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Role of serum biomarkers in detecting early oral squamous cellcarcinoma – A Literature review

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Abstract

Oral cancer is one of the causes of major morbidity and mortality in the world although incidence varies in the different geographical locations and races. Advances in molecular biology and cancer research have allowed elucidating serum biomarkers to improve diagnostic methods. The aim of this article literature review is to highlight the utility and clinical value of serum biomarkers in the diagnosis and prognosis of oral cancer. A systematic literature review using PubMed was carried out. We included studies published in English in the last ten years, developed in human as cases and controls studies, retrospective or prospective studies and specific studies that analyzed a certain biomarker in serum. The study of serum as a biological matrix has been identified as a new landmark initiative in search of a useful biomarker to diagnose oral cancer. Most oral cancers are oral squamous cell carcinoma. Using serum for early oral cancer detection in the search for new clinical markers is a promising approach because of its noninvasive sampling and easy collection method. Identification of this serum biomarker could help to screen patients at risk, predict disease outcome and effectively contribute to planning treatment strategies. Biomarker use for diagnosis and prognosis is supported by clinical and scientific evidence is relevant. Nevertheless, after selecting a certain biomarker, monitoring protocols should be established in oral and maxillofacial surgeons teams so as we have a correct understanding of biological values.

Keywords: Serum biomarkers, oral cancer, diagnosis, prognosis.

Introduction

Oral cancer is one of the most common malignancies.[1] Oral cancer is the sixth most common malignancy worldwide. Approximately, 90% of cancer located in the oral cavity are oral squamous cell carcinoma (OSCC)[1]. Most oral cancers are superficial and easily detected, but deeply located tumors may not be noted until they have grown large and reached an advanced stage. This

malignant neoplasm occurs most commonly in the postero-lateral border and ventral surfaces of the tongue. The second most common location is the floor of the mouth.[2] Due their aggressiveness, oral cancer invades surrounding organs and causes regional or distant metastases.[3] The overall survival rate for oral cancer is considerably lower than that of other cancers due to metastasis and recurrence.[4]

According to GLOBOCAN 2018, there are approximately 149.102 new cases and 89.377 deaths due to oral cancer both in all ages and sexes, and the fifth most common cancer that occurs in the Southeast Asian countries.[2] In the United States, the 5-year Oral Squamous Cell

Carcinoma (OSCC) survival rate is 60%, but a higher incidence and lower survival rates have been reported in some South Asian countries.[3] Oral cancer can occur anywhere in the mouth, lowers lip, mouth floor and the most affected sites are the tongues. Most oral cancers are squamous cell carcinomas. It is estimated that more of 90% of all oral neoplasms are OSCC.[4] Tobacco consumption, alcohol, and human papillomavirus infections are major risk factors for oral cancer. Prevention of oral cancer is critically important and can be accomplished by understanding the cause, effect and modifying associated risks, recognizing and controlling precancerous lesions, establishing the earliest possible diagnosis and administering timely and appropriate therapy and effectively managing the complications of treatment.[5,6] The key challenge to reduce the mortality and morbidity of oral cancer is to develop strategies to identify and detect oral cancer. A critical factor in the lack of prognostic improvement is the fact that a significant proportion of cancers initially are asymptomatic lesions and are not diagnosed or treated until they reach an advanced stage. Detection of the OSCC is currently based on the expert clinical examination and histological analysis of suspicious areas, but it may be undetectable in hidden sites. Therefore, sensitive and specific biomarkers for OSCC may be helpful in screening high-risk patients.[7,8]

Epidemiological studies showed variable incidences depending on the region. Incidence is particularly high in India, Brazil, Pakistan and France. Tobacco (particularly chewing) and alcohol have been large demonstrated as risk factors in the development of oral cancer.[5] Additionally, these risk factors have been showed a synergist effect when they have been combined.[6] The determination of serum biomarkers is accepted as a valuable tool for diagnosis, finding therapeutic targets and prognosis in different kind of tumors.[7] Literature has been showed overexpression in serum of some proteins[8], p53 antibody[9], and VEGF[8] as an indicator of oral cancer. Several biomarkers have been proposed, but they are sometimes variable with race, lifestyle, and carcinogen exposure. The global knowledge of all of them would lead to the improvement of diagnostic and prognosis methods of tumor recurrence and metastasis to assess changes in oral lesions.[3]

