

REVIEW

## Tumour Markers in Oral Neoplasia

Sanjay Reddy B<sup>1</sup>, Madhavi Reddy B<sup>2</sup>, Shyam NDVN<sup>3</sup>

Dept. of Oral Maxillofacial & Pathology

Associate Professor<sup>1</sup>  
Lecturer<sup>2</sup>  
M.N.R Dental College and Hospital.

Associate Professor<sup>3</sup>,  
Dept. of Oral Maxillofacial & Pathology  
Government Dental College & Hospital,

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### Abstract:

Tumour markers are substances that are produced either by the tumour itself or by the body in response to the presence of cancer or certain benign conditions that can aid in the diagnosis of cancer. The subject of tumour markers is a broad one, and there is an abundance of data. A literature review of potential molecular markers relevant to oral neoplasia was undertaken in terms of a perspective for the role of tumour markers in prevention and detection.

**Key words:** *Tumour Markers, Oral Neoplasia, Biological markers, SCC*

## INTRODUCTION

Tumour markers are substances that are produced either by the tumour itself or by the body in response to the presence of cancer or certain benign (noncancerous) conditions that can aid in the diagnosis of cancer and in the assessment of tumour burden. Tumour markers can often be detected in higher than normal amounts in the blood, urine, or body tissues of some patients with certain types of cancer. Measurements of tumour marker level can be useful-when used along with radiographs or other tests-in the detection and diagnosis of some types of cancer.

The subject of tumour markers, is a broad one, and there is an abundance of data.<sup>1</sup> This can be reviewed in terms of a perspective for the role of tumour markers in prevention and detection; and a review of the types of tumour markers that have been developed focusing mainly on head and neck tumours.

Tumour markers are a major part of the secondary prevention (detection) efforts. There are major logistic and economic constraints which could be overcome if a simple laboratory test could be devised that would (based on a sample of blood or urine) indicate the presence of cancer-with a high degree of specificity and sensitivity-before there is metastasis.

Hence, it could serve as an acceptable screening test for initiating definitive diagnostic procedures with a goal of making an 'early diagnosis' and when simple removal of the tumour would result in normal survival characteristics for a population of patients. No such test exists, although extensive efforts have been made and a number of tumour markers have been described and tested. To date, no combination of markers has been found that meets the criteria set. Tumour markers have principally been used to monitor therapy i.e., predict outcome or signal a recurrence.

Address for correspondence:  
[dentistsanjay@gmail.com](mailto:dentistsanjay@gmail.com)

Morphologically, pathologists recognize cancer tissue as resembling fetal tissue more than normal adult differentiated tissue. Tumours are graded according to their degree of differentiation as (1) well differentiated, (2) poorly differentiated, or (3) anaplastic (without form). Tumour markers are the biochemical or immunological counterparts of the differentiation state of the tumour. In general, tumour markers represent re-expression of substances produced normally by embryogenically closely related tissues (oncodevelopmental markers)

Few markers are specific for a single individual tumour (tumour-specific marker); most are found with different tumours of the same tissue type (tumour-associated markers). They are present in higher quantities in cancer tissue or in blood from cancer patients than in benign tumours or in the blood of normal subjects. (**Table 1**)

#### **CLASSIFICATION OF TUMOUR MARKERS**

Earlier classification given by Neville AM & Cooper EH<sup>2</sup> is considered to be arbitrary with considerable overlap and grouped Tumour markers into Hormones, Oncofetal products, Enzymes/ isoenzymes and other macromolecules. Even though broader classification was proposed in later years (**Table 2**)<sup>3</sup> there is no single universally acceptable classification of Tumour markers to date.

