INTRODUCTION

The term field cancerization was first coined by Slaughter et al in 1953.¹ 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. 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. 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. Moreover, the prognosis of treatment of primary malignancy depends on occurrence of second primary tumors (SPTs), the incidence of which is about 30 to 35%. Hence this article tries to explain the theories of field cancerization, defines the terminologies related to field cancerization like “second primary tumors (SPT)”, “synchronous/metachronous primaries”, and “distant primaries”, etc. The article also briefs the molecular methods for the detection of clonality, the therapeutic implications and chemoprevention for field cancerization in relation to second primary tumors.

ORAL FIELD CANCERIZATION

This concept of field cancerization can be interpreted in various ways to explain the phenomenon of SPTs.

1. In the “classical view”, which is most commonly referred to, large areas of the aerodigestive tissue are affected by long-term exposure to carcinogens. In this preconditioned epithelium, multifocal carcinomas can develop as a result of independent mutations, and thus would not be genetically related. Although this mechanism was accepted for a quite a long time, the controversies began with the advent of new mechanism called the “clonal theory”, which explains that a single cell, on exposure to carcinogens, is transformed and gives rise to one large extended premalignant field by clonal expansion and gradual replacement of normal mucosa. In this field of various subclones, two separate tumors can develop after accumulation of additional genetic alterations. Both tumors have the same clonal origin, and would thus share at least one early genetic event, which occurred before the initial clonal expansion. Also, the molecular studies regarding OFC have been expanding exponentially since a few years. The need for chemoprevention and the management of OFC with its resultant effect of development of second primary tumors has been challenging till today. Hence, the article tries to explain the conflicting aspects of various mechanisms by which SPTs develop, the molecular techniques, chemoprevention and therapeutic implications for oral field cancerization.

Keywords: Oral field cancerization, Second primary tumors, Molecular methods, Synchronous/Metachronous tumors, Metastasizing/Nonmetastasizing tumors.
Second primaries (SPTs) are named as metachronous primaries if separating period is more than 6 months. The incidence of second primary synchronous or metachronous tumor is increasing due to elevated risk from carcinogen exposure alone. However, in the cases of synchronous tumors separated by large distances, it is of interest if these tumors arose as a result of independent events or from the same progenitor clone that subsequently migrated.

Patients with head and neck squamous cell carcinomas and concurrent esophageal squamous cell lesions have been studied for the relationship between the two tumors. One study looking at 16 such patients demonstrated, by the use of microsatellite markers, that the lesions were not clonally related in 14 of the patients (Califano et al, 1999a). However, two of the 16 patients had lesions that demonstrated clonal relatedness, one migrating at a distance of 40 cm. Therefore, it is generally assumed that esophageal lesions in conjunction with head and neck squamous cell carcinoma represent two separate primary tumors rather than metastases.

A different study examined the question of synchronous lung tumors and their relationship to HNSCC (Leong et al, 1998). Samples from 16 patients with HNSCC and a concurrent solitary lung lesion were tested by microsatellite analysis. Ten of sixteen samples (63%) demonstrated concordant patterns of loss at all loci tested, suggesting that the majority of solitary lung lesions were in fact metastases rather than separate primary tumors. Another study looked at second primary tumors of the upper aerodigestive tract after primary HNSCC (Chung et al, 1993) by p53 mutation analysis. Although this study did not find a high rate of clonally related second primary tumors, it relied solely on a single genetic alteration, when tumors were compared.

Therefore, the distance between two malignancies does not necessarily predict clonality. As a general rule, distant, peripheral, solitary, squamous lung lesions in conjunction with HNSCC are thought to be metastases, and concurrent esophageal tumors are thought to be separate primary tumors. While the probability of synchronous aerodigestive tract tumors remains high with environmental exposure, the relationship between them is often predicted by anatomic subset rather than distance.
MOLECULAR METHODS FOR DETERMINATION OF CLONALITY

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 underlying technique utilizes few basic points namely identification of early, shared genetic alterations that are unique to the lesions and not found elsewhere in normal mucosa. Thus, these molecular patterns form a type of a DNA fingerprint.

DETECTION OF SECOND PRIMARIES/METASTATIC LESIONS

Despite the molecular methods, the specialized radiography like CT, MRI and PET plays an important role in detection of SPTs and metastatic lesions. David L Schwartz in 2003 performed extended field FDG-PET in 33 patients of stage II-IV squamous cell carcinoma of oral cavity, esophagus, or larynx. Of these extended field FDG-PET in 33 patients of stage II-IV squamous cell carcinoma of oral cavity, esophagus, or larynx. Of these 33 patients, 7 (21%) had evidence of distant disease, 4 with metastasis and 3 patients with synchronous primary cancers of aerodigestive tract. Hence, it was concluded that FDG-PET is feasible for detection of SPT and distant metastases. Such similar reports were also presented by Mark k wax et al and Gerhard W Goerres et al.

