INTRODUCTION

Head and neck squamous cell carcinoma is the fifth most common cancer worldwide. Oral cancer is a disfiguring, potentially fatal disease that continues to rise in incidence among younger and older people alike. In developing countries like India, controlling the devastating, widespread consequences of oral cancer requires interventions in persons at-risk ideally before the disease becomes invasive but certainly before it becomes locally advanced or metastatic. Once the neoplastic process sets in, it is rather difficult to control and endangers the life of the host. Therefore detection of a malignancy before it arises would be the best possible mode of preventing the dreaded disease in its earliest form or by intervening before it reaches uncontrollable proportions. Advances in the analysis of molecular alterations in cells undergoing malignant transformation have increasingly revealed the mechanisms that lead to the occurrence and progression of malignancies. Malignant cells have different histologic and biochemical behavior as compared to their normal counterparts. Earlier the most common determinant or marker of carcinomatous transformation in a tissue was the histopathologic presence or absence of epithelial dysplasia. However the expanding field of oncology has revealed new and more specific markers that would help to determine the degree of cell alteration and enable a better understanding of the degree of malignant transformation of these cells. Data obtained from clinical examination and routine histopathologic study are not always accurate about the potential or risk (to varying degrees) of the lesion in question becoming malignant. In recent years there have been a number of approaches to the problem of precancerous tissue with the aim to establish a more fundamental biochemical basis of understanding.

Several abnormal cellular products are synthesized by the neoplastic cells and also by the body in the presence of such an abnormal situation. Such cellular products can be detected in the various body fluids and on the surface of the cancer cells either by biochemical methods or by immunochemistry. These products that are detected and measured are known as ‘tumor markers’. These tumor markers can be effectively made use of for early screening and detection of cancer. Diagnosis can be aided by the use of these and clinical staging can be better applied in the light of the revelations by these markers. The prognostic evaluation and effectiveness of treatment can be noted. These tumor markers can facilitate early detection of recurrences.

The specialist in oral medicine comes across a variety of clinical situations where the exact demarcation between a premalignancy and malignancy cannot be ascertained, thus posing a problem in diagnosis, leading to a delay of the treatment of these dangerous lesions. The tumor markers can aid the clinician greatly in such situations, if the clinicopathologic picture is not accurately suggestive or indicate, if the picture would soon change. This overview attempts to forge an understanding of these tumor markers, their interactions and clinical applications as shown relevant by the recent advances in research.

DEFINITION

“A tumor marker is a substance present in or produced by a tumor or by the tumor’s host in response to the tumor’s presence that can be used to differentiate a tumor from normal tissue or to determine the presence of a tumor based on measurement in the blood or secretions.”

Tumor markers can also be defined as “specific, novel or structurally altered cellular macromolecules or temporarily spatially or quantitatively altered normal molecules that are associated with malignant (and in some cases benign) neoplastic cells.”

Another group of investigators have defined tumor markers as “cellular products that are abnormally elaborated by malignancies that can be detected in various body fluids and on the surface of cancer cells.”

Keywords: Tumor marker, Oral cancer.
Tumor markers can be found in cells, tissues or body fluids. They can be measured quantitatively or qualitatively by chemical, immunological or molecular biological methods to determine the presence of neoplasia. Few markers are specific for a single individual tumor (tumor specific markers). Most are found with different tumors of the same tissue type (tumor associated markers). They are present in higher quantities in cancer tissues or in blood from cancer patients than in benign tumors or in the blood of normal subjects. Few tumor markers are specific to the organ where the tumor resides.

Tumor markers can also be broadly defined as “biological or molecular attributes of tumor cells that distinguish them from normal cells.”

Tumor markers may be unique genes or their products that are found only in tumor cells, or they may be genes or gene products that are found in normal cells but are aberrantly expressed in unique locations in the tumor cells. They are present in abnormal amounts or function abnormally in response to cellular stress or to environmental signals. Tumor markers may be located intracellularly or on the cell surface, or they may be secreted into the extracellular space, including the circulation. The distinguishing biological characteristics of tumor cells, such as their capacity for invasion, metastasis, unlimited proliferation, evasion of apoptosis and angiogenesis, are all mediated by complex molecular pathways, any of the components of which are potential tumor markers.

**CLASSIFICATION**

Classification of tumor markers can be based upon their structure or biological functions, or the class or type of marker that is in consideration.

A comprehensive organization of the tumor markers on the basis of their type of tissue interaction was provided by Scully and Burkhardt (1993) (Table 1).

**USES OF TUMOR MARKERS**

The applications of tumor markers are as varied as the number of tumor markers described over the years. The newer emerging concepts have delineated newer roles for the usage of these tumor markers.