#### **IMMUNOHISTOLOGICAL MARKERS FOR TUMOUR PROGNOSTICATION**

Immunohistochemistry is an invaluable adjunct to morphological diagnosis especially in the area of oncological pathology. Increasingly sensitive techniques and highly specific antibodies enable immunolabelling to be correlated with cytomorphology and cellular organelle distribution so that the alternative term "immunohistology" has been popularized<sup>4</sup>

Besides rendering diagnosis, a major purpose of histological examination of tumours is the prediction of prognosis and outcome. The ever increasing sophistication of cancer treatment regimes demand, that a variety of biological parameters be assessed to predict tumour behavior and response to specific therapies. Current clinical and morphological parameters do not provide precise identification of

patient subsets that are likely to relapse and there is now a focus on identification of oncogenes, tumour suppressor genes and enzymes that may more accurately predict the biological behavior of tumours. Immunohistology provides an important method of analysing many of these prognostic parameters. In addition, immunohistology can be employed for the microscopic staging of tumours such as invasion of basal lamina and detection of micrometastases. Specific proteins implicated in various forms of therapy may be identified including hormone receptors for hormonal therapy, *c-erbB-2* for Herceptin antibody treatment and multi-drug resistance gene products to predict response to chemotherapy.<sup>5</sup>

#### **1. Markers to predict response to therapy:**

- A. Oestrogen and progesterone receptors<sup>6,7,8</sup>
- B. Androgen receptors<sup>9</sup>
- C. Steroid-regulated proteins- Cathepsin D and pS2<sup>10</sup>
- D. *c-erbB-2* Gene<sup>11</sup>

#### **2. Markers to monitor drug resistance:**

- P-glycoprotein (a transmembrane protein)<sup>12,13</sup>
- *c-erbB-2*<sup>14</sup>

#### **3. Growth factors and receptors:**

Epidermal growth factor receptors, *erb-2* oncoprotein, insulin and insulin-like growth factor receptors, transforming growth factor - receptors, fibroblast growth factor receptors and the somatostatin receptors.<sup>15</sup>

#### **4. Tumour angiogenesis:**

Microvascular density has been found to be an independent marker of prognostic relevance.<sup>16</sup>

#### **5. Tumour growth fraction:**

Ki 67 ANTIBODY<sup>17</sup>, Proliferating Cell Nuclear Antigen (PCNA) & P27<sup>KIP1</sup> Gene<sup>18</sup>

#### **6. Tumour suppressor genes:**

p53 tumour suppressor gene and Retinoblastoma susceptibility suppressor gene

## 7. Anti-apoptosis genes:

*bcl-2*<sup>19</sup>

## 8. Nm23 Anti-metastasis gene:

The nm23 gene family was originally identified in a murine melanoma cell line and nm23-H1 was found to be transcribed at a 10-fold higher rate in cells of lower metastatic potential.<sup>20</sup>

## 9. DNA Repair genes- microsatellite instability (MSI):

The human genome is punctuated with an enormous number of short repetitive nucleotide sequences known as microsatellites. They are less likely to be associated with lymphatic and distant metastasis and the improved prognosis applies even they are stratified by stage.<sup>21,22</sup>

## 10. Miscellaneous markers:

*K-ras* and *c-myc* oncogenes, transforming factors TGF- $\alpha$ , TGF- $\beta$ , adhesion proteins E-cadherin and CD 44, and the matrix metalloproteases and inhibitors, etc.

## Specific tumour markers implicated in oral neoplasms

### Alpha-1-antichymotrypsin (1-ACT) & factor XIIIa antibodies:

Study on peripheral giant cell lesions and central giant cell lesions for characteristics of both cell types by evaluating for Alpha-1-Antichymotrypsin (1-ACT) & Factor XIIIa antibodies (markers specific for histiocyte/macrophage) concluded that giant cell lesions of the oral cavity may arise from precursor cells that express markers for both macrophages and osteoclasts.<sup>23</sup>

### BCL-2:

Bcl-2 has been suggested as a significant prognostic indicator in early Squamous Cell Carcinoma of head and neck.<sup>24</sup> The predictive role in terms of pathological response and prognostic role of biomarkers such as GST-pi, p53, bcl-2 and bax expression, immune-histochemically detection of the S-phase cell fraction, and autoradiographically determined as thymidine labeling index (TLI), were investigated within a prospective randomized phase

III clinical trial on squamous cell carcinomas (SCC) of the oral cavity, including surgery or primary chemotherapy.<sup>25</sup> Upon study on Salivary gland tumours, Norberg-Spaak L et al<sup>26</sup> concluded that neither clinical stage nor histological grade of Adenoid cystic carcinomas correlated with the degree of bcl-2 tumour cell positivity.