FLUORESCENCE VISUALIZATION OF SECOND PRIMARY TUMORS

Visualization of “Field Cancerization” is not reliable by routine direct visual examination or even microscopic examination. Assisted visualization of oral neoplasia in the intraoperative setting is being developed along several lines. Some have advocated staining the oral mucosa with the vital dye toluidine blue as a means of visualizing the presence of subclinical disease. Abnormal staining of the oral mucosa has been shown to correlate with the presence of histologic dysplasia, the presence of LOH, and increased cancer risk. Others have explored visual assessment of oral cavity luminescence following a chemical reaction (i.e. chemiluminescence) as a means to discriminate between normal and neoplastic mucosa. Still others have used blue excitation light (400-460 nm) to discern the presence of subclinical oral neoplasia. Although the precise mechanisms are not well understood, changes in the metabolic activity of the surface epithelial cells induce spectral changes that impart “tissue fluorescence signatures.” At certain wavelengths, premalignant lesions of the oral cavity show less fluorescence than surrounding normal oral mucosa. Given this enhanced ability to directly visualize premalignant lesions, fluorescent visualization has been in use, in some populations at risk for developing squamous cell carcinoma of the lung, oral cavity, and other sites.

METASTATIC AND NONMETASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMAS (HNSCS)

Bockmuhl U et al in 1997 investigated a total of 29 metastasizing (pN+) and 19 nonmetastasizing (pN0) head and neck squamous cell carcinomas by comparative genomic hybridization. The analysis indicated that the pN0 tumors carried preferentially over-representations of chromosomes 5p, 6p, and 7p and the pN+ tumors were frequently characterized by deletions on chromosomes 7q, 10q, 11p, 11q, 15q, and 20q and over-representations of the chromosomes 19q and 20q. Hence, these molecular studies detecting chromosomal alterations might help in predicting that which tumor would end up in a metastatic lesion, and provides new targets for positional clonal efforts to define the underlying genetic defect. The data also suggests that distinct patterns of genetic lesions are responsible for the metastatic phenotype of head and neck squamous cell carcinomas.

DIFFERENTIATION OF RECURRENT/METASTATIC AND SPTS

The appearance of a new neoplasm often poses a problem of differential diagnosis between recurrence and new primary tumor, in an already treated case of primary malignancy. A study conducted by Gasparotto D et al in 1995 concluded that p53 mutations help us to differentiate between recurrent and second primary tumors. p53 mutations are a very early and polymorphic phenomenon, a recurrence/metastasis must retain the same mutation as the primary tumor, whereas independent tumors are likely to display a different p53 gene status.

THERAPEUTIC IMPLICATIONS FOR FIELD CANCERIZATION

The controversy between lateral spread of clones vs. multiple foci of independent alterations does not currently affect the surgical and medical management of these premalignant and malignant lesions. However, detection and therapy based on molecular techniques depend on an answer to this question. The presence of altered fields of mucosa remaining beyond the limits of resection has been shown both histologically and on a molecular basis. Initial studies performed demonstrated that p53 mutations noted in histologically normal margins could be detected, and in fact, there was a higher incidence of local recurrence in those patients with known mutations in the altered margins (Brennan et al, 1995). The histologically benign mucosa often can progress to further premalignant or malignant disease (Califano et al, 1999b). Microsatellite alteration has been shown to be predictive of malignant progression (Partridge et al.). In the future, the presence of altered clones at mucosal margins may be an indication for more aggressive therapy, including chemopreventive or radiotherapy to treat altered clonal patches that are unable to be detected grossly and are beyond the initial scope of surgical excision.

The issue of whether those with an extensive, visible mucosal field defect are more likely to benefit from chemotherapy, radiotherapy, or chemoprevention is a complex one.
Current management is often site-specific: Recurrent oral premalignant disease is often treated by surgical excision, whereas diffuse high-grade premalignant changes in the laryngeal mucosa are frequently treated with radiotherapy. Determination of the role for these and other treatment modalities for clinically occult, clonally altered patches of epithelium is likely to be a difficult issue, since treatment of mucosa with widespread visible alterations is already challenging. Further studies need to be performed to elucidate the mechanisms behind lateral clonal spread. It is not known exactly what factors control the ability of certain cells to migrate. Cell adhesion genes may be altered, or there may simply be a mass effect due to the growth advantage conferred on these affected clones by other genetic alterations. Identification of these genes would provide additional targets for therapy and the prevention of metastasis/migration.

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 premalignant lesions could have them reversed or halted. BCG vaccine, hepatitis b vaccine, oral contraceptive pills, etc. were once considered as chemopreventive agents against various cancers of human body. 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 (Armstrong and Meyskens, 2000). 13-cis retinoic acid has been shown to up-regulate the retinoic acid receptor-beta leading to a good clinical response in head and neck premalignant lesions (Lotan et al., 1995). High doses of 13-cis retinoic acid led to a regression in response in head and neck premalignant lesions (Lotan et al., 1998). 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 chemopreventive agents has been on the use of retinoid-based compounds, the toxicity [conjunctivitis, mucositis, dry skin, hypertriglyceridemia, and malaise (Lippman et al, 1987)] 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 (Chan et al, 1999).

CONCLUSION

In conclusion, both the theories of oral field cancerization hold good. Of course, theories, the classical and alternative model may not be mutually exclusive, and may be simultaneous and/or complementary events. Though a lot of research has already been done and ongoing in this area of oral field cancerization, further application of molecular studies would help to solve the mysteries behind them.

REFERENCES

Oral Field Cancerization: A Review


