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Tumor markers in oral cancer

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Abstract

Tumor markers are substances that are produced either by the tumor itself or by the body in response to the presence of cancer or certain benign conditions that can aid in the diagnosis of cancer.

These markers mostly are the proteins that are produced at a greater rate by the cancer cells. Increased levels of these substances can be detected in urine, blood, or body tissues of the patients with certain types of cancer.

These markers may be employed to predict primary or secondary tumor risk. Sometimes, non-cancerous conditions can also cause elevation of some tumor markers to be higher than normal.

Essential understanding and knowledge about the development of oral cancer, transformation of precancerous lesion to malignant lesion is very essential for making early diagnosis leading to success and prognosis of the treatment.

Complete awareness of Tumor marker can aid in earlier detection of oral cancer. In combination with other diagnostic modalities, tumor marker can support in staging, assess tumor volume and to ascertain tumour metastasis.

For these reasons, the knowledge regarding these biomarkers has increased tremendously. This article classifies the different types of tumor markers and implicates their role in some diseases.

Keywords: Biomarkers, Tumor, Oral cancer

Introduction

Oral cavity cancer is amongst the most prevalent cancers worldwide and incidence rates are higher in men than women. Oral cancer is a dreadful condition affecting a lot of humankind and serves to report the lowest survival rate all over the world. Among the cancers, oral cancer is a common malignancy affecting the individuals.

There are an estimated 529,000 new cases of cancers of the oral cavity and pharynx each year, and more than 300,000 deaths. Oral cancers include the main subsites of lip, oral cavity, nasopharynx and pharynx and have a particularly high burden in South Central Asia due to risk factor exposures[1,2].

The process of development of oral cancer usually occurs in 2-steps i.e., the presence of a precursor (potentially malignant) lesion and its subsequent transformation into cancer. Studies have shown that between 1 and 18% of oral pre-malignant lesions will develop into oral cancer[3,4]

The diagnosis of cancer is based on the analysis of tissue and cytology specimens obtained through several procedures. When a cell becomes cancerous, new antigens unfamiliar to the immune system appear on the cell's surface. The immune

system identifies these new antigens, called tumor antigens, as foreign and may be able to contain or destroy the cancerous cells[5,6].

A tumor marker can be defined as a molecule that indicates the likely presence of cancer or can also be defined as one that provides information about the likely future behavior of an existing cancer (e.g., ability to metastasize or to respond to therapy). Most existing tumor markers are mostly useful in making a clinical decision after initial suspicion of cancer or its behavior which has been already raised by more conventional means[7].

History

The first tumour marker was identified incidentally by Bence-Jones in 1846 from patients suffering from "Mollities ossium"[8].

In 1930, Zondek identified the first modern tumour marker Human Chorionic Gonadotropin (HCG). Generally, HCG is used to detect pregnancy, but presence of high level of HCG in the blood in nonpregnant women may be the sign of a cancer of the placenta called Gestational Trophoblastic Disease (GTD)[9].

In 1965, Gold et al. discovered the first "tumour antigen" from specimens of human colonic cancer, which was later identified as carcino-embryonic antigen (CEA).

Till date, numerous tumour markers are identified[10].

Ideal requisites of a tumor markers

- It should be highly sensitive and should have low false negatives.
- It should be highly specific and should have low false positive.
- It should have high positive and negative predictive value.
- 100% accuracy in differentiating between healthy individuals and tumor patients.
- It should be able to differentiate between neoplastic and non-neoplastic disease and show positive correlation with tumor volume and extent.
- It should predict early recurrence and have prognostic value.
- It should be clinically sensitive i.e. detectable at early stage of tumor.
- Its levels should be preceding the neoplastic process, so that it should be useful for screening early cancer.
- It should be either a universal marker for all types of malignancies or specific to one type of malignancy.
- It should be easily assayable and be able to indicate all changes in cancer patients receiving treatment[11,12]

Classification of tumor markers

Earlier classification given by Neville AM & Cooper EH 2 is arbitrary with considerable overlap and grouped tumor markers into Hormones, Onco-fatal products, Enzymes/isoenzymes and other macromolecules. Even though broader classification was proposed in later years there is no single universally acceptable classification of tumor markers to date[13]

Neville am and cooper eh classification.

