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內文：

Abstract:

Recent advances in genomic technology, in particular gene expression profiling, may elucidate novel tumor markers or signatures that will predict how various tumors will behave and respond to various treatment modalities. In head and neck cancer, tumor markers may address current functional deficits in treating locally advanced disease. Progress in high-throughput techniques, will greatly promote identification and development of novel biomarkers that distinguish normal oral epithelia from potentially malignant lesions and early stage oral cancer. Further validation of these biomarkers and application in combination with routine histological studies will lead to improved diagnostic approaches and therapeutic strategies when the cancer is most curable.

I: Introduction

Malignant neoplasms are major causes of fear, morbidity and mortality all over the world. Globally ‘oral cancer’ is the sixth most common cause of cancer-related deaths.¹ Oral cancer accounts for approximately 30- 40% of all cancers in India.² Despite the recent advances in tumor surgery and multimodal treatment regimes, the prognosis of oral squamous cell carcinoma is still relatively poor. This may be because symptoms that indicate the presence of the carcinoma often appear when the tumor is in an advanced stage.³ Advances in the analysis of molecular alterations in cells undergoing malignant transformation have increasingly revealed the mechanisms that led to the occurrence and progression of malignancies. The identification of individual molecules that are associated with malignant transformation has led to an ever increasing number of molecular markers that have been shown to be related to tumor stage and grading or may be indicative for the prognosis and the clinical course of the disease.⁴

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 (noncancerous) conditions that can aid in the diagnosis of cancer and in the assessment of tumor burden. Tumor markers have principally been used to monitor therapy i.e., predict outcome or signal a recurrence. Few markers are specific for a single individual tumor (tumor- specific marker); most are found with different tumors of the same tissue type (tumor-associated markers). They are present in higher quantities in cancer tissue or in blood drawn from cancer patients than in benign tumors or in the blood of normal subjects.⁵ The subject of tumor markers is a broad one, and there is an abundance of data.⁶ This can be reviewed in terms of a perspective for the role of tumor markers in prevention and detection; and a review of the types of tumor markers that have been developed focusing mainly on head and neck tumors.⁶ To date, no combination of markers has been found that meets the criteria set. The purpose of this review is to evaluate the available tumor markers in our arsenal and to ascertain their specificity to head and neck cancer so as to definitely aid in developing effective management strategy

II. Classification I. According to Spieght and Morgan (1993)

Proliferative markers: PCNA, Ki67, BrU,

Histones & AgNORs Genetic markers: Ploidy

Oncogene: C-myc

Tumor suppressor markers: P53 mutations

Cytokines

Blood group antigens

Integrins ECM ligands

II. According to Schliephake H4

A. Tumor growth markers:

- Epithelial growth (EGF)
- Cyclin
- Nuclear cell proliferation antigens
- AgNORs(Agryophilic nucleolar organizer region)
- Skp2(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 keratinization

- Filagrins
- Invoucrin
- Desmosomal proteins
- Intercellular substances antigen
- Nuclear analysis

H. Arachidonic acid products

- Prostagladin E2
- Hydroxyeicosatetraenoic acid
- Leucotriene B4

I. Enzymes

- Glutathione S-transferase

III. Epidermal growth factor receptor:

This protein, also known as HER1, is a receptor found on cells that helps them grow. Test done on a piece of cancer tissue can look for increased amounts of these receptors, which is assign that the cancer may grow fast, spread quickly, and be harder to treat. Patients with elevated EGFR may have poorer outcomes and need more aggressive treatment, particularly with drugs that block (or inhibit) the EGFR receptors. EGFR may be used to guide treatment and predict outcomes of non-small lung, head and neck, colon, pancreas, or breast cancers. The results are reported as a percentage based on the number of cell tested.⁸

IV. Alfa fetoprotein:

Human alpha-fetoprotein (HAFP) is a tumor-associated fetal glycoprotein involved with both ontogenic and oncogenic growth. The fetal protein is a 69-kDa single-polypeptide chain that contains 3-5% carbohydrate and is produced in the yolk sac and fetal liver. A vast biomedical literature has amassed concerning the use of HAFP during pregnancy as a biomarker in human maternal serum (MS) and amniotic fluid. Studies have addressed the measurement of serum levels of AFP outside the normal levels in the sera of pregnant women; such values are indicative of multiple congenital malformations of the embryo and fetus. The first developmental abnormalities to be associated with abnormal AFP levels were neural tube defects and brain/spinal cord malformations.⁹⁻¹⁰⁻¹¹

