Role of Tumor Markers in Oral Cancer: An Overview

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Authors’ contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

The oral mucosa represents the first part of the digestive tract and is exposed to various exogenous toxins. Exposure for longer duration can lead to changes that lead to potentially malignant diseases or cancers / Tumors. Eventually these can be diagnosed by routine histopathology, but few of them are difficult to diagnose by this method alone. There arises the role of tumor markers in distinguishing different pathologies is well established. A marker can be described as some inconspicuous object used to distinguish or mark certain things. Mostly tumor markers are proteins and these markers may be detected within exfoliated or distributed cells, or as circulating agents within the peripheral blood or plasma. In the recent years, there is a renewed interest about tumor markers, providing window of opportunity for management of cancer patients by enhancing the efficiency in detection and treatment plan. Recent technological advancement has enabled the examination of many potential markers. This paper focuses on the tumor markers in the head and neck neoplasms.

Keywords: Cancer; tumor markers (T.M); potentially malignant lesion.

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1. INTRODUCTION

Oral cancer, mainly represented by oral squamous cell carcinoma (OSCC), is the eighth most common cancer worldwide accounting for more than 300,000 new cases and 145,000 deaths in 2012. Usually detection of oral cancer depends on the clinical examination of the oral cavity followed by biopsy for histopathological conformation. OSCC is most often identified in the advanced stages of the disease, which may be a reason for reduced survival rate of cancer patients. Even though we are advancing in treatment modalities, less than 50% of OSCC patients have reduced survival rate. Tumor markers play an important role in screening high risk cancer patient and they can predict the prognosis of the disease.

Tumor markers are substances produced by tumor cells or by other cells within the body in response to cancer or certain benign conditions. It includes a variety of substances like cell surface antigens, cytoplasmic proteins, enzymes, hormones, oncofetal antigens, receptors, oncogenes and their products [1-3]. There are different tumor markers, some of which are seen in specific tumors known as Tumor specific markers, while many markers can be found in various other tumors known as Tumor associated markers [1,4].

Although an abnormal level of these markers may suggest tumorigenic pathology, but their presence does not confirm it. Other uses of tumor markers, is to assess a cancer response to treatment and to check for its recurrence. In some types of cancers, tumor marker levels may reflect the presence of the disease but are not predictive of the stage of the disease.

Tumor markers present in circulating body fluids and in the tissue. In the circulating body fluids we can see VEGF/VEGF-R (Vascular endothelial growth factor/receptor) PD-ECGF (Platelet-derived endothelial cell growth factor) FGFs (Fibroblast growth factor), BCL2, Cathepsin –D, CD44, CD80, CD105, Endoglin, Cytokeratins, CEA, CA-19-9, CA-125, SCC-Ag, calretinin, C-erb2, Cyclin, MIB and p53 [4,5].

In tissue we can see Epithelial markers (Cell surface markers – Histocompatibility, Intracellular markers – Cytokeratins, Basement membrane markers – Type 4 collagen, Matrix markers – Tenascin, Membrane antigen – Blood group antigens), Connective tissue markers (Intermediate filament proteins – Desmin, Other filament proteins – Laminin, Cellular enzymes – Amylase, lysozyme, Cytoplasmic non-filamentous non-enzymatic proteins – Myoglobin, S100 protein, Membrane antigen – Leukocyte specific antigen) [6].

The concept of Ideal Tumor Markers (Theoretically) [7,8]

1) They should be highly sensitive and should have low false negative.
2) They should be highly specific and should have low false positive.
3) They should have high positive and negative predictive value.
4) It should be accurate in differentiating between healthy individuals and tumor patients.
5) They should be able to differentiate between neoplastic and non-neoplastic disease and show positive correlation with tumor volume and extent.
6) They should predict early recurrence and have prognostic value.
7) Their levels should be preceding the neoplastic process, so that it should be useful for screening early cancer.
8) They should be either a universal markers for all types of malignancies or specific to one type of malignancy.
9) Be easily assayable and able to indicate all changes in cancer patients receiving treatment.