**Screening in General Population**

The concept of screening an apparently healthy population is to find out the presence of occult disease at an early stage, wherein effective therapeutic intervention is likely to be beneficial. However, inadequate test sensitivity and specificity in discrimination of a low prevalence situation, limits the role of these markers to smaller confines. For instance, human chorionic gonadotropin is produced in measurable amounts in choriocarcinoma by as few as 1,00,000 malignant cells/l mg of tissue.

<table>
<thead>
<tr>
<th>1st Classification</th>
<th>2nd Classification</th>
<th>Markers of tumor invasion and metastatic potential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell surface markers</strong></td>
<td><strong>Tumor growth markers</strong></td>
<td>1. MMPs (matrix-metallo proteases)</td>
</tr>
<tr>
<td>1. Carbohydrates—particularly blood group antigens</td>
<td>1. Epithelial growth factor (EGF)</td>
<td>2. Cathepsins</td>
</tr>
<tr>
<td>2. Squamous carcinoma antigens Ca-1, TA-4, SQM1 and 3H-1</td>
<td>2. Cyclins</td>
<td>3. Cadherins and catenins</td>
</tr>
<tr>
<td>3. Histocompatibility antigens—HLA class I and II HLA class II</td>
<td>3. Nuclear cell proliferation antigens</td>
<td>4. Desmoplakin</td>
</tr>
<tr>
<td>4. Growth factors and receptors</td>
<td>4. AgNORs (Agryophilic nucleolar organizer region)</td>
<td><strong>Cell surface markers</strong></td>
</tr>
<tr>
<td><strong>Intracellular markers</strong></td>
<td>5. Skp2 (S-phase kinase-interacting protein 2)</td>
<td>1. Carbohydrates</td>
</tr>
<tr>
<td>1. Cytoskeletal components—Cytokeratins</td>
<td>6. HSP 27 and 70 (Heat shock proteins)</td>
<td>2. Histocompatibility antigen (HLA)</td>
</tr>
<tr>
<td>3. Carcinoma antigen 17, 13</td>
<td><strong>Markers of tumor suppression and anti-tumor response</strong></td>
<td><strong>Intracellular markers</strong></td>
</tr>
<tr>
<td>4. Silver binding nucleolar organizing regions</td>
<td>1. Retinoblastoma protein (pRb)</td>
<td>Cytokeratins</td>
</tr>
<tr>
<td>5. Oncogenes</td>
<td>2. Cyclin dependant kinase inhibitors</td>
<td><strong>Markers of anomalous keratinization</strong></td>
</tr>
<tr>
<td>6. Tumor suppressor genes</td>
<td>3. p53</td>
<td>1. Filagrin</td>
</tr>
<tr>
<td>7. Arachidonic acid products- PGE2, leukotrine B4 and 5,12, and 15 hydroxyeicosatetraenoic acids</td>
<td>4. bax</td>
<td>2. Invoulerin</td>
</tr>
<tr>
<td>8. Enzymes—Gamma-glutamyltranspeptidase, LDH</td>
<td>5. Fas/FasL</td>
<td>3. Desmosomal proteins</td>
</tr>
<tr>
<td>9. Basement membrane markers—fibronectin, laminin</td>
<td><strong>Angiogenesis markers</strong></td>
<td>4. Inter cellular substance antigen</td>
</tr>
<tr>
<td>10. Matrix markers—Tenascin</td>
<td>1. VEGF/VEGF-R (Vascular endothelial growth factor/receptor)</td>
<td>5. Nuclear analysis</td>
</tr>
<tr>
<td><strong>Arachidonic acid products</strong></td>
<td>2. PD- EGF (Platelet-derived endothelial cell growth factor)</td>
<td><strong>Markers of tumor invasion and metastatic potential</strong></td>
</tr>
<tr>
<td>1. Prostaglandin E2</td>
<td>3. FGFs (Fibroblast growth factor)</td>
<td>1. MMPs (matrix-metallo proteases)</td>
</tr>
<tr>
<td>2. Hydroxyeicosatetraenoic acid</td>
<td></td>
<td>2. Cathepsins</td>
</tr>
<tr>
<td>3. Leucotriene B4</td>
<td></td>
<td>3. Cadherins and catenins</td>
</tr>
</tbody>
</table>