### Beta 2-Microglobulin:

A definite increase in the level of beta 2-microglobulin was observed in patients with oral submucous fibrosis and oral cancer.<sup>27</sup>

### CD44, CD80, CD105 (ENDOGLIN):

Differences in the expression of HA and CD44 among different types of salivary gland tumours was noted, but are not correlated with biologic behavior.<sup>28</sup> In oral SCC's decreased expression of CD80 may serve as a marker for increased tumorigenicity during early development,<sup>29</sup> and decreased expression of CD44 correlated with decreased survival rate.<sup>30</sup> Increasing evidence suggest that endoglin (CD105) is a new powerful marker of neovascularization in solid malignancies<sup>31</sup> and positive CD105 vessels in Adenoid cystic carcinomas increases risk of metastasis.<sup>32</sup>

### Cytokeratins:

Monospecific keratin antibodies are useful for evaluation of epithelial differentiation changes in oral dysplasia's and oral SCC.<sup>33</sup> Simple epithelial keratins (K8, K18, K19) are not confined to the more poorly differentiated tumours which may be relevant to tumour prognosis.<sup>34</sup> CK19 and CK8 are markers of sequential premalignant changes in head and neck carcinogenesis.<sup>35,36</sup> Non expression of CK5 may be an early event occurring in tobacco-associated pathological changes in the buccal mucosa.<sup>37</sup> Analysis of some intermediate CK filaments can reflect the biological behavior and aggressiveness of some tongue SCCs.<sup>38</sup>

### Cathepsin-d:

Cathepsin D is postulated to promote tumour invasion and metastasis. It is a potential independent predictor of cervical lymph node metastasis in Head and Neck SCC.<sup>39</sup>

**TABLE 1.**

| YEAR | AUTHOR                           | MARKER                             |
|------|----------------------------------|------------------------------------|
| 1846 | H.Bence-Jones                    | Bence-Jones protein                |
| 1928 | W.H.Brown                        | Ectopic hormone syndrome           |
| 1930 | B.Zondek                         | HCG (human chorionic gonadotropin) |
| 1932 | H.Cushing                        | ACTH                               |
| 1949 | K.Oh-Uti                         | Deletions of blood group antigens  |
| 1959 | C.Markert                        | Isoenzymes                         |
| 1963 | G.I.Abelev                       | AFP ( -fetoprotein)                |
| 1965 | P.Gold & S.Freeman               | CEA (Carcinoembryogenic antigen)   |
| 1969 | R.Heubner and G.Todaro           | Oncogenes                          |
| 1975 | H.Kohler and G.Milstein          | Monoclonal antibodies              |
| 1980 | G.Cooper, R.Weinber, M.Bishop    | Oncogene probes and transfection   |
| 1985 | H.Harris, R.Sager, and A.Knudson | Suppressor gene                    |

**Brief history of tumour markers**

**TABLE - 2**

|                                    |   |
|------------------------------------|---|
| I. PROLIFERATION MARKERS           | <b>Ki-67, PCNA, p27 Kip/gene, DNA polymerase alpha, p 105, p120, Statin</b>   |
| II. ONCOGENES                      | <b>c-erbB-2 gene, ras gene, myc gene, bcl-2 gene</b>  |
| III. GROWTH FACTORS AND RECEPTORS: | <b>EGFR (Epidermal growth factor receptor)<br/>Transforming growth factor <math>\beta</math>-HCC<br/>Fibroblast growth factor receptor<br/>Insulin and insulin like growth factor receptor.</b>   |
| IV. TUMOUR SUPPRESSOR GENES:       | <b>p<sub>53</sub>, Retinoblastoma susceptibility suppressor gene.</b>   |
| V. SEROLOGICAL TUMOUR MARKERS:     | <ul style="list-style-type: none"> <li>a. <b>Markers associated with cell proliferation</b></li> <li>b. <b>Markers related to cell differentiation:</b><br/>(Carcinoembryonic proteins like Carcinoembryonic Ag, <math>\alpha</math>-Feto protein)</li> <li>c. <b>Markers related to metastasis:</b></li> <li>d. <b>Related to other tumour-associated events.</b></li> <li>e. <b>Related to malignant transformation.</b></li> <li>f. <b>Inherited mutations.</b></li> <li>g. <b>Monoclonal Ab-defined tumour markers</b></li> </ul> |