But unfortunately none of the tumor markers reported till date have above ideal characteristics.

2. CLASSIFICATION [7]

According to Schliephake H

A. Tumor growth markers - Epithelial growth (EGF), Cyclin, Nuclear cell proliferation, antigens AgNORs (Argyrophilic nucleolar organizer region) Skp 2 (S-phase kinase interacting, protein 2) HSP 27 and 70 (Heat shock protein) Telomerase

B. Markers of tumor suppression and anti-tumor response - Retinoblastoma protein (pRb), Cyclin dependent kinase, inhibitors p53, bax, Fas/FasL

C. Angiogenesis markers - VEGF/VEGF-R (Vascular endothelial growth factor/receptor) PD-ECGF (Platelet-derived
endothelial cell growth factor) FGFs (Fibroblast growth factor)

**D. Markers of tumor invasion and metastatic potential** - MMPs (matrix-metallo proteases) Cathepsins Cadherins and catenins Desmoplakin

**E. Cell surface markers** Carbohydrates - Histocompatibility antigen, CD57 antigen

**F. Intracellular markers** – Cytokeratins

**G. Markers of anomalous keratinisation** - Filaggrins, Involution, Desmosomal proteins, Intercellular substances, antigen Nuclear analysis.

**H. Arachidonic acid products** – Prostaglandin E2, Hydroxyeicosatetraenoic, acid Leucotriene B4

**I. Enzymes** - Glutathione S-transferase

### 3. USES OF TUMOR MARKERS [2,5,9, 10,11]

Clinical staging of cancer is aided by quantization of the marker; i.e. serum level of marker reflects the burden of the tumor.

- Screening in general population
- Diagnosis
- Differential diagnosis
- Clinical staging of cancer
- Nuclear scanning of injected radioactive antibodies
- Prognostic indicators for disease progression
- Evaluating the success of treatment /monitoring the response to therapy
- Detecting the recurrence of cancer

**Different Tumor Markers role in Oral Cancer:**

Most commonly encountered potentially malignant lesions of the oral cavity are leukoplakia, erythroplakia and erosive lichen planus. Clinical & histological features alone cannot accurately predict whether potentially malignant disorders will remain stable, regress or progress to malignancy. Some of them with or without epithelial dysplasia may transform to invasive oral SCC. Hence identification of T.M which can predict disease progression is necessary to improve the management of these lesions [4,6].

In one study it was that a significant association was found between the decrease of serum EGFR and the absence of distant metastasis in HNC. The most interesting result was that combining sEGFR and EGF, 100% in HNC were reached without losing specificity (97.8% in both cases). These data demonstrate a potentially interesting value of the serum levels of sEGFR and EGF, especially when combined, as markers for HNC [10].

Srinivasan M and Jewel SD observed the elevated expression of TGF & EGFR in premalignant lesions with dysplasia, as intermediate marker of malignancy. Quantitative measurement of these proteins may provide intermediate endpoints in prospective chemopreventive trials [12]. Kang et al. [13] showed an enhanced Bmi (B lymphoma Mo-MLV insertion region 1 homolog) (an oncogene) expression in pre malignant lesion and cancerous condition, they may act through p16INK4A-independent pathways to regulate cellular proliferation during oral carcinogenesis. Survivin, an apoptotic inhibitor might act as a prognostic marker, which is unregulated when the premalignant lesions are transforming to oral cancer. Survivin was present in 10/30 cases (33%) of oral precancerous lesions, and in 15/16 cases (94%) of oral precancerous lesions evolved into full-blown squamous cell carcinoma. [13] P53 is a tumor suppressor gene which plays an important role in normal regulation of cellular growth and proliferation. P53 alterations were noted about 10-50 % in potentially malignant diseases. Mutations in this gene are mostly reported in oral cancer with reported prevalence of 30 - 60%. [14] In recent literature it is revealed that mutant p53 is not just one protein, but a multitude of proteins that can contribute to a wide range of oncogenic processes. Designing drug strategies to target mutant p53 tumors is therefore highly challenging [15].