**Table 1: Classification of tumor markers**

**Notes**

1. MMPs: Matrix metalloproteinases
2. Cathepsins: A group of lysosomal proteinases
3. Cadherins and catenins: Cell adhesion molecules
4. Desmoplakin: A protein involved in cell-cell and cell-matrix adhesion
5. Carbohydrates: Complex molecules formed by sugars
6. Squamous carcinoma antigens: Markers specific to squamous cell carcinoma
7. Histocompatibility antigens: Markers that determine tissue compatibility
8. Cytoskeletal components: Components that maintain cell shape and structure
9. Filagrin, Involucrin, Desmosomal proteins: Proteins involved in keratinization and cell adhesion
10. Silver binding nucleolar organizing regions: Ribosomal RNA synthesis sites
11. Oncogenes: Genes that promote cell growth and division
12. Tumor suppressor genes: Genes that inhibit cell growth and division
13. Arachidonic acid products: Derivatives of fatty acids involved in inflammation
14. Cytokeratins: Protein markers specific to epithelial cells
15. Enzymes: Catalytic proteins involved in metabolic processes
16. Gamma-glutamyltranspeptidase: An enzyme involved in amino acid metabolism
17. LDH: Lactate dehydrogenase, an enzyme involved in energy metabolism
18. Fibronectin, laminin: Matrix proteins involved in cell adhesion
19. Tenascin: A matrix protein that regulates cell attachment and migration

**References**


**Additional Information**

- Tumor markers are used in the early detection of cancer, monitoring disease progression, and evaluating treatment efficacy.
- The specificity and sensitivity of tumor markers can vary widely.
- The integration of multiple markers often provides more accurate and comprehensive diagnostic information.
- Tumor markers can be used in conjunction with clinical and imaging data for a more comprehensive diagnostic approach.

**Conclusion**

Tumor markers hold significant promise in the field of oncology, offering valuable insights into the biology of cancer and potential therapeutic targets. Their continued development and optimization will likely further enhance their diagnostic and therapeutic applications.
Diagnosis

The identification of primary disease is an important function of any tumor marker. For definitive results it is essential that the marker be 100% specific and 100% sensitive. A tumor marker that aids in diagnosis will be helpful in identifying the most appropriate treatment plan. For example, the presence of Bence Jones proteins in the urine remains one of the strongest diagnostic indicators of multiple myeloma.

In the vast majority of diagnostic situations, circulating tumor markers are used. If appropriate, in conjunction with diagnostic imaging and tissue biopsy, perhaps coupled with immunohistochemical staining of tumor-specific antigens. Tumor markers are commonly employed to decide the histogenetic origin of oral cavity neoplasms and therefore help ruling out at least some of the entities on the differential diagnosis list.

Differential Diagnosis

Most of the tumor markers are present in normal, benign and cancerous tissue and are usually ambiguous. However, they can still be used in differential diagnosis of suspicious lesions. The tumor markers are used to decide the histogenetic origin of oral cavity neoplasms and therefore help ruling out at least some of the entities on the differential diagnosis list.

Clinical Staging of Cancer

Clinical staging of the cancer is aided by quantitation of the marker, that is, the serum level of the marker reflects the tumor burden present. Markers can also detect microscopic metastasis with radioimmune detection.

Nuclear Scanning of Injected Radioactive Antibodies

Radioactive labeled antibody specific tumor marker is injected into patients suspected of having undetected tumor metastasis. Accumulation of specific antibody in tumor cells may be visualized by isotope scanning with appropriate subtraction techniques to overcome background activity or by emission tomographic scanning. The labeled antibody can be injected intravenously or into the lymphatic circulation for more efficient binding to metastatic sites.

Prognostic Indicators for Disease Progression

Tumor markers can provide prognostic information, which may include indications for choice of therapy and likelihood of response. The estimate of survival time based on evidence of metastatic disease can also be predicted.

Evaluating the Success of Treatment/Monitoring the Response to Therapy

After successful initial treatment, such as surgery, the marker value should decrease. The rate of the decrease can be predicted by using the half-life of the marker. If the observed half-life of the marker after treatment is longer than the expected half-life, then the treatment has not been successful in completely eliminating the tumorous tissue. The magnitude of marker reduction may, however, reflect the degree of success of the treatment or the extent of disease involvement. Most tumor marker values correlate with the effectiveness of treatment and responses to therapy. Sometimes, however, the values may show an initial delay before demonstrating the expected pattern of change.

Detecting the Recurrence of Cancer

It is of utmost importance to precede and to predict recurrence so that relapse can be picked up as soon as possible and appropriate measures may be undertaken. A clinically sensitive tumor marker will reflect the amount of viable tumor burden, assuring homogeneity of production in tumor cell population. This quantitative relationship is of great importance not only to monitor response to therapy, but also to alert the clinician to the onset of drug resistance.

