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Review article

Tumor markers – A bird's eye view

Diana Daniel[a,*], R.M. Lalitha[b]

[a] Bangalore Institute of Dental Sciences, # 5/3, Hosur Main Road (Near Lakkasandra Bus Stop), Bangalore, Karnataka 560029, India
[b] MS Ramaiah Dental College & Hospital, MSRIT Post, MSR Nagar, Bengaluru, Karnataka 560054, India

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ABSTRACT

Objective: The subtle differences between normal and tumor cells are exploited in the detection and treatment of cancer. These differences are designated as tumor markers and can be either qualitative or quantitative in their nature. This means that both the structures that are produced by tumor cells and the structures that are produced in excessive amounts by host tissues under the influence of tumor cells can function as tumor markers. An ideal tumor marker should be highly sensitive, specific, and reliable with high prognostic value, organ specificity and it should correlate with tumor stages. However, none of the oral tumor markers reported to date has all these characteristics. Apart from their limitations, tumor markers are precious tools for screening a healthy and a high risk population for the presence of cancer, making a diagnosis of a specific type of cancer, along with determining the prognosis and monitoring the course of the disease in the patient, at the time of remission or during the course of treatment. This review aims at understanding the role of tumor markers in a nutshell.
Methods: This article is based largely on our experience, discussions with colleagues, reviews, and original articles on the subject, as well as on a textbook on chromosomal rearrangement in tumor cells. We used the following key words for Medline searches for cancer, tumor markers, carcinogenesis.
Results: Several national and international expert groups have developed guidelines for use of markers for most cancers. None of these markers are currently validated for use in oral cancer.
Conclusions: Tumor markers cannot be construed as primary modalities for the diagnosis of oral 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. Tumor markers are reliable predominately in monitoring the treatment response, as well as in early detection of disease recurrence (prior to development of clinically notable signs). Due to their incompetence, tumor markers' determinations can be only exceptionally applied as screening methods and not as the sole diagnostic tool; however, in combination with other diagnostic methods, they play an important role in the diagnostic process and in treatment planning. Besides, by combining various tumor markers we can achieve a greater specificity and sensitivity in the follow-up of one type of malignancy.

Contents

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

* Corresponding author at: S 201, Green Meadows Apartment, Ramakrishnappa Road, Cox Town, Bangalore 560005, India.
E-mail addresses: drdianadaniel@gmail.com (D. Daniel), drrmlalitha@yahoo.co.in (R.M. Lalitha).

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1. Introduction

According to the National Cancer Institute (NCI), a biomarker is "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease," such as cancer [1]. Every cell type has a unique molecular signature, referred to as biomarkers, which are identifiable characteristics such as levels or activities (the abilities of genes or proteins to perform their functions) of a myriad of genes, proteins or other molecular features. Biomarkers are therefore an objective measure or evaluation of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [2]. There is tremendous variety of biomarkers, which can include proteins (e.g., an enzyme or receptor), nucleic acids (e.g., a microRNA or other non-coding RNA), antibodies, and peptides, among other categories. A biomarker can also be a collection of alterations, such as gene expression, proteomic, and metabolomic signatures. Biomarkers can be detected in the circulation (whole blood, serum, or plasma) or excretions or secretions (stool, urine, sputum, or nipple discharge), and thus easily assessed non-invasively and serially, or can be tissue-derived, and require either biopsy or special imaging for evaluation. Genetic biomarkers can be inherited, and detected as sequence variations in germ line DNA isolated from whole blood, sputum, or buccal cells, or can be somatic, and identified as mutations in DNA derived from tumor tissue [1]. Biomarkers have many potential applications in oncology including risk assessment, screening, differential diagnosis, determination of prognosis, prediction of response to treatment, and monitoring of progression of diseases. Because of the critical role the biomarkers play at all stages of disease, it is important that they undergo rigorous evaluation including analytical validation and clinical validation and assessment of clinical utility prior to incorporation into routine clinical care [1]. In the recent years, knowledge about cancer biomarkers has increased tremendously providing great opportunities for improving the management of cancer patients by enhancing the efficiency of detection and efficacy of treatment. Recent technological advancement has enabled the examination of many potential biomarkers and renewed interest in developing new biomarkers. A comprehensive understanding of the relevance of each biomarker will be very important not only for diagnosing the disease reliably, but also help in the choice of multiple therapeutic alternatives currently available that is likely to benefit the patients [3]. Cancer continues to be a major cause of morbidity and mortality among men and women [4]. More than 11 million people are diagnosed with cancer every year. It is estimated that there will be 16 million new cases every year by 2020 [5]. Oral cancer accounts for approximately 30–40% of all cancers in India [6]. Head and neck tumors belong among the six leading causes of cancer death worldwide. The predominant type of head and neck tumors consists of squamous cell carcinomas (HNSCC) [7].

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 [8].

Therefore tumor markers can act as precious tools for screening a healthy and a high risk population for the presence of cancer, making a diagnosis of a specific type of cancer, along with determining the prognosis and monitoring the course of the disease in the patient, at the time of remission or during the course of treatment [9]. This overview attempts to impart an overall understanding about tumor markers.

2. Definition

1. According to the National Cancer Institute (NCI), a biomarker is "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease," such as cancer [1].
2. A tumor marker is a substance present in or produced by a tumor or by the tumor's host in response to the tumor's presence that can be used to differentiate a tumor from the normal tissue or to determine the presence of a tumor based on measurement in the blood or secretions [10].
3. Tumor markers can also be defined as 'specific novel or structurally altered cellular macromolecules or temporarily spatially or quantitatively altered normal molecules that are associated with malignant (and in some cases benign) neoplastic cells' [11].
4. Cellular products that are abnormally elaborated by malignancies that can be detected in various body fluids and on the surface of the cancer cells [12].
5. Tumor markers can also be broadly defined as 'biological or molecular attributes of tumor cells that distinguish them from Normal cells' [13].

3. Brief history

The first known attempt to find markers for malignancy was made 2000 years ago and is described in an Egyptian Papyrus where breast cancer was distinguished from mastitis [14]. Incidentally the first tumor marker in modern medicine was identified by Bence-Jones, who in 1846 detected a heat precipitate in samples of acidified urine from patients suffering from "Mollities ossium" [15] (Table 1 [16]).

4. Classification

I) **According to Schliephake** [17]

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

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