**BCL-2** (B-cell lymphoma 2), is the regulator protein that regulates cell death (apoptosis). The aberrant bcl-2 expression and loss of p53 function was observed, which may play an important role in the tumorigenesis of oral cancers by allowing escape from apoptosis and enabling additional genetic alterations to accrue. [13] Bcl-2 has been suggested, as a significant prognostic indicator in early Squamous Cell Carcinoma of head and neck. The predictive role in immune-histochemical detection of the S-phase cell fraction were investigated within a prospective randomized phase III clinical trial on
squamous cell carcinomas (SCC) of the oral cavity, including surgery or primary chemotherapy [16].

**Beta 2-Microglobulin:** also known as B2M is a component of MHC class I molecules, which are present on all nucleated cells. A definite increase in the level of beta 2-microglobulin was observed in patients with leukoplakia, oral submucous fibrosis and oral cancer [17,18].

**Cathepsin-D (CD):** A protease, which is an invasion promoter and plays a central role in oral cancer, is postulated to promote tumor invasion and metastasis. It is a potential independent predictor of cervical lymph node metastasis in Head and Neck SCC [19]. In one study they have concluded that CD expression can be used for the assessment of patient survival in cases of OSCC [20].

**CD44, CD80, CD105 (ENDOGLIN):** In oral SCC’s, expression of CD80 may serve as a marker for increased tumourogenicity, during early development and expression of CD44 correlated with decreased survival rate [1,8,17].

**Cytokeraotins:** Cytokeratins (CK) and vimentin are epithelia and mesenchymal predominant intermediate filament proteins respectively. Monospecific keratin antibodies are useful for evaluation of epithelial differentiation, changes in oral dysplasias and oral SCC. Simple epithelial keratins (K8, K18, K19) may be relevant to tumor prognosis. CK19 and CK8 are markers of premalignant lesions, which are changing to head and neck cancer [1,5,8]. Serum-soluble fragments of cytokeratin 19 can be measured in terms of CYFRA (cytokeratin-19 fragment) levels, this marker has shown 95% specificity and 60% sensitivity for head and neck squamous cell carcinoma at a cut-off value of 2.2 ng/mL, significantly lower CYFRA levels were detected in both smaller and earlier-staged tumors [21].

**CEA, CA19-9, CA125, SCC-Ag:** Examination of tumor markers in the saliva of OSCC patients showed significant increase in Cyfra 21-1 a tissue polypeptide antigen, and CA125. Salivary concentrations of CA19-9, SCC-Ag, and carcinoembryonic antigen were also increased with no statistical significance [22-24].

**p53:** (also known as protein 53 or tumor protein 53), is a tumor suppressor protein that in humans is encoded by the TP53 gene. p53 expression may be a valuable marker for identifying individuals at high risk of developing a
recurrence of primary disease and second primary tumors of SCCHN [28,31,32] (Table 1).

Even Serum \(\beta_2\)-microglobulin, Total Sialic Acid (TSA), Lipid-Bound Sialic Acid (LSAB) and elevated salivary defensin-1 were found to be indicative for malignant changes [33,34].

4. CLINICAL APPLICATIONS OF TUMOR MARKERS

Ideally, a tumor marker should be produced by the tumor cells and be detectable in body fluids. It should not be present in healthy people or in benign conditions. Therefore, it could be used for screening for the presence of cancer in asymptomatic individuals in a general population. However certain tumor markers may be detected in normal individuals also, for example the values in smokers for CEA is higher than normal individuals but, the pattern of change is indicative of pathology, yet the smokers CEA is still lower than certain level, comparative to a malignancy (Table 2) [1,8,16].

Clinical utility depends on the specificity, sensitivity, positive predictive accuracy and negative predictive accuracy of the tumor marker [5,7,28]. Role of tumor markers in oral squamous cell carcinoma were mentioned in Table 3. The salivary biomarkers which are significantly altered in OSCC patients are inhibitors of apoptosis (IAP), squamous cell carcinoma associated antigen (SCC-Ag), carcino-embryonic antigen (CEA), carcino-antigen (CA19-9), CA125, serum tumor marker (CA125), intermediate filament protein (Cyfra 21-1), tissue polypeptide specific antigen (TPS), reactive nitrogen species (RNS) and 8-OHdG DNA damage marker, lactate dehydrogenase (LDH) and immunoglobulin (IgG), s-IgA, insulin growth factor (IGF), metalloproteinases MMP-2 and MMP-11 [35-44].

