPT, at least three years had to have elapsed between detection of the tumors. SPTs can be divided into two groups: synchronous SPTs, which develop simultaneously with or within six months after the index tumor, and metachronous SPTs, which develop > six months after the initial tumor. Most SPTs are metachronous and develop during follow-up of HNSCC patients after curative treatment of the first tumor. [11, 12] .The term "SPT" was proposed to be allocated for the second tumor that has developed independently from the first tumor. When a second tumor arises from the same field in which a first tumor has developed, it was preferred to designate it as a "second field tumor" (SFT). [14]

## DISTANT LESIONS

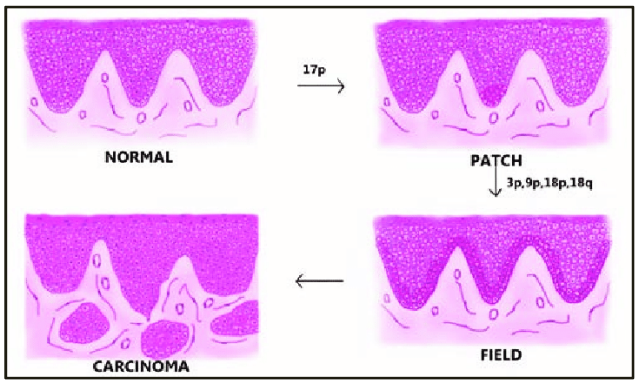
Distant Lesions High incidence of recurrence observed in patients with this disease is due to the distinctive ability of head and neck cancer cells to migrate and persist outside the




field of treatment. The phenomenon of field cancerization observed in head and neck tumors can be caused either by molecular events affecting several cells from different locations at the same time or by molecular events in a single clonal progenitor that is capable of widespread clonal expansion or lateral spread.[15,16]The process of local tumor spread has been associated with epithelial-mesenchymal transition, a conserved morphogenic process that involves loss of E-cadherin function that contributes to the migration of individual tumor cells.[16-17] Kristy A Warner et al. in their study demonstrated that CXC chemokines secreted by tumor-associated endothelial cells induce tumor cell invasion through CXCR2. Bcl-2 upregulation correlates with increased expression of CXCL1 and CXCL8 in endothelial cells. The results in the study position the neovascular endothelial cells as the source of a chemotactic gradient that will induce tumor cell movement away from its original niche. [18]

## FIELD CANCERIZATION AND ITS CLINICAL IMPLICATIONS IN THE MANAGEMENT OF POTENTIALLY MALIGNANT DISORDERS

The current treatment protocols for potentially malignant disorders such as leukoplakia are centered on the removal of the morphologically altered area. This management strategy is based on the belief that oral cancers will occur on the morphologically altered area.[19] However, the current evidence shows that the adjacent clinically normal appearing mucosa also harbours genetic aberrations of early malignant transformation.[20] These fields of cancerization can extend from 4 mm to 7 cm.[21]Based on these newer insights, we would like to reinforce the following management strategies along with the conventional surgical removal of morphologically altered lesion.




- Counselling and reinforcement during follow-up visits regarding habit cessation. The continued exposure to tobacco carcinogens will induce more genetic mutations to the already existing precancerous fields [22]

- Emphasis should be placed on long-term follow-up and monitoring of the patients. It is estimated that it takes 67–96 months to transform into an invasive carcinoma [23]
- Importance should be given in the examination of the whole oral cavity not only the lesional area

## CONCLUSION

The current developments in the genetic aspects of multistage carcinogenesis and field cancerization have made a rethink in the nomenclature and behaviour of these diseases. Understanding these developments in the field of oral cancer and precancers will improve the clinician's management strategies. A reemphasis on the importance of habit cessation, long-term follow-up and the examination of clinically normal appearing mucosa during follow-ups can help in the early detection of malignant changes. These steps should help in improving the prognosis of the patients with potentially malignant disorders. The future development should be aimed at incorporation of relevant molecular markers in the assessment of potentially malignant disorders and the use of minimally invasive brush biopsy techniques to identify field lesions

## SUMMARY

Field cancerization is a well-known and well documented process of malignant transformation. Several studies confirm the importance of this phenomenon in tumor development. The presence of field with genetically altered cells is a rock factor for cancer. The large number of pre-neoplastic cells in the proliferating fields is likely to increase the cancer risk dramatically. The finding that field changes frequently in the tissue altered mucosa of the HNSCC patients creates a different view on tumor excision margins that contain molecularly altered cells. Early detection and monitoring of the field may have profound implications for Cancer Prevention.

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