**Broad classification of tumour markers<sup>3</sup>**

**TABLE - 3**

**CELL SURFACE MARKERS:**

- Carbohydrates-particular blood group antigens
- Squamous carcinoma antigens Ca-1, TA-4, SQM & 3H-1
- Hitocompatibility antigens
- Growth factors and receptors

**INTRACELLULAR MARKERS:**

- Cytokeratins
- Filaggrin
- Involucrin
- Desmosomal proteins
- Carcinoma antigen 17.13
- Quantitative DNA
- Silver binding Nucleolar Organizer Regions
- Oncogenes
- Arachidonic acid products
- Gamma-glutamyl transpeptidase, lactate dehydrogenase and guanidine benzoatase

**BASEMENT MEMBRANE MARKERS:**

- Laminin
- Collagen IV

**Matrix Markers**

- Tenascin

**Some tissue markers of potential and established malignancy<sup>107</sup>**

**TABLE - 4**

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

**Potential uses of tumour markers**

### **CEA, CA19-9, CA125, SCC-Ag:**

Serum and saliva values of carcinoembryonic antigen (CEA) in benign oral lesions and confirmed SCC was not of any clinical significance<sup>40</sup> but play a role in the management of patients with adenoid cystic carcinoma (ACC).<sup>41</sup> Immunostaining for CA 19-9 and CA 125 provide no reliable data to predict the clinical course of patients with Mucoepidermoid Carcinoma and ACC of the salivary glands.<sup>42</sup> No significant correlation was detected between serum levels and tumour localization, staging, grading or performance status for CEA, SCC Ag, Thymidine Kinase (TK), CA 19-9 and deoxythymidine-5'-triphosphatase (dTTPase) in patients with head and neck cancer.<sup>43,44</sup>

Examination of tumour markers in the saliva of oral squamous cell carcinoma (OSCC) patients showed significant increase in Cyfra 21-1, tissue polypeptide antigen, and CA125, but Salivary concentrations of CA19-9, SCC, and carcinoembryonic antigen were increased without statistical significance.<sup>45</sup>

### **Carbohydrate associated antigens:**

Expression of carbohydrates may supplement histologic diagnosis in the evaluation of the prognosis of premalignant lesions.<sup>46</sup> They are regarded as markers of glandular differentiation pattern in salivary gland carcinomas<sup>47</sup> but may not be considered as independent prognostic factors.<sup>48</sup>

### **Calretinin:**

Calretinin (29-kDa calcium binding protein) appeared to be specific immunohistochemical marker for neoplastic ameloblastic epithelium and it may be an important diagnostic aid in the differential diagnosis of cystic odontogenic lesions and ameloblastic tumours.<sup>49</sup>

### **C-erb2:**

Oral carcinoma transformation was related to C-erb2 interaction<sup>50</sup> but of little significance in salivary gland tumours.<sup>51</sup> The aberrations of erbB-1 and erbB-2 are additional markers in premalignant oral lesions at the beginning of the carcinogenic process<sup>52</sup> but are not considered to be valuable tumour markers in squamous cell carcinomas of head and neck

(SCCHN).<sup>53</sup> Expression of C-erbB2 was associated with significantly decreased progression free survival and overall survival in recurrent head and neck cancers<sup>54</sup> also predict high risk of recurrence of tongue SCC.<sup>55</sup>

### **Cyclin, MIB:**

Proliferation markers cyclins and Mib in the basal and superficial cells of premalignant lesions may serve as surrogate end point biomarkers for chemoprevention trials.<sup>56</sup> Cyclin may be a variable alternative to BrdU for the study of the cells in the S-Phase in precancerous lesions.<sup>57</sup> Cyclin D1, Ki67<sup>58</sup> CKD2<sup>59</sup> overexpression were positively correlated in OSCC and Cyclin A activity predicts clinical outcome in oral precancer and cancer.<sup>60</sup>