Altered expression of miRNA is a common finding in OSCC tumorigenesis. Molecular regulators like miRNAs, 18–25 nucleotides long, noncoding RNA molecules, have recently gained significant attention as potential regulators and biomarkers for human carcinogenesis. Deregulated expression of miRNAs in OSCC when compared to their normal counterparts, indicating their potential role in oral cancer development [14,47].

In the literature it was observed that OSCC showed significantly downregulated expression of miR-26a and miR-26b in OSCC tissues, suggesting that miR-26a and miR-26b may act as tumour suppressors [48].

<table>
<thead>
<tr>
<th>Sl. no</th>
<th>Cell type</th>
<th>Tumor</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Epithelial</td>
<td>Adenomas, carcinoma such as SCC, BCS, adenocarcinoma</td>
<td>Cytokeratins, CEA</td>
</tr>
<tr>
<td>2</td>
<td>Melanocytes</td>
<td>Malignant melanoma</td>
<td>S-100 protein, HMB-45, MART-1/Melan-A, Mitf</td>
</tr>
<tr>
<td>3</td>
<td>Myoepithelial cells</td>
<td>Benign mixed tumor, carcinoma with myoepithelial differentiation</td>
<td>Cytokeratin, CEA, S-100 protein, Actin, Desmin, GFap, Calponin.</td>
</tr>
<tr>
<td>4</td>
<td>Langerhans cell</td>
<td>Langerhans cell</td>
<td>S-100 protein</td>
</tr>
<tr>
<td>5</td>
<td>Neuroendocrine</td>
<td>Neuroendocrine carcinoma (arcinoid, malignant carcinoid, small cell carcinoma, adrenal cortical tumors)</td>
<td>Chromogranin, NSE, S-100 protein, Synaptophysin, Inhibin</td>
</tr>
<tr>
<td>6</td>
<td>Merkel cell</td>
<td>Merkel cell carcinoma</td>
<td>cytotkeratin</td>
</tr>
<tr>
<td>7</td>
<td>Neural (schwann cell)</td>
<td>Benign and malignant peripheral nerve sheath tumors, granular cell tumors</td>
<td>S-100 protein, GFAP.</td>
</tr>
<tr>
<td>8</td>
<td>Skeletal muscle</td>
<td>Rhabdomyoma, Rhabdomyosarcoma.</td>
<td>Desmin, Myoglobin</td>
</tr>
<tr>
<td>9</td>
<td>Smooth muscle</td>
<td>Leiomyoma, leiomyosarcoma</td>
<td>Actin, Desmin</td>
</tr>
<tr>
<td>10</td>
<td>Adipose tissue</td>
<td>Lipomas, liposarcoma</td>
<td>S-100 protein</td>
</tr>
<tr>
<td>11</td>
<td>Chondrocytes</td>
<td>Chondromas, chondrosarcomas</td>
<td>S-100 protein</td>
</tr>
<tr>
<td>12</td>
<td>Endothelial cells</td>
<td>Angiosarcoma, Kaposi’s sarcoma, Hemangioma</td>
<td>CD-31, CD-34, FVIII</td>
</tr>
</tbody>
</table>
### Table 2. Methods of detection of tumor marker \[8,9,10,11,12\]

<table>
<thead>
<tr>
<th>Method Type</th>
<th>Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology</td>
<td>Immunohistochemistry, Radio immunoassay, Enzyme linked immunosorbent assay</td>
</tr>
<tr>
<td>Immunological</td>
<td></td>
</tr>
<tr>
<td>Enzyme assays</td>
<td>Flow cytometry, Fluorescent in situ hybridization, Special karyotyping, Comparative genomic hybridization</td>
</tr>
<tr>
<td>Cytogenetic analysis</td>
<td></td>
</tr>
<tr>
<td>Genetic analysis</td>
<td>Sequencing (automated), Reverse transcription, Gel electrophoresis</td>
</tr>
<tr>
<td>Proteomics</td>
<td>Surface enhanced laser, Desorption/ionization</td>
</tr>
</tbody>
</table>