V. Carcinoembryonic antigen:

Carcinoembryonic antigen (CEA), a glycosylated protein of MW 180 kDa, is over expressed in a wide range of human carcinomas, including colorectal, gastric, pancreatic, non-small cell lung and breast carcinomas.¹² CEA was first identified in 1965 by Phil Gold and Samuel O. Freedman in human colon cancer tissue extracts.¹³ CEA measurement is mainly used as a tumor marker to identify recurrences after surgical resection, or localize cancer spread though dosage of biological fluids. The CEA blood test is not reliable for diagnosing cancer or as a screening test for early detection of cancer. Most types of cancer do not produce a high CEA. Elevated CEA levels should return to normal after successful surgical resection or within 6 weeks of starting treatment if cancer treatment is successful. CEA levels may also be raised in some non-neoplastic conditions like ulcerative colitis, pancreatitis, cirrhosis, COPD, Crohn's disease as well as in smokers.¹⁴

VI. Hormones:

Calcitonin: The story of thyroid calcitonin is an illuminating example of the voyage of hormone from a therapeutic tool for bone disease to a tumor marker to screen for subclinical forms of cancer. Identified as a new thyroid hormone implicated in calcium metabolism, its pharmacological action offered a new therapeutic tool for the management of bone disease. By measuring the circulating calcitonin, a range of values was obtained for oncologists because the evolution of a newly identified form of thyroid cancer--medullary (MTC)--was poorly understood. Researchers' interest shifted from calcitonin physiological action to its use as tumor marker able to diagnose MTC, especially in genetically predisposed families

Beta human chorionic gonadotropin:

Human chorionic gonadotropin can be used as a tumor marker, as its β subunit is secreted by some cancers including seminoma, choriocarcinoma, germ cell tumors, hydatidiform mole formation, teratoma with elements of choriocarcinoma, and islet cell tumor. For this reason a positive result in males can be a test for testicular cancer. The normal range for men is between 0-5 mIU/mL. Combined with alpha-fetoprotein,

β -HCG is an excellent tumor marker for the monitoring of germ cell tumor

VII. AgNORs:

The nucleolar organizer regions (NORs) are loops of DNA which transcribe ribosomal RNA. They are associated with proteins, which are considered to be required for RNA transcription.¹⁷ The AgNOR number is directly proportional to the speed of the cell cycle. For this reason, cell proliferation has a prognostic value, since high proliferative activity is associated with poor prognosis.¹⁸ Various AgNOR parameters have been established to objectively evaluate the variations that occur between one tissue condition and another. These include number and distribution pattern (the most commonly used parameters), as well as mean nucleus area, size, shape and AgNOR location, which have proven to be significant factors in previous studies on oral mucosa lesions.¹⁹

VIII. C-myc:

Myc is a highly pleiotropic transcription factor known to control proliferation, metabolism, differentiation, and apoptosis.²⁰ Normally its expression is tightly regulated. In human cancer, however, Myc's deregulated expression is often observed and is considered a poor prognostic factor. Indeed, during development, myc family gene expression is highest during embryonic stages and is down regulated in mature organs, due to cell growth arrest and differentiation.²¹ Genetic knockout of the c-myc gene leads to embryonic lethality and, as elegantly shown by Baudino et al,²² this is partially due to defects in vasculogenesis caused by the lack of proper Vascular Endothelial Growth Factor (VEGF) signaling.

