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Tumor Markers- A Review

Nagalaxmi Velpula[1], Chandra Neela Yathavakilla[2,*], Aditi Ramesh[3]

[1]Professor & HOD, [2]PG Student, [3]Assitant Professor, Dept. of Oral Medicine & Radiology, Sri Sai College of Dental Surgery, Vikarabad, Telangana

***Corresponding Author:**
Email: chandraneelay@gmail.com

Abstract

The role of tumor markers in clinical oncology has increased tremendously over last decade, a trend that continues to grow as technology progresses and our understanding about human body and the disease processes increase. Tumour markers have wide applications in cancer care, starting from screening, choosing modality of management, assessment of prognosis to follow-up after treatment. Their judicious use in clinical practice needs a thorough understanding of the basics of pathophysiology and techniques of identification in any given malignancy. Of the numerous tumor markers identified, described and extensively researched upon, only a handful of them are used in routine clinical practice; and even of these, only a few have support of established consensus guidelines for use in day- to-day care of patients. This article discusses the uses of tumor markers, classification, some commonly used tumour markers and general principles for their optimal use.

Keywords: Tumor marker, Serum markers, Salivary markers, Early diagnosis, Malignancy

Introduction

Tumor markers are molecules that may be present in higher than usual concentrations in the tissue, serum, urine, or other body fluids of patients with cancer.[1-4] Apart from being useful as screening tests in diagnosing malignancy, they can also be used in assessing prognosis, guiding choice of treatment, and to monitor progress during and after treatment. In a relevant clinical setting, they undoubtedly help treating physician in management of malignancy, but also understanding the limitations of tumour markers is of utmost importance for their judicious use.

Ideal Tumour Marker

Although the characteristics of an ideal tumor marker depend to some degree on the classification and application of the marker, the general properties of such an ideal tumor marker include:[5]

1. Specific production by premalignant or malignant tissue early in the progression of disease;
2. Produced at detectable levels in all patients with a specific malignancy;
3. Expression in an organ site-specific manner;
4. Evidence of presence in bodily fluids obtained noninvasively or in easily accessible tissue;
5. Levels related quantitatively to tumor volume, biological behavior, or disease progression;
6. Relatively short half-life, reflecting temporal changes in tumor burden and response to therapy; and
7. Existence of a standardized, reproducible, and validated objective and quantitative assay.

Uses of Tumour Markers

1. Screening for early malignancy
2. Acting as a diagnostic aid for malignancy
3. Predicting therapeutic efficacy-e.g., tissue markers such as estrogen receptor and HER-2 (human epidermal growth factor receptor-2) predicting response to endocrine therapy and trastuzumab respectively.[6]
4. Monitoring therapy in advanced malignancy.[3]
5. Determining prognosis in malignancy
6. Maintaining surveillance following surgery of the primary tumor and for detecting disease recurrence.

Limitations of Tumour Markers

1. Tumor markers are not in themselves specific enough to permit a diagnosis of malignancy to be made and not an alternative for histopathological diagnosis (biopsy).
2. False positives lead to unnecessary anxiety and further investigations
3. False negatives lead to false assurance, delayed diagnosis, and advancement of malignancy
4. They may be elevated in benign conditions
5. Economic implications

Classification of Tumour Markers

Tumor markers can be broadly classified based on the type of tissue as follows:[8]

a. Epithelial markers
   - Cell surface markers – Histocompatibility
   - Intracellular markers – Cytokeratins
   - Basement membrane markers – Type 4 collagen
   - Matrix markers – Tenascin
   - Membrane antigen – Blood group antigens.

b. 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.

c. Salivary gland markers

- Epithelial markers – Cytokeratins
- Myoepithelial cell markers – Actin, myosin
- Serum acinar cell markers – Salivary amylase
- Myoepithelial cells + acinar cells – S100 protein.

Classification depending on Functional Utility

Tumour markers can also be classified depending on their functional utility into following types according to NCCN (National Comprehensive Cancer Network).[9]

Diagnostic Markers: These markers are mainly useful in establishing the disease from analysis of patient's sample (serum, body fluid, tissue etc.). Demonstration of Philadelphia chromosome in chronic myelogenous leukemia through fluorescence in situ hybridization (FISH) technique is an example of diagnostic marker.[10]

Prognostic Markers: Prognostic markers aid in assessment of disease outcomes, such as overall survival independent of the management options.[11] An example of a prognostic marker is *p53* mutations, which correlates with aggressive disease course and poor outcomes.[12]

Predictive Markers: Predictive markers help in assessing response of a tumour to a particular modality of management, thus aid in treatment planning.[11] An example is favourable response of *HER2* (Human epidermal growth factor receptor 2) positive breast cancer patients to trastuzumab.[13-15]

Companion Diagnostic Markers: Companion diagnostic markers may be diagnostic, prognostic, or predictive, but are used to identify a subgroup of patients for whom a therapy has shown benefit (*BRAF* V600E mutation in melanoma).[16, 17]