- Hormones.
- Oncofetal products.
- Enzymes/isoenzymes.
- Macromolecules.

Markers to predict response to therapy

- Estrogen and progesterone receptors.
- Androgen receptors.
- Steroid regulated proteins Cathepsin D and pS2.
- c-erbB-2 Gene.

Markers to monitor drug resistance

- P-glycoprotein (a transmembrane protein).
- c-erbB-2.

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.

Tumor angiogenesis

- Microvascular density has been found to be an independent marker of prognostic relevance.

Tumor growth fraction

- Ki 67 ANTIBODY, Proliferating Cell Nuclear Antigen (PCNA) and P27 KiP1 Gene.

Tumor suppressor genes

- p53 tumor suppressor gene and Retinoblastoma susceptibility suppressor gene.

Anti-apoptosis genes

- bcl-2.

Nm23 Anti-metastasis gene

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

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.

Miscellaneous markers

- K-Ras and c-myc oncogenes
- Transforming factors TGF-a,
- TGG-b, adhesion proteins E-cadherin
- CD 44,

- Matrix metaloproteases and inhibitors, etc.

Broad classification of tumor markers

Proliferation markers

- Ki-67
- PCNA
- DNA polymerase alpha
- p27 Kip/gene
- p105
- p120
- Statin

Oncogenes

- c-erb-2 gene
- Ras gene
- myc gene
- bcl-2 gene

Growth factors and receptors

- EGFR
- TGF β-HCC
- FGFR
- Insulin and
- IGFR

Tumour suppressor genes

- p53
- Retinoblastoma susceptibility suppressor gene

Serological tumour markers

- Markers associated with cell proliferation.
- To cell differentiation.
- To metastasis.
- To other tumor associated events.
- To malignant transformation.
- Inherited mutations.
- Monoclonal Ab defined tumor markers.

Tissue markers of potential and established malignancy

Cell surface markers

- Carbohydrates

- Squamous carcinoma antigens
- Histocompatibility antigens
- Growth factors and receptors

Intracellular markers

- Cytokeratin's
- Filaggrin
- Involucrin
- Desmosomal proteins
- Carcinoma antigen 17.13
- Quantitative DNA
- Ag NOR
- Oncogenes
- Arachidonic acid products
- Enzymes

Basement membrane markers

- Laminin
- Collagen IV

Matrix markers

- Tenascin

Mechanism of tumor markers

Cancer is a cluster of diseases involving alterations in the status and expression of multiple genes that confer a survival advantage and undiminished proliferative potential to somatic or germinal cells[14].

Alterations occur primarily in 3 main classes of genes viz., (proto) oncogenes, tumour suppressor genes and DNA repair genes results in the development of cancer cell, which will resists the natural and inherent death mechanism(s) embedded in cells (apoptosis and like processes), coupled with dysregulation of cell proliferation events[15].

This conversion of normal cells to cancer cells includes gene rearrangement, point mutations, and gene amplifications resulting in changes in molecular pathways. Biomarkers are therefore invaluable tools for early cancer detection at molecular level[16,17].

Tumor markers in saliva

The blood and saliva are the most widely studied body fluids that may contain reliable biomarkers for cancer detection. The saliva is an informative body fluid containing an array of analytes (protein, mRNA, and DNA) that is used as biomarkers for translation and clinical applications.

Among all the malignancies, oral cancer is one such malignancy, where the saliva examination for detection shows the greatest benefit because of its direct contact with oral cancer lesions. The most important point for selecting saliva as a

diagnostic tool is that it also contains the fallen cells in oral cavity which allow saliva to be the first choice of screening and identify cation of potential biomarkers in the oral cancer.

