**Oral Field Cancerization: An Update**

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**ABSTRACT:** In up to 20% of the patients affected by head and neck squamous cell carcinoma (HNSCC), the mucosa of the aerodigestive tract shows widespread precancerous lesions and additional tumors within 5 years. This phenomenon has led Slaughter et al. to propose the field cancerization theory, which claims that, after repeated carcinogenic exposures, the mucosa accumulates genetic alterations, resulting in the induction of multiple, independent, malignant lesions. An important clinical implication is that fields often remain after surgery of the primary tumor and may lead to new cancers, designated presently by clinicians as “second primary tumor” or “local recurrence,” depending on the exact site and time interval. This hypothesis has also been postulated in other organ systems. Organ systems in which field cancerization has been described since then are: head and neck (oral cavity, oropharynx, and larynx), lung, vulva, esophagus, cervix, breast, skin, colon, and bladder. Recent molecular findings support the carcinogenesis model in which the development of a field with genetically altered cells plays a central role.

**KEY WORDS:** Field cancerization, Second primary tumor, Local recurrence

**INTRODUCTION**

Head and neck squamous cell carcinoma (HNSCC) is one of the common malignancies in humans. The average 5-yr survival rate is one of the lowest among aggressive cancers, and has not been significantly improved during the last two decades. Head and neck squamous cell carcinoma (HNSCC) develops in the mucosal lining of the oral cavity, pharynx, larynx, and cervical esophagus and comprises about 5% of all newly diagnosed cancer cases in developed countries. Worldwide, there is a prevalence of approximately 20 HNSCC cases per 100,000 individuals per year, ranking it number five on the list of the most prevalent cancer types.

The prognosis of HNSCC patients is adversely influenced by the development of second primary tumors. Approximately 2-3 per cent of oral cancer patients develop a second primary cancer each year after removal of the primary tumour and 90 per cent of recurrences manifest within two years of initial treatment. Unfortunately, tumour recurrence or a second primary tumour has a significant adverse effect on survival of oral cancer. The development of locally recurrent cancer and SPTs has frequently been explained by the concept of “field cancerization.”

**ORAL FIELD CANCERIZATION**

In 1953, Slaughter and colleagues used the term field cancerization for the first time and proposed the concept of “field cancerization” also known as field defect or field effect in cancer. The investigators examined pathology slides from 783 patients with head and neck cancer 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.

They hypothesized that the entire epithelial surface of the upper aerodigestive tract (UADT) has an increased risk for the development of premalignant lesions because of multiple genetic abnormalities in the whole tissue region. 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. At the time of this study, there was no molecular basis for the observation. However, many investigators have since attempted to use recent molecular techniques to elucidate the mechanism that underlies the clinical phenomenon of field cancerization.

It is now well established that an accumulation of genetic alterations forms the basis for the progression from a normal cell to a cancer cell, referred to as the process of multistep carcinogenesis. Until now, the number of genetic alterations is known to increase with the level of malignancy as judged by histopathological examination. The process of field cancerization can be defined in molecular terms, and its position in the process of multistep carcinogenesis can be delineated.
Based on histological examinations, field cancerization was described as follows: (a) oral cancer develops in multifocal areas of precancerous change, (b) histologically abnormal tissue surrounds the tumors, (c) oral cancer often consists of multiple independent lesions that sometimes coalesce, and (d) the persistence of abnormal tissue after surgery may explain SFTs and local recurrences. The terms field cancerization and “field effect” were used when (pre)neoplastic processes at multiple sites were described, and it was often assumed that these had developed independently. Organ systems in which field cancerization has been described are: HNSCC in oral cavity(1), oropharynx, and larynx (2); lung (3); esophagus (4); vulva (5); cervix (6); colon (7); breast (8); bladder (9); and skin (10).

SECOND PRIMARY TUMORS (SPT)

For a definition of SPT, most clinicians currently use the criteria of Warren and Gates, which were published in 1932: (a) Each of the tumors must present a definite picture of malignancy, (b) each must be distinct, and (c) 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.

A new classification method of second primary tumors was recently proposed, to account for the information we have gained from molecular studies. 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 second tumor, at least three years had to have elapsed since detection of the tumors. 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 followup of HNSCC patients after curative treatment of the first tumor. 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). It is important to make this discrimination, because a different etiology may have clinical consequences. SFTs will be followed relatively easily by third and fourth field tumors. Recently, however, genetic studies have shown that, in a proportion of cases, the first and second tumors have originated from the same precursor cell.

LOCALLY RECURRENT TUMORS

After surgical removal of an HNSCC, patients have a considerable risk for developing locally recurrent cancer. This type of lesion can be the result of remaining tumor cells, but also the local remnants of a field may develop into cancer. So, in fact a local recurrence can be a “second field tumor” (SFT) as well.

CLONALITY & MOLECULAR METHODS OF DETERMINING CLONALITY

The idea of clonality has formed the basis for the way researchers view cancer and its development. A single cell, altered by inactivation of a tumor suppressor gene(s) and/or activation of an oncogene(s), will gain a growth advantage and expand to form a clonal mass of cells, or tumor. In more practical terms, this is a dynamic process. The common theme in all of the techniques utilized to pinpoint a clonal relationship is identification of early, shared genetic alterations that are unique to the lesions and not found elsewhere in normal tissue. Thus, these molecular patterns form a type of DNA fingerprint. An early cytogenetic technique used to determine clonality is karyotype analysis. However, this is a rather insensitive method of detection, and since the cells may be constantly changing on a sub-microscopic basis, it is difficult to draw conclusions based only on such large-scale alterations.