There are numerous tumour markers which may be diagnostic, prognostic or predictive that are used in day to day clinical practice for various neoplastic conditions. Most commonly used tumour markers are given in **Table 1**.[18]

Molecular basis of Tumour Markers: Genetic alteration in a tumor cell affects directly or indirectly the gene expression pattern of the tumor cell or the surrounding tissue.[19-20] These genetic alterations can be reflected at various levels **[Table 2]**, from genetic defects like mutation, deletion of gene to viral genomic incorporation, forming the molecular basis of tumour markers.[21]

Methods of Detection of Tumour Markers: There are several methods used in the detection of tumour markers, of which serological enzyme assay is the most commonly used method. Tumour markers can also be detected through immunohistochemistry *(IHC)*, radioimmunoassay *(RIA)*, or enzyme-linked immunosorbent assay *(ELISA)*.[22-24,26,27] Immunological detection is based on Monoclonal antibodies specifically binding to epitopes on tumor markers, which can be identified with dyes in immunohistochemistry *(IHC)*, radioactive tags in radioimmunoassay *(RIA)*, or enzymes in enzyme-linked immunosorbent assay *(ELISA)*. Flow cytometry is an alternative method to analyze the presence and percentage of antibody-tagged cells in a suspension.[26–28]

The above mentioned methods are highly sensitive and are useful in semi-quantitative or quantitative estimation of tumour markers. IHC is the most commonly used method in the detection of tumour markers nowadays. Immunohistochemistry (IHC) in oncology is used to categorize undifferentiated malignant tumors, leukemias and lymphomas, to determine the site of origin of metastatic tumors and also to detect the molecules of prognostic or therapeutic significance (e.g., Estrogen/progesterone receptors (ER/PR) in breast cancer).[22–26]

Source of Tumour Markers: Tumor markers can be detected either in tissue (tissue tumor markers; for example, in solid tumors, lymph nodes, bone marrow or circulating tumor cells in the blood) or in body fluids like ascitic or pleural fluid or serum (serological tumor markers).[26,28] Tissue tumor markers are of prime importance to a diagnostic pathologist, while the serological tumor markers are more often used by a clinician.

Specific tumour markers in Oral neoplasms

While many tumour markers appear attractive theoretically, none of them is either specific or sensitive enough to be used as a mass screening test in low risk population. Some of the tumour markers and their significance in management of oral neoplasms is given in **Table 3**.

Salivary biomarkers

With new techniques of detecting small quantities of salivary components including proteins and messenger Ribonucleic acid (mRNA), almost anything that can be measured in blood can be measured in saliva. Hence, saliva is considered as the blood stream of oral cavity. Alterations in the levels of certain mRNA molecules and of certain proteins have been detected in several cancers, including oral cancers indicating their possible use in cancer detection and follow-up. Tumour markers CA 15-3, Her2/neu and CA 125 are found in saliva.

In breast cancer cases, Her2/neu is the first salivary biomarker reported. The levels of CA 15-3, Her2/neu are raised and p53 levels are low. Raised levels of CA 125 in the saliva is noticed in ovarian cancer cases.[39]

Saliva can also be used for the detection of oral cancer. p53 gene is mutated in the salivary DNA of oral cancer patients. IL-8, SAT, IL-1B, OAZ 1, H3F3A,

DUSP and S100P are some of the OSCC associated RNAs present in saliva.[40] Increased salivary levels of cell cycle regulatory proteins Cyclin D1 and Ki67, lactate dehydrogenase (LDH), matrix metalloproteinase (MMP)-9, reduction in DNA repair enzyme, 8-oxoquanine DNA glycosylase (OGG1) and tumor suppressor protein, Mapsin is noticed in oral cancer patients.[39]

Human Plasma Proteome

The human plasma proteome holds the promise of a revolution in disease diagnosis and therapeutic monitoring, provided that major challenges in proteomics and related disciplines can be addressed.

Plasma is not only the primary clinical specimen, but also represents largest and deepest version of the human proteome present in any sample. In addition to the classical "plasma proteins", it contains all tissue proteins (as leakage markers) plus very numerous distinct immunoglobulin sequences. Current progress in proteomics has been largely due to recent developments in mass spectrometry (MS) - based technologies. New techniques for the ionization of proteins and peptides, such as matrix assisted laser desorption-ionization (MALDI) and electrospray ionization (ESI) combined with time of flight (TOF), as well as new hybrid mass spectrometers, are now becoming the tools of choice for protein characterization.

Urine

Lida W Chan et al (2004)[29] determined the predictive value of urinary levels of two angiogenic factors, vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMPs), in a longitudinal study to determine their correlation with 1-year progression-free survival in patients with cancer. This small exploratory study suggests that the angiogenic urinary trends of VEGF and MMPs may be useful predictive markers for progression-free survival in cancer patients after the completion of radiotherapy.