IX. P53 mutations:

p53 (the product of the human TP53 and mouse TRP53 genes) is best known and most extensively studied as a pivotal signaling node that converts diverse upstream stress signals into downstream responses including cell cycle arrest, senescence, DNA repair, and programmed cell death. These activities limit the contribution of corrupted genomes to tissue and have earned p53 the august designation —guardian of the genome||. ²³An emerging role for p53 in regulating cellular differentiation, self-renewal, and plasticity has generated intense interest, particularly among cancer researchers. Enforced differentiation is a powerful tumor-suppressive mechanism because normal development and differentiation are antithetical to the abnormal development and incomplete differentiation that hallmark cancer. p53 has been implicated as an enforcer of differentiation by virtue of its ability to limit the cardinal stem cell characteristic of self-renewal in several systems.^{24,25} Although p53 mutation and pathway inactivation are found in the majority of tumors, they appear to be especially concentrated among tumors showing plasticity and loss of differentiation characteristics. p53 loss was almost exclusively associated with poorly differentiated thyroid cancers.²⁶ In breast cancer, p53 mutations are most frequently found within the poorly differentiated basal-like, metaplastic, and medullary types.^{27,28} A similar association between p53 loss and loss of differentiation characteristics has been observed in lung cancer,²⁹ and recent work in a murine lung cancer model indicates that p53 reactivation suppresses malignant adenocarcinoma progression without affecting less aggressive adenomas

X. Glycosaminoglycan-binding cytokines:

Glycosaminoglycan-binding proteins are relatively easy to study, since heparin can be usually used as a ligand to isolate them. These proteins include diverse classes of molecules such as membrane proteins, extracellular matrix proteins, and serum proteins.³¹ Among them are interesting classes of low molecular weight proteins

called cytokines, which include growth factors in a broader sense. Typical examples of glycosaminoglycan-binding cytokines are the family of fibroblast growth factors (FGFs), the binding of which to heparin sulfate proteoglycans is necessary for signaling by forming a trimolecular complex, comprising the receptor, proteoglycan and FGF.³² Other glycosaminoglycan binding cytokines include chemokines such as Interleukin-8 (IL-8) and Monocyte Chemo attractant Protein-1 (MCP-1), Vascular Endothelial Growth Factor (VEGF), Hepatocyte Growth Factor (HGF), Granulocyte Colony Stimulating factor (G-CSF), Midkine, and Pleiotrophin. Generally speaking, glycosaminoglycans are involved in signaling, stabilization, and/or storage of these cytokines. Since cytokines produced by tumors and host cells in the tumor microenvironment promote cell growth, inflammation and angiogenesis, and play central roles in tumor pathogenesis.³³⁻³⁴ (Table 1).

Malignant tumors	Cytokines
Gastric cancer	HGF, IL-8, VEGF, VEGF-C
Colorectal cancer	G-CSF, HGF, IL-8, VEGF
Hepatocellular carcinoma	bFGF, Midkine, VEGF
Pancreatic cancer	MCP-1, pleiotrophin
Oral squamous cell carcinoma	VEGF
Esophageal squamous Carcinoma	HGF, Midkine, VEGF
Lung cancer	bFGF, G-CSF, HGF, IL-8, pleiotrophin, VEGF-C
Head and neck cancer	bFGF, HGF, IL-8, VEGF
Renal carcinoma	bFGF, VEGF
Bladder cancer	HGF
Testicular cancer	bFGF, pleiotrophin
Prostate cancer	bFGF, HGF
Breast cancer	bFGF, HGF, MCP-1, VEGF, IL-8
Ovarian cancer	bFGF, G-CSF, IL-8, MCP-1, midkine, VEGF
Cervical cancer	Midkine, VEGF, VEGF-C
Thyroid gland tumors	bFGF, HGF, VEGF
Neuroblastoma	Midkine
Melanoma	VEGF, VEGF-C
Myeloma	bFGF, HGF, pleiotrophin
Lymphoma	bFGF, HGF, IL-8, VEGF
Leukemia	HGF, IL-8, VEGF
Soft tissue sarcoma	bFGF, IL-8, VEGF

Table 1: Glycosaminoglycan-binding cytokines of potential clinical importance as tumor markers.³⁴