### **Growth factors:**

Growth factors were correlated with short term prognosis in advanced tongue cancers.<sup>61</sup> Vascular endothelial growth factor (VEGF) may be an important angiogenic factor associated with cancer cells and endothelial cells in SCCHN<sup>62,63</sup> but does not appear to be associated with field cancerisation or transition to dysplasia<sup>64</sup> but VEGF-C or LVD (lymphatic vessel density) can effectively predict lymphatic metastasis of oral SCC.<sup>65</sup> Basic Fibroblast growth factor (FGF) has prognostic relevance for advanced head and neck cancer.<sup>66,67</sup> A literature review of potential molecular markers relevant to SCCHN in the early part of this decade suggested EGFR, TGF- $\alpha$ , Cyclin D1 and p53 as emerging molecular markers that might provide independent prognostic information.<sup>68</sup>

### **p<sup>53</sup>:**

Mutation in the p<sup>53</sup> tumour suppressor gene is the most common genetic alteration in human cancer. p<sup>53</sup> expression may be a valuable marker for identifying individuals at high risk of developing a recurrence of primary disease<sup>69</sup> and second primary tumours of SCCHN who may benefit from adjuvant therapy and chemoprevention after definitive local therapy.<sup>70,71,72,73,74,75</sup> It may also predict radioresistance of the tumours.<sup>76</sup> When used as a single marker, p<sup>53</sup> is unsuitable for the prediction of tumour development in high risk subjects of epithelial dysplasia.<sup>77,78</sup> Preoperative serum p<sup>53</sup> antibody is a significant prognostic factor for nodal metastasis of SCCHN<sup>79</sup> and may act as a important prognostic marker.<sup>80</sup>

Small groups of cells expressing p<sup>53</sup> and p<sup>16</sup> were found in the surgical resection margin of SCC that appeared to be histologically normal which may represent early malignant changes.<sup>81</sup>

Immunoreactivity of p<sup>53</sup> cannot be used to determine the malignant potential of melanomas in the head and neck.<sup>82</sup> Immunodetection of p<sup>53</sup> and PCNA on archival tissues of inflammatory papillary hyperplasia of the palate is neither specific nor sensitive enough to be used as indicators for malignant potential in the absence of cytological dysplastic changes.<sup>83</sup> p<sup>53</sup> inactivation by MDM2 expression may be involved in the pathogenesis of giant cell lesions of jaws and long bones.<sup>84</sup> p<sup>53</sup> oncoprotein along with Ki-67 cannot be relied on to distinguish benign from malignant lesions of the salivary glands.<sup>85</sup> Immunohistochemical p<sup>53</sup> overexpression is valuable marker of early neoplastic transformation and together with PCNA are presumed predictors for malignant transformation of oral papillomas.<sup>86</sup>

AgNOR count and p<sup>53</sup> protein detection in odontogenic lesions can be of great consequence to predict the biological behaviour and prognosis.<sup>87</sup> The expression of the cell-cycle proteins p<sup>16</sup> and p<sup>53</sup> in the dysplastic epithelium, in association with Ki-67, may represent significant markers to recognize evolution of precancerous disease in the oral cavity and to improve identification of the degree of dysplasia.<sup>88</sup>

#### Miscellaneous markers:

The studies on Epithelial Membrane antigen (EMA) in salivary gland function,<sup>89</sup> Endothelial Cell Markers in Kaposi's sarcoma,<sup>90</sup> Free and acetylated polyamines in SCC and benign oral lesions,<sup>91</sup> Galectins in SCCHN,<sup>92</sup> HCG (human chorionic gonadotropin),<sup>93,94</sup> Heat shock proteins,<sup>95,96,97</sup> in oral SCC and serum ferritin levels in head and neck cancer<sup>98</sup> showed little significant results.