Salivary genomic markers	Salivary transcriptome markers	Salivary protein markers	Salivary microbiota
Somatic mutations in tumor suppressor genes (p53)	IL-8	Elevated levels of defensin-1	Significant increase in the levels of Porphyromonas gingival is, Tannerella Forsythia and Candida albicans
Loss of heterozygosity in chromosome 3p, 9q, 13q and 17p	H3F3A	Elevated CD44	
Promoter hypermethylation of genes (p16, MGMT, or DAP-K)	IL1β	Elevated IL-8	Significantly elevated levels of Bacteroides melaninogenica and Streptococcus mitis
Cyclin D1 gene amplifi cation	S100P	SCC-Ag	
Decrease in 8-oxoguanine DNA glycosylase, phosphorylated-Src and mammary serine protease inhibitor (Maspin)	DUSP1	Cal cyclin, Rho GDP dissociation inhibitor	Presence of HPV and EBV
Microsatellite alterations of DNA	OAZ1	CEA, carcinoantigen (CA19-9), CA128	
	SAT (spermidine/ spermine N1-acetyltr ansferase)	Intermediate filament protein (Cyfra 21-1)	

Tumor markers in blood & urine

Alpha-1 chymotrypsin and Factor XIIIa antibodies are specific markers for histiocyte and macrophages and are used for giant cell lesions, since they have been found to arise from precursors cells that express these markers[18].

p53 inactivation by MDM2 (Murine Double Minute***)*** expression may occur in the pathogenesis of giant lesions of the jaws and long bones.

Bcl-2 is used as a prognostic indicator in early oral squamous cell carcinoma. Decrease in CD-80 expression serves as marker for increased tumorigenicity during early OSCC[19].

Cytokeratins- CK19 and CK8 are markers of progressive premalignant changes in head and neck carcinomas. The aberrations of C-erb-1 and C-erb-2 are indicators of early changes during carcinogenesis process in oral premalignant lesions[20].

Expression of cell cycle proteins p16 and p53 along with Ki-67 can be used as markers to identify evolution of oral precancerous disease and improves the identification of the degree of dysplasia[21].

Immunohistochemical p53 over expression is valuable marker for early malignant transformation. Over expression of p53 along with PCNA is presumed predictors for malignant transformation of oral papilloma.

Beta-2 microglobulin was increased in oral submucous fibrosis (OSF) and oral cancer Survivin expression levels were higher in OSCC transformed from OSF[22]

Ameloblastin (AMBN) gene mutations are responsible for the tumorigenesis of epithelial odontogenic tumours without Odontogenic ectomesenchyme. Reduced ameloblasts in the odontoma displayed most intense Amelogenin expression.

Calretinin is a calcium binding protein and is primarily expressed in central and peripheral nervous system and it is used as the diagnostic marker for malignant mesotheliomas[22].

Bone morphogenetic proteins (BMP) might play an important role in the formation of calcified dental tissues and the development of odontogenic tumours containing such tissues.

Lysozyme is an enzyme primarily found in monocytes and neutrophils. Serum lysozyme levels are elevated in acute granulocytic leukaemia, acute myelomonocytic leukaemia, and acute myeloid leukemia[23].

Tests used in conducting tumor marker detection

- EIA: Enzyme immunoassay
- FISH: Fluorescence in-situ hybridization
- ICC: Immunocytochemistry
- ICMA: Immunochemiluminometric assay
- IHC: Immunohistochemistry
- IRMA: Immunoradiometric assay
- MEIA: Micro particle enzyme immunoassay
- PCR: Polymerase chain reaction
- RIA: Radioimmunoassay
- RT-PCR: Reverse transcriptase polymerase chain reaction[24]

Uses of tumor markers

- Screening in general population
- Diagnosis of primary tumour
- Differential diagnosis of suspicious lesions
- Clinical staging of cancer
- To identify the undetected tumour metastasis
- Estimating tumour volume

- To indicate the prognosis of disease progression
- Evaluating the success of treatment
- Detecting the recurrence of cancer
- Monitoring responses to therapy
- Radio immunolocalization of tumour masses
- Determining direction for immunotherapy[25]

Conclusion

Tumor 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.

Recent advances in molecular biology have resulted in mind boggling array of tumour markers being developed, each with its characteristic sensitivity and specificity. It is therefore imperative on the part of the clinicians to tap into this pool and utilize the task-specific marker in various orofacial diseases in order to be able to contribute towards early diagnosis and prompt management, which will go a long way in reducing morbidity and improving survival.