Chan and Sell have summarized the potential uses of tumor markers as follows:

- Screening in general population
- Differential diagnosis in symptomatic patients
- Clinical staging of cancer
- Estimating tumor volume
- Prognostic indicator for disease progression
- Evaluating the success of treatment
- Detecting recurrences
- Monitoring responses to therapy
- Radioimmunolocalization of tumor masses
- Determining direction for immunotherapy.

The Concept of the Ideal Tumor Marker

Tumor markers that are to be put to clinical use should have certain characteristics that are applicable in all situations. An ideal tumor marker should fulfill the following criteria:

1. Be easy and inexpensive to measure in readily available body fluids.
2. Be specific to the tumor being studied and commonly associated with it.
3. Have a stoichiometric relationship between plasma level of the marker and the associated tumor mass.
4. Have an abnormal plasma level, urine level or both in the presence of micrometastases, that is, at a stage when no clinical or presently available diagnostic methods reveal their presence.
5. Have plasma levels, urine levels or both, that are stable and not subject to wild fluctuations. If present in the plasma of healthy individuals, exist in a much lower concentration than that found in association with all stages of cancer.

In addition to the above, Kaplan and Pesce have stated that the ideal tumor marker should relate to the clinical setting and comply with the following:

1. They should prognosticate a higher or lower risk for eventual development of recurrence.
2. They should change as the current status of the tumor changes over time.
3. They should precede and predict recurrences before they are clinically detectable.
Limitations of Tumor Marker Use

Each year clinicians are faced with the discovery of a multitude of new molecular markers, often with claims that they will provide new information that is important for determining prognosis or improving cancer treatment. The clinician is then faced with the arduous task of trying to keep with the technology and sorting through the literature to determine which of these tumor markers are relevant to the care of their individual patients.13

The pertinent question that needs to be answered is whether the tumor marker in question will alter the clinical decision-making to result in a favorable outcome for the patient and unfortunately most often it does not! The absence of large, prospective, multicentre trials to assess the utility of any of the tumor markers only adds to the confusion. Despite the specificity of some tumor markers, a negative marker value does not rule out recurrent disease and other diagnostic modalities such as imaging still have to be performed as part of the surveillance program.13

Despite the advent of monoclonal antibody and immunoassay technologies, which have dramatically increased our ability with a high degree of reproducibility to identify minute quantities of particular substances in serum, there are currently no tests for tumor markers of adequate sensitivity and specificity to permit routine screening or early diagnosis of a particular type of cancer. Ultramicroscopy may help the diagnosis of potentially malignant lesions but its many limitations have precluded a more routine use in the clinical setup.16

The lack of adequately sensitive and specific test can be attributed to a multifactorial situation. Most tumor markers are substances produced by some types of non-neoplastic cells; although perhaps in much lower quantities than they are produced by tumor cells. Varying levels of these markers may be present at all times in different tumor free individuals and varying levels of the particular marker may be present in different individuals with a particular tumor type. Most tumor markers show some overlap between the levels seen in controls and in cancer-affected individuals. Thus it becomes necessary to choose a threshold at which level particular marker is considered abnormal and suggestive of the presence of that tumor type. Setting the threshold lower increases sensitivity by including a higher number of patients with a particular tumor, but decreases the specificity by also including more tumor free individuals, while raising the threshold will have the reverse effect.

Considering the relative prevalence of a particular tumor type, to the population at large, reveals another factor that prevents routine screening using tumor marker. Even for common malignancies the annual incidence is in the order of 100,000 new cases per year. Because most solid tumors presumed to arise by slow growth over a number of years prior to becoming clinically detectable, 500,000 cases might be detected by a suitably sensitive test for a particular marker. However, the population at risk for adult solid tumors is in the order of 100 million. If a tumor marker assay was 95% sensitive or 95% specific and were to be applied to population described containing 500,000 cases in a population of 100 million people, it would yield 475,000 true positive and 5 million false positive results. Thus for every cancer case detected there would be 10 cancer free individuals who would needlessly undergo further work up and psychological stress resulting from a false positive test. These numbers in reality would become even worse because tumor marker in current use have sensitivity and specificity below 95% particularly for small lesions.

Knowledge by the patient of a rising tumor marker may cause significant anxiety, particularly, if this information does not alter the treatment plan as patients equate rising tumor marker levels with worsening disease.13 Thus the financial and psychological cost to the society of routine screening for early cancers using currently available tumor marker would be prohibitive.

CONCLUSION

The preceding discussion describes our current understanding of tumor markers, which though progressive also points out the lacunae therein. The patchy perceptions of tumor marker application in clinical situations therefore point to a potential direction for research studies and furthering knowledge in that domain. This overview hopefully offered the reader an improved insight into the world of tumor markers.

REFERENCES

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150