HMB45 and S-100 antigens in melanomas, intramucosal and blue nevi were found to be complimentary in the diagnosis of undifferentiated tumours.<sup>99</sup> Heat stable alkaline phosphatase was of potential usefulness in the management of patients with SCCHN.<sup>100</sup>

The loss of syndecan-1 is associated with dysplastic changes in oral epithelium,<sup>101</sup> and in SCCHN a low number of syndecan-1 positive tumour cells were associated with low histological grade of differentiation, a larger primary tumour size, positive nodal status and high clinical stage.<sup>102</sup>

Proto-oncogene eIF4E (4E) is elevated in 100% of SCCHN and in premalignant lesions of the larynx but not in normal mucosa.<sup>103</sup>

IL1RN, MAL and MMP1 (matrix metalloproteins) are prospective tumour diagnostic markers for SCCHN. MMP1 overexpression is the most promising marker, and its detection could help identify tumour cells in tissue or saliva.<sup>104</sup>

Podoplanin is a mucin-like glycoprotein that is important in lymphangiogenesis but not blood vessel formation. Podoplanin is involved in oral tumourigenesis and may serve as a predictor for lymph node metastasis and poor clinical outcome of SCCHN.<sup>105</sup>

Various molecular markers in oral epithelial dysplasia has been reviewed elsewhere<sup>106,107</sup> (Table-3)<sup>107</sup>

#### Clinical applications of tumour markers:

It is essential that the meaning of test sensitivity and the specificity of a tumour marker be understood before discussing the applications of tumour markers.<sup>108,109</sup> In fact, the clinical utility of a tumour marker depends almost totally on the specificity, sensitivity, positive-predictive accuracy and negative-predictive accuracy of the tumour marker.<sup>109</sup>

In general, tumour markers may be used for diagnosis and prognosis of carcinomas and for monitoring effects of therapy as well as targets for localization and therapy. Ideally, a tumour marker should be produced by the tumour 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. Most tumour markers are present in normal, benign, and cancer tissues and are not specific enough to be used for screening cancer.

### Potential uses of tumour markers: (Table 4)

The clinical staging of cancer is aided by quantitation of the marker; that is the serum level of the marker reflects tumour burden. The tumour marker value at the time of diagnosis may be used as a prognostic indicator for disease progression and patient survival. This is possible for an individual patient, but different levels of markers produced by different tumours do not usually allow one to determine the prognosis of a tumour from the initial level. However, 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. For example, the half-life of prostate specific antigen (PSA) is 3 days, that of human chorionic gonadotropin (hCG) is 12 to 20 h, and that of alpha fetoprotein (AFP) is 5 days. If the half-life after treatment is longer than the expected half-life, then the treatment has not been successful in removing the tumour. The magnitude of marker reduction may, however, reflect the degree of success of the treatment or the extent of disease involvement.

Most tumour marker values correlate with the effectiveness of treatment and responses to therapy.

### CONCLUSION:

Tumour markers cannot be construed as primary modalities for the diagnosis of cancer. Their main utility in clinical medicine has been a laboratory test to support the diagnosis. A host of tumour markers have been described, and new ones appear every year. Only a few have stood the test of time and proved to have clinical usefulness. New investigative techniques at the cellular and molecular level show great promise at defining potentially malignant lesions but further prospective, in-depth studies are required to determine their practical usefulness.

With the evolving understanding of the genetics and molecular basis of human malignancies, there has been much interest in determining whether specific molecular changes in different premalignant & malignant tumours might guide treatment decisions.

A literature review of potential molecular markers relevant to head and neck tumours was

undertaken and evaluated. It is evident that the published information is promising but, oftentimes limited by a scarcity of large, uniformly staged and treated patients, from which the value of novel molecular markers can be assessed.

With the evolving understanding that human malignancies have developed and progressed on the basis of accumulated molecular abnormalities, there is an existing body of work trying to determine whether such abnormalities can predict clinical behavior of various head and neck tumours. Such studies have to be conducted rigorously to derive useful information. Nevertheless the role of such molecular markers, and the possibility to exploit them for therapeutic gain is already at the horizon.

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