XI. VEGF/VEGF-R (Vascular endothelial growth factor/receptor):

VEGF also called VEGF-A, has potent angiogenic activity and is a principal molecule involved in tumor angiogenesis. Serum VEGF levels are elevated in patients with various malignancies especially at the advanced stage.^{35,36} A high level of serum VEGF is a marker of poor prognosis in patients with hepatocellular carcinoma.^{37,38} Levels are significantly higher in patients with bone metastasis than those in patients without bone metastasis or patients with cirrhosis/chronic hepatitis.³⁹ Although serum VEGF is largely released from platelets, the serum VEGF level has been shown to reflect tumor VEGF expression in patients with hepatocellular carcinoma.⁴⁰ Platelets appear to serve as a reservoir of serum VEGF. Serum VEGF levels are elevated in patients with non small cell lung cancer, and high levels are generally correlated with a poor prognosis.⁴¹ They serve as a prognostic factor in completely resected patients with non small cell lung cancer, especially squamous cell carcinoma,⁴² or in resected

patients with stage I/II disease but not in those with stage III disease.⁴³ A high serum level of VEGF is associated with poor survival among patients with small cell lung cancer,⁴⁴ but is not an independent prognostic factor

XII. Telomerase:

Telomerase, a critical enzyme responsible for continuous cell growth, is repressed in most somatic cells except proliferating progenitor cells and activated lymphocytes, and activated in approximately 85% of human cancer tissues. Telomerase activity is a useful cancer-cell detecting marker in some types of cancers in which almost all cases show telomerase activation. In other types in which telomerase becomes upregulated according to tumor progression, it is a useful prognostic indicator. Detection of human telomerase reverse transcriptase (hTERT) mRNA or protein in various clinical samples is also applicable. However, careful attention should be paid to the false negative results due to the instability of this enzyme or hTERT mRNA and the existence of polymerase chain reaction inhibitors as well as the false-positive results due to the contamination by normal cells with telomerase activity.⁴⁶

XIII. Heat shock protein

Heat shock proteins (HSPs) are highly conserved and inhabit nearly all sub cellular locations where they perform a variety of chaperoning functions including folding and unfolding of nascent polypeptides, proteins, transport of proteins and support of antigen presentation processes. Apart from their intracellular location HSPs with a molecular weight of 70 kDa (HSP70) also have been found on the plasma membrane of malignantly transformed cells, on virally/bacterial infected cells and in the extracellular space. Depending on their intra- and extracellular location HSPs exert either protection against environmental stress or act as potent stimulators of the immune response

XIV. Uses of tumor marker:

1. Screening and Early Detection: Screening refers to looking for cancer in people who have no symptoms of the disease. Early detection is finding cancer at an early stage, when it is less likely to have spread and is easier to treat. Most markers are not suited for general screening, but if use, helps to find out the presence of occult disease at an early stage, wherein effective therapeutic intervention is likely to be beneficial. Due to lack of specificity of most biological markers and to insufficient evaluation of their true benefit for the patients. Only two markers, calcitonin and alpha- fetoprotein, markers of medullary thyroid carcinomas and of hepatocellular carcinomas respectively, have been proved useful in screening high risk populations for tumors.⁴⁸
2. 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 as differential diagnosis of suspicious lesion.CA-125 helps to differentiate ovarian cancer from other conditions.⁴⁹
3. 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.⁵⁰
4. Diagnosis: The identification of primary disease is an important function of any tumor marker. To detect any disease, a tumor marker has to be 100% sensitivity and specificity. In the vast majority of diagnostic situations, circulating tumor marker is used. Example, the presence of Bence Jones proteins in the urine remains one of the strongest diagnostic indicators of multiple myeloma.⁵¹
5. Determine prognosis: Tumor markers helps in determining the response of

treatment, prognosis and estimation of survival time based on evidence of metastatic disease.⁵²

6. Localization of tumor with radioactive labeled antibody specific tumor marker: The previous uses of tumor-associated markers were to detect neoplasms early, before they had metastasized, and to monitor their treatment. Recently, antibodies to these tumor associated markers have been radiolabeled, and the radiolabeled antibodies have been used to localize the neoplasms by external scintillation imaging. Potential now exists for treatment of the neoplasm by combining radiotherapeutic agents with the monoclonal antibodies to the neoplasm and infusing the patient with this combination. Three tumor-associated markers that are most often used are - fetoprotein, carcinoembryonic antigen, and human chorionic gonadotropin β - subunit. In addition, recently developed tumor-associated marker enzymes include galactosyl transferase isoenzyme II, creatine kinase BB, and radioimmunoassay of prostatic acid phosphatase isoenzyme.⁵³