This paper has highlighted some of the commonly used tumour markers in benign and malignant conditions that are frequently encountered by dental surgeons. It is therefore important for us to continuously update our knowledge regarding the effective usage of tumour markers in day-to-day practice in order to do justice to our patients

References

1. Homann N, Tillonen J, Meurman JH, Rintamaaki H, Lindqvist C, et al. (2000) Increased salivary acetaldehyde levels in heavy drinkers and smokers: A microbiological approach to oral cavity cancer. Carcinogenesis 21: 663-668.

2. Liao CT, Chang JT, Wang HM, Ng SH, Hsueh C, et al. (2008) Analysis of risk factors of predictive local tumor control in oral cavity cancer. Ann Surg Oncol 15: 915-922.

3. Pindborg JJ, Mehta FS, Gupta PC, Daftary DK. Prevalence of oral submucous fibrosis among 50,915 Indian villagers. Br J Cancer 1968;22(4):646-54.

4. Schepman KP, van der Meij EH, Smeele LE, van der Waal I. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. Oral Oncol 1998;34(4):270-5.

5. Silverman S (1998) Early diagnosis of oral cancer. Cancer 62: 1796- 1799.

6. Remmerbach TW, Weidenbach H, Pomjanski N, Knops K, Mathes S, et al. (2001) Cytologic and DNA-cytometric early diagnosis of oral cancer. Anal Cell Pathol 22: 211-221.

7. Ludwig JA, Weinstein JN (2005) Biomarkers in cancer staging, prognosis and treatment selection. Nat Rev Cancer 5: 845-856.

8. Sharma S. Tumor markers in clinical practice: General principles and guidelines. Indian J Med Paediatr Oncol 2009;30(1):1-8.

9. 6. Lehto VP, Ponten J. Tumor markers in human biopsy material. Acta Oncol 1989;28(5):743-62.

10. Barak V, Goike H, Panaretakis KW, Einar son R. Clinical utility of Cytokeratins as tumor markers. Clin Biochem 2004;37(7):529-40.

11. Cooner WH (1993) Definition of the ideal tumor marker. Urol Clin North Am 20: 575-579.

12. Sharma S (2009) Tumor markers in clinical practice: General principles and guidelines. Indian J Med Paediatr Oncol 30:

13. Suresh MR (1996) Classification of tumor markers. Anticancer Res 16: 2273-2277

14. Baylin SB, Ohm JE. Epigenetic gene silencing in cancer - a mechanism for early oncogenic pathway addiction? Nat Rev Cancer 2006;6(2):107-16.

15. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 2003;33 Suppl:245-54.

16. Weissleder R, Ntziachristos V. Shedding light onto live molecular targets. Nat Med 2003;9(1):123-8.

17. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med 2004;10(8):789-99

18. Dietz A, Rudat V, Conradt C, et al. Prognostic relevance of serum levels of the angiogenic peptide bFGF in advanced carcinoma of the head and neck treated by primary radio chemotherapy. Head Neck 2000;22(7):666-73.

19. Vaidya MM, Sawant SS, Borges AM, Ogale SB, Bhisey AN. Cytokeratin expression in precancerous lesions of the human oral cavity. Oral Oncol 1998;34(4):261-4.

20. Eisma RJ, Spiro JD, Kreutzer DL. Vascular endothelial growth factor expression in head and neck squamous cell carcinoma. Am J Surg 1997;174(5):513-7.

21. Gerdes J, Schwab U, Lemke H, Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J Cancer 1983;31(1):13-20.

22. Perdigao PF, Carvalho VM, L DEM, Gomez RS. Mutation of Ameloblastin gene in calcifying epithelial odontogenic tumor. Anticancer Res 2009;29(8):3065-7.

23. Mori M, Yamada K, Kasai T, et al. Immunohistochemical expression of Amelogenin in odontogenic epithelial tumours and cysts. Virchow's Arch A Pathol Anat Histopathol 1991;418(4):319- 25.

24. Jilani S, Prystupa A, Krakowski P, Załuska W, Mosiewicz J. A clinical guide to tumour markers categorized under cancer types–A review. J Chromatogr B Analyt Technol Biomed Life Sci 2011; 879:573-78.

25. Chan DW, Sell S. Tumor Markers. (2nd ed) ed: WB Saunders; 1994.