### Table 3. Tumor markers in relation to squamous cell carcinoma \[6,8,45,46\]

<table>
<thead>
<tr>
<th>Marker</th>
<th>Expression</th>
<th>Presence of cancer</th>
<th>Prognostic/therapeutic value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD44(v3, v6 &amp; v10 isoforms)</td>
<td>Strong expression</td>
<td>Metastatic lymphnode</td>
<td>Expression of CD44 (switch v3 &amp; v6) in advanced T stage, regional (v3) and distant (v10) metastasis, peri-neural invasion (v6), and radiation failure (v10)</td>
</tr>
<tr>
<td>CD46, CD55, and CD59.</td>
<td>highly expressed</td>
<td>HNSCC cells including T1/T2N0M0 stages.</td>
<td>Expression - much lower or absent in non-neoplastic squamous epithelia or in the submucosa of both normal and tumour tissue.</td>
</tr>
<tr>
<td>Cytokeratin markers</td>
<td>CK 13 and CK 20 (less frequently)</td>
<td>Act as markers for poorly differentiated squamous cell</td>
<td>prognostic markers help in tumour progression and metastasis formation</td>
</tr>
<tr>
<td>Endothelins</td>
<td>Salivary endothelin-1 (ET-1) marker</td>
<td>In OSCC developed from OLP patients regardless of the degree of OLP disease activity.</td>
<td>For detecting recurrence of OSCC in patients in remission.</td>
</tr>
<tr>
<td>P53</td>
<td>P53 gene mutations</td>
<td>50% of all types of cancers.</td>
<td>Including in OSCC</td>
</tr>
<tr>
<td>TNF-a and -b genes</td>
<td>In one study these genes were investigated with risk of oral cancer</td>
<td>High-expression A2 TNF-a allele and B1 TNF-b allele</td>
<td>significantly increased in cancer patients compared to control</td>
</tr>
<tr>
<td></td>
<td>The normal upper limits - SCC Ag, CEA and Cyfra 21-1 were set at 1.5, 2.5 and 2.0 ng/ml, respectively.</td>
<td>Elevated concentrations of Cyfra 21-1 correlated with age (somewhat), whereas elevated CEA levels with the site of tumor involvement. Overall</td>
<td>Cyfra 21-1 marker is most useful tool in head and neck squamous cell carcinoma.</td>
</tr>
<tr>
<td>In one study serum concentrations of three separate tumor markers, SCC Ag, CEA and Cyfra 21-1 were clinically correlated in 86 patients with SCCHN</td>
<td>Positivity rates were 20.6% for SCC Ag, 14.0% for CEA and 41.7% for Cyfra 21-1.</td>
<td>Elevated concentrations of Cyfra 21-1 correlated with age (somewhat), whereas elevated CEA levels with the site of tumor involvement. Overall</td>
<td>Cyfra 21-1 marker is most useful tool in head and neck squamous cell carcinoma.</td>
</tr>
</tbody>
</table>
5. CONCLUSION

Tumor markers play an important role in screening high risk population for the presence of neoplasm, these markers help in making diagnosis they also determine the prognosis of the lesion in the patient, during the treatment course or at remission period. Every year clinicians are discovering new tumor markers. Despite the specificity of some tumor markers, a negative marker value does not rule out recurrent disease and other diagnostic modalities have to be performed. To identify minor quantity of substances in serum, currently there are no test for tumor marker of adequate sensitivity and specificity for early diagnosis.

Even though we are advancing in the field of medicine but still certain amount of confusion exists about the value of tumour markers in a patient with cancer. Intuitively, a panel of tumour markers should help to establish the origin of the tumour. Unfortunately, most tumour markers are too nonspecific for this purpose.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


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