7. Determining how well treatment is working: One of the most important uses for tumor markers is to watch patients being treated for cancer, especially advanced cancer. If a tumor marker is available for a certain type of cancer, the level of the marker may be able to be used to see if the treatment is working, instead of doing other tests like x-rays, CT scans, bone scans, or other tests. If the tumor marker level in the blood goes down, it is almost always a sign that the treatment is working. On the other hand, if the marker level goes up, then the cancer is not responding and the treatment may need to be changed. (One exception is if the cancer is very sensitive to a certain chemotherapy treatment. In this case, the chemo can cause many cancer cells to die and release large amounts of the marker into the blood, which will cause the level of the tumor marker to rise for a short time).⁵

There is a great interest in the development of new diagnostic markers that can aid cancer patients and their physicians in the process of clinical decision making. There are two general categories of diagnostic markers: Prognostic markers: indicate the likelihood of outcome (tumor recurrence, patient survival) regardless of the specific treatment the patient receives. For example, in most solid tumor the spread of cancer cells to lymph nodes indicate an increased likelihood of tumor recurrence, no matter which particular form of therapy the patient receives, following surgery predictive markers indicate the likelihood of response to a specific therapy. Some markers are an aid to the pathologist in confirming the tissue of origin of a tumor; others can be used to monitor a patient's response to therapy or to detect the growth of metastases. Markers of precancerous conditions are also sought in order to serve as the basis for screening strategies or to identify populations at high risk for cancer who might benefit from preventive measures. Finally, there is increasing interest in defining molecules target for new therapeutic agents. The successful outcome of research in cancer diagnostics is the developments of a new assay, procedure or techniques that provide information useful to physician and patient in designing the course of cancer treatment

XV. Limitations of tumor marker

- Difficulty in identify minute quantities of particular substances in serum.
- Existence of proliferation related rather than tumor associated antigen. Cross reactive antigens for instances a common domains in different proteins.
- Cross reaction with degradation products of normal proteins taken up by tumor cells.
- Malignant tumors with extensive necrosis have increased hydrolytic enzymes. Antigenic degradation products may then form which would normally be absent

from non-necrotic control tissue.

- The financial and psychological cost to the society of routine screening for early cancers using currently available tumor marker would be prohibited.

XVI. Advances in tumor marker:

More recent research has focused on the elucidation of gene expression profiles distinguishing metastatic disease from non- metastatic disease. Tumors of the oropharynx, hypopharynx and larynx have been found to group significantly according to metastatic cervical lymph node status.⁵⁸ A study evaluating the gene expression profiles of 34 hypopharyngeal tumor specimens identified a subset of 164 genes that were associated with metastatic potential, as indicated by patients with or without clinical evidence of metastasis three years after surgery.⁵⁹

A great deal of research has also been conducted into attempting to correlate gene expression profiles from tumors with patient clinical outcomes. In an excellent study, Chung and co-authors identified gene signatures from tumors that clustered into four groups, which exhibited significantly different rates of disease recurrence-free survival.⁵⁹ A recent study has shown that elevated protein expression of one particular marker, osteonectin, was a powerful, independent predictor for short disease-free interval and poor overall survival in an independent group of 62 patients, following expression profiling of seven tumor specimens and autologous matched normal controls.⁶⁰ These gene expression markers have the potential to become routinely used tumor markers. It may be possible to detect some or all of these changes by a simple biopsy or even a blood test. The pattern of alteration in these genes may be used as a diagnostic, prognostic and treatment modality indicator. There is also significant validation work required to correlate the changes in expression pattern with clinical outcome.

XVIII. 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. A host of tumor markers have been described, and new ones appear every year. 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.

題號	題目
1	p53屬於哪種tumor marker (A) Markers of tumor suppression and anti-tumor response (B) Markers of tumor invasion and metastatic potential (C) Arachidonic acid products (D) Enzymes
答案(A)	出處：本篇 Classification
題號	題目
2	下列哪個不是頭頸部腫瘤的cytokine (A) HGF (B) IL-8 (C) VEGF (D) IL-7
答案(D)	出處：本篇 TABLE 1