Serum biomarkers are defined as substances changing quantitatively in the serum during tumor development. Classically, a marker is synthesized by the tumor and released into circulation or expressed at the cell surface in large quantity by malignant cells.[10] These markers can been used in the prognosis of tumor recurrence or metastasis[11] because the development of the malignant tumor changing their concentrations.[7] The tumor marker/substance can be classified as tumor specific and tumor associated. Tumor specific substance are considered as a direct result of oncogenesis, while tumor associated marker are various proteins, enzymes, hormones and immunoglobulins which occur in the blood

and are mediated by the tumor itself or by the influence of the tumor on the involved tissues.[12] Repeating test of serum biomarker allows following treatment and assessing response to treatment, monitoring tumor progression and metastasis.[13] However, there are not yet unified para- meters to determinate which biomarker would be useful for oral cancer.

The main focus of this systematic review is to analyze the utility of serum biomarkers in the diagnosis and prognosis of oral cancer.

Search strategy and selection criteria

A systematic, computerized database search was conducted using the National Center for Biotechnology Information (NCBI) to search PubMed. The search was conducted using the following MeSH terms:" mouth neoplasms" AND marker AND (serum OR blood) [Mesh].

For the initial selection, article titles and/or abstracts were analyzed and the following inclusion criteria were observed: studies published in English in the last ten years; studies of human beings; specific studies that analyzed a certain biomarker in serum; and study type: cases and controls studies, prospective and/or retrospective clinical studies. The exclusion criteria were: studies which do not mention the measurement method, studies that analyses markers in serum.

Current State of Oral Squamous Cell Carcinoma Specific Serum Biomarkers

Serum can be used as indicators of disease. According to the World Health Organization (WHO), the definition of a biomarker is following "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease".[14] A biomarker must be verified and validated before it can be used in a clinical assay and have any impact or application in health risk assessment. Scientists are working on serum biomarkers around the world, in order to indicate, prognosis and diagnose various conditions. They would serve as a non-invasive, painless, rapidly collected method, easily and economically performed by minimally trained personnel.[15,16]

Over the last decade, serum has attracted attention as a method for the detection of oral diseases like dental caries, gingivitis, periodontitis, Bechet disease, oral squamous cell carcinoma, cleft palate and lips, salivary gland diseases, oral leukoplakia and systematic diseases such as breast cancer, diabetes, human immune deficiency virus (HIV). The clinical realization of any biomarker used for health risk assessment or prognosis.[17,18]

Analysis of these markers in oral secretions and other accessible specimens may allow for early detection and screening of individuals at high risk for cancer. Depending on the location of the tumour, one may not be able to access and swab the tumor bed easily. Thus, the use of serum may show unique advantages over the use of exfoliated cells. Although the use of serum biomarkers did not identify the site from which the tumour originated, they were able to identify patients at risk.[13,14]

In conventional clinical procedures, the diagnosis of OSCC, especially at an early stage, relies on the experience of the dentist and pathologist. It is essential to recognize that early diagnosis is a prerequisite for improving the cure rate and promoting the quality of life of OSCC patients. Patients at an early stage have a better survival rate with single surgical therapy.

In contrast, patients at an advanced stage have to undergo multidisciplinary synthetic and sequential treatment, which gives rise to longstanding pain and mental trauma. Moreover, less than half of them survive and they have a poor quality of life.[11] Existing therapy

for OSCC patients is based on traditional stage-predicting guides mostly used are the TNM criteria [tumour, node, metastasis] and histological grading. The development of particular saliva biomarkers and their associated could facilitate point of care diagnostics.[19]

Table 1: shows various serum biomarkers identified in studies.

1. Adiponectine	Adiponectin is an adipokine produced predominantly by Adipocytes. It functions as an anti-diabetic, anti- atherogenic, anti-inflammatory and anti-angiogenic hormone.	Associated biomarker
2. Annexin A1 mRNA	Annexin A1, an anti-inflammatory and calcium-dependent protein of the superfamily of annexins, may have important regulatory roles in tumor development and progression	Associatedbiomarker
3. CRP	C-Reactