REVIEW ARTICLE

Oral Field Cancerization: A Review

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ABSTRACT

Patients with head and neck squamous cell carcinoma (HNSCC) often develop multiple (pre) malignant lesions. This finding led to the field of the cancerization theory, which hypothesizes that the entire epithelial surface of upper aerodigestive tract has an increased risk for development of (pre) malignant lesions, because of multiple genetic abnormalities in the whole tissue region. Cancer begins with multiple cumulative epigenetic and genetic alterations that sequentially transform a cell or group of cells in a particular organ. These early genetic events may lead to clonal expansion of preneoplastic daughter cells in a particular tumor field. Subsequent genomic changes in some of these cells drive them toward the malignant phenotype. These transformed cells are diagnosed histopathologically as cancers, owing to changes in the cells morphology. 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. Conceivably, a population of daughter cells with early genetic changes (without histopathology) remains in the organ, demonstrating the concept of field cancerization.

KEYWORDS: Head and Neck Squamous Cell Carcinoma, Second Primary Tumor, Molecular Methods, Field Cancerization, Upper Aerodigestive Tract.

INTRODUCTION

One of the most common malignancies in humans is head and neck squamous cell carcinoma (HNSCC). The average 5-year survival rate of HNSCC is one of the lowest among aggressive cancers and has not improved during the last two decades.[1] HNSCC develops in the mucosal lining of the oral cavity, larynx and pharynx. HNSCC comprises about 5% of diagnosed cancer cases in developed countries.[2] Worldwide, there is a prevalence of approximately 20 HNSCC cases per 100,000 individuals per year.[3] HNSCC is ranked at number five on the list of the most prevalent cancer types.[4]

The prognosis of squamous cell carcinoma patients is adversely influenced by development of a new tumor. Squamous cell carcinoma may arise as a recurrence of an incompletely resected index tumor or second primary tumor (SPT) or second field tumor (SFT).[5] Depending on both the location of the first primary tumor and the age of the patient the incidence rate of SPT is 10-35%.[6]

These findings led to the field of cancerization

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theory given by Slaughter and colleagues (1953) which hypothesized that the entire epithelial surface of the upper aero digestive tract (UADT) has an increased risk for the development of (pre)malignant lesions because of multiple genetic abnormalities in the whole tissue region.[7] The investigators examined pathology slides of 783 patients with HNSCC 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 the tumor possessed histologic changes, and 88 out of 783 patients were found to have more than one independent area of malignancy.[8] At the time of 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.[9]

An accumulation of genetic alterations form the basis for progression from a normal cell to a cancer cell, referred to as the process of multistep carcinogenesis.[7,9] Until now, the number of genetic alterations is known to increase with the level of malignancy as judged by histo-pathological examination. The process of field cancerization can be defined in molecular terms.[10] 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 SPTs and local recurrences.[4,10] The terms "field effect" and field cancerization were used when (pre)neoplastic processes at multiple sites were described, and it was often assumed that these had developed independently.[11]

ORAL FIELD CANCERIZATION

The mucosal changes in the entire upper aero digestive tract (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

- Monoclonal theory in which single cell is transformed, and through the mucosal spread, give rise to multiple genetically related tumors.
- 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.[12]

Two types of migration are involved in the concept of this theory: a) Migration of tumor cells by for ex. Saliva (micro metastases) b) Intraepithelial migration of the progeny of the initially transformed cells.Information about all of the different theories can be gathered in two different types of investigations.[13]

- To search for differences in alterations between the histologic normal tumor adjacent mucosa (TAM) from smokers/ alcohol drinkers and normal TAM from non-smokers / non-drinkers. If there are migrating tumor cells, one expects them to be present in the TAM from smoking as well as non-smoking HNSCC. Thus TAM from smoking as well as non-smoking HNSCC patients must exhibits the same alterations. These alterations

must be absent in smoking healthy individuals, as in those cases, there is no source for migrating tumor cells.

- Second way is to examine the clonality of the multiple (pre) malignant lesions. This can be done by analysis of early genetic alterations in the development of HNSCC. The separate lesions will share common genetic alterations if they have developed from a single clone. The clonal relationship between multiple lesions points to the migration of tumor cells or progenitor cells.