Another common method used by many investigators is the use of p53 mutations. p53 is the most widely mutated gene across all cancer types and has been shown to be important in the regulation of apoptosis and many other pathways. In head and neck cancer, approximately half of tumors have been found to contain some form of p53 mutation. However, p53 mutations are among the most reliable markers for head and neck cancer and have been used in a variety of studies to determine clonality. Finally, microsatellite alterations have been widely utilized to determine clonality between lesions. Microsatellites are tandem-repeat sequences found usually in non-coding regions that are scattered randomly throughout the genome. Loss of allelic material adjacent to microsatellite markers, known as loss of heterozygosity (LOH), is a marker that can be used to characterize lesions by means of a simple, Polymerase chain reaction (PCR) based technique.

IMPORTANCE OF THE SFT CONCEPT FOR PREVENTION

The realization that many, if not all, HNSCCs are preceded by genetically defined precursor lesions opens new possibilities for early diagnosis and prevention. This would be particularly valuable if a subgroup of lesions could be defined with a very high risk for progression. Once a more reliable risk assessment has been developed, it can be exploited to identify high-risk fields. Patients with such high-risk fields in surgical margins should theoretically be followed by lifelong surveillance at regular intervals. Moreover, this technique could indicate a more
conservative approach to adjuvant radiotherapy as far as the primary site is concerned. 5

IMPLICATIONS FOR THERAPY

It is a well-known clinical experience that after surgical removal of a tumor, there is still a high risk for another tumor in the same anatomical area. For some cases the new tumor is explained by the growth of incompletely resected carcinoma. However, for the cases where the tumor had radically been removed it seems logical to assume that a genetically altered field is the cause of new cancer. The presence of a field with genetically altered cells appears to be a continuous risk factor for cancer. Clinical investigations are hampered by the fact that a field needs to be detected with molecular biological techniques or nonroutine visualization techniques, like fluorescence in situ hybridization. 21,22 Additional research is needed to identify the fields that carry the highest risk for cancer. Besides host factors, like the amount of cigarettes smoked 23, the biological characteristics of the field itself might be of importance for HNSCC development. Patients who have been surgically treated for HNSCC and are at risk for SFT can be enrolled to study the risk profile of a genetically altered field. A clinical trial of this type has an obvious advantage: it is known approximately where the lesion will develop (where the tumor has been), and it is possible to monitor the disease process (for instance by brushing cells). Furthermore, knowledge of the genetic alterations that precede the development to cancer will provide a basis for a rational therapy (e.g., a gene-therapy based approach) of these preneoplastic lesions. 9

An important clinical utility of field cancerization is in complementary evaluation of pathologic biopsy specimen. Currently, biopsies for cancer diagnosis are reviewed by histology, the gold standard, and the absence of abnormal cells often precludes the diagnosis of cancer. However, histologically normal biopsy specimen that possess molecular signatures of cancer fields suggest either the tumor was missed by the biopsy procedure, or that some cells in the tissue are progressing towards malignancy. Such high risk patients will require close surveillance for early detection of disease. 24

CHEMOPREVENTION

Whether they are clonally related or not, it is clear that there are wide fields of mucosa that undergo genetic alterations in patients. It would not be feasible to remove all of the areas with molecular alterations surgically. Thus, using the knowledge gained from molecular studies, researchers have attempted to come up with protective measures that could render the mucosa less sensitive to DNA alterations. Patients at risk could be treated to prevent the development of disease, and patients with pre-malignant lesions could have them reversed or halted. And finally, chemoprevention could be used to prevent the recurrence of cancer after surgery.

There have been several proposed compounds thought to be potential chemotherapeutic agents, but perhaps the most widely studied compound in the upper aerodigestive tract has been 13-cis retinoic acid. This family of chemicals has been shown to play a role in the differentiation, development, and growth of epithelial cells. 25 13-cis retinoic acid has been shown to up-regulate the retinoic acid receptor-β, leading to a good clinical response in head and neck pre-malignant lesions. 26 High doses of 13-cis retinoic acid led to a regression in oral cavity leukoplakias as compared with placebo, as well as the prevention of second primary tumors. 27 However, an additional study noted that, despite clinical regression of pre-malignant lesions, genetic alterations in mucosal fields remain unchanged. 24 This implies that definitive therapy for genetically altered fields of mucosa will ultimately consist of targeted ablation of altered clonal populations, repair of genetic damage in affected cells, or ongoing treatment with chemopreventive agents that will continue for years or decades.

While the focus of clinical trials for chemoprevention agents has been on the use of retinoid-based compounds, the toxicity (conjunctivitis, mucositis, dry skin, hypertriglyceridemia, and malaise 28) of this drug at higher doses may limit its utility. Other compounds, such as cyclooxygenase-2 (COX-2) inhibitors, are being studied as chemopreventive agents because of a known increase in COX-2 expression in patients with head and neck cancer as well as in normal epithelium adjacent to tumors. 1

CONCLUSION

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 field cancerization theory suggests that there is a high probability of occurrence for other synchronous or metachronous tumors in patients with head and neck carcinoma. Therefore, clinical screening and controlled biopsy punches are mandatory for postoperatively detected lesions in these patients; those at high risk (smokers and chronic alcohol consumers) must be present more frequently to their dentist or primary care physician for common examinations. An important clinical implication is that the field often remains after surgery of the primary tumor and may lead to new cancers. Thus the diagnosis and treatment of epithelial cancers should be focused not only on the tumor but also on the field from which it developed.

REFERENCES


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