Judicious use of tumor marker

One has to keep in mind following things while asking for tumour markers:

1. They can be raised in several benign or non-neoplastic conditions
2. Population based screening of asymptomatic people with most serum tumour markers is not recommended owing to low diagnostic sensitivity and specificity
3. Pitfalls in assessing prognosis: results within normal limits do not exclude malignancy or progression
4. Tumour markers cannot replace biopsy or histopathology for establishing the primary diagnosis of cancer
5. Tumour marker results are often method dependent – patients should, ideally, be monitored using the same method and its name indicated on the report form
6. Tumour marker results should always be interpreted in the context of all available information including clinical findings, imaging investigations, and other blood tests (such as renal and liver function and hematological tests).

Table 1: Table representing most commonly used tumour markers in clinical practice.[18]

Tumor Markers	Cancer	Non neoplastic Conditions
Hormones		
Human Chorionic Gonadotropin	Gestational trophoblastic disease, Gonadal germ cell tumor	Pregnancy
Calcitonin	Medullary cancer Thyroid	
Catecholamines	Pheochromocytoma	
Oncofetal Antigens		
α Fetoprotein	Hepatocellular carcinoma, Gonadal germ cell tumor	Cirrhosis, Hepatitis
Carcinoembryonic antigen	Adenocarcinomas of the Colon, Pancreas, Lung, Breast, Ovary	Pancreatitis, Hepatitis, IBD, Smoking
Enzymes		
Prostatic acid phosphatase	Prostate cancer	Prostatitis, Prostatic hypertrophy
Neuron-specific enolase	Small-cell cancer of the lung, Neuroblastoma	
Lactate dehydrogenase	Lymphoma, Ewing's sarcoma	Hepatitis, Hemolytic anemia,
Tumor-Associated Proteins		
Prostate-specific antigen	Prostate cancer	Prostatitis, Prostatic hypertrophy
Monoclonal immunoglobulin	Myeloma	Infection, MGUS
CA-125	Ovarian cancer, some lymphomas	Menstruation, Peritonitis, Pregnancy
CA 19-9	Colon, Pancreatic, Breast cancer	Pancreatitis, Ulcerative colitis
CD30	Hodgkin's disease, Anaplastic large-cell lymphoma	
CD25	Hairy cell leukemia, Adult T cell leukemia/lymphoma	

MGUS: Monoclonal gammopathy of uncertain significance.

Table 2: Molecular basis of Tumour Markers[21]

Levels of classification	Examples
DNA Epigenetic	Promoter Hyper-methylation, e.g., GSP1, DAP in lung cancer; p15, p16 in liver cancer
Endogenous Mitochondrial genetic	Mutations, e.g., NADH dehydrogenase 4 (ND4) in urine in bladder cancer
Oncogene	Mutation, e.g., K-ras in pancreatic cancer; micro-satellite alterations in head and neck cancers
Exogenous viral RNA	EBV in NPC, Burkitt's lymphoma; HPV in cervical cancer
Cell based endogenous	Tissue-specific markers, e.g., PSA mRNA in prostate cancer, cytokeratin 20 mRNA in breast cancer
Cell free	Circulating mRNA, e.g., Tyrosinase mRNA in melanoma
Exogenous viral Translational protein	Viral RNA, e.g., EBV-coded RNA in NPC
Native protein	PSA in prostate cancer, CEA in colonic cancer
Glycan	Aberrant glycosylation, e.g., monosialytactec AFP in HCC

AFP: Alfa fetoprotein; CEA: Carcinoembryonic antigen;
EBV: Epstein-Barr Virus; HCC: Hepatocellular carcinoma;
HPV: Human papilloma virus; mRNA: Messenger RNA;
NPC: Nasopharyngeal carcinoma; PSA: Prostate-specific antigen

Table 3: Tumour markers significant in oral neoplasms

Tumour Markers	Significance
VEGF, EGFR, TGF-α , Cyclin D1[30]	Prognostic information in SCCHN
Mutation in the p53 tumour suppressor gene[31]	Identifying individuals at high risk of SCCHN
bcl-2[32]	Prognostic indicator in early SCCHN
Proto-oncogene eIF4E (4E)[33]	SCCHN, Premalignant lesions of the larynx
Beta 2-microglobulin[34]	Oral sub mucous fibrosis and Oral cancer
Cathepsin D[35]	Independent predictor of cervical lymph node metastasis in SCCHN
Cytokeratins-CK19 and CK8[36-37]	Markers of sequential premalignant changes in head and neck cancer
Non expression of CK5[38]	May be an early event occurring in tobacco-associated pathological changes in the buccal mucosa
MMP1 (Matrix Metallo Proteins)	Diagnostic markers of SCCHN

SCCHN: Squamous Cell Carcinoma of Head and Neck

Conclusion

Hence with an evolution in the understanding of genetics and molecular basis of human malignancies, tumor markers have been better understood and are being progressively used not only in determination of the risk of tumors but also in treatment guidelines and decisions. A wide variety of tumor markers have been described in the literature but only a few have proved to be clinically useful, and therefore tumor markers cannot be construed as primary modalities but can be used as adjuncts in diagnosis and treatment planning of cancer.

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