SECOND PRIMARY TUMOR

Despite advances in therapy long term survival of head and neck cancer patients has not significantly improved in the last 20 years. An important reason for this lack of progress is the development of secondary primary tumor in the upper aerodigestive tract. Patients at highest risk are those with early-stage disease, when control of the first tumor, and therefore survival, is greatest.[14]

For SPT, most clinicians currently use the criteria given by Warren and Gates,[15] 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.[4,15] 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.[11,15]

Another criteria 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.[4,15]

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).[16]

DISTANT SECOND LESIONS

Because of common pathway between the oral cavity, lungs and esophagus, there is a similar exposure pathway to the mucosa from the environmental carcinogens. Patients with HNSCC and concurrent esophageal squamous cell lesions have been studied for the relationship between these two tumors. One study was conducted by Califano et al to study clonal relationship in sixteen patients by the use of microsatellite markers. Result of the study showed that the lesions were not clonally related in the fourteen of patients. However two of the sixteen patients had lesions that demonstrated clonal relatedness, one migrating at a distance of 40 cm.[17] Therefore it is generally assumed that esophageal lesions in conjugation with HNSCC represent two separate primary tumors rather than metastases.

Another study conducted by Leong et al examined the question of synchronous lung tumors and their relationship to HNSCC. Sixteen patients with HNSCC and a concurrently solitary lung lesion were tested by microsatellite analysis. 63% demonstrated

concordant patterns of loss at all loci tested, suggesting that the majority of the solitary lung lesions were in fact metastases rather than separate primary tumors.[18]

Therefore, the distance between two malignancies does not necessarily predict clonality but 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 the anatomic subset rather than distance.[19]

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.[20]

The underlying technique utilizes a few basic points namely identification of early, shared genetic alterations that are unique to the lesions and are not found elsewhere in the normal mucosa. Thus, these molecular patterns form a type of DNA fingerprint. An early cytogenetic technique used to determine clonality is karyotype analysis. Another common method is the use of p53 mutations. p53 mutated gene has been shown to be important in the regulation of apoptosis and many other pathways.[21]

DETECTION OF SECOND PRIMARIES / METASTATIC LESIONS

Despite the molecular methods, the specialized radiography like CT, MRI and PET plays an important role in the detection of SPTs and metastatic lesions. David L Schwartz (2003) performed extended field FDG-PET in 33 patients of stage II-IV squamous cell carcinoma of oral cavity, esophagus or larynx. Of these thirty three patients, seven had evidence of distant lesions, four with metastasis and three patients with synchronous primary cancers of aerodigestive tract.[22] Hence it was concluded that FDG-PET is feasible for detection of SPT and distant metastases. Similar reports were also found in their study by Marx K Wax et al. and Gerhard W Goerres et al.[23,24]

THERAPEUTIC IMPLICATIONS FOR FIELD CANCERIZATION

The controversy between lateral spread of clones versus 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.

It is a well-known clinical experience that even after surgical removal of a tumor, there is a high risk for another tumor to develop in the same anatomical area. In some cases, the new tumor formation can be explained because of the growth of incompletely resected carcinoma. However, for the cases where the tumor had been removed, a genetically altered field is the cause of new cancer.

The presence of altered fields of mucosa 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 in those patients with known mutations in altered margins.[25]

The histological benign mucosa often can progress to further premalignant or malignant disease. Microsatellite alterations have been shown to be predictive of malignant progression. 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.

Current management is often site-specific. Recurrent oral premalignant disease is often treated by surgical excision whereas diffused high grade premalignant changes in laryngeal mucosa are frequently treated with radiotherapy.

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 is not 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 has been 13 cis-retinoic acid.[26] This family of chemicals has shown to play a role in the differentiation, development, and growth of epithelial cells.[27] 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.[28] High doses of 13 cis-retinoic acid led to a regression in leukoplakia as compared with placebo and also lead to the prevention of second primary tumors.[29] However, an additional study noted that, despite clinical regression of pre-malignant lesions, genetic alterations in mucosal fields remain unchanged.[30] 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.

CONCLUSION

While the focus of clinical trials for chemoprevention agents has been on the use of retinoid-based compounds but the toxicity of this drug (conjunctivitis, mucositis, dry skin, hypertriglyceridemia, and malaise) at higher doses may limit its utility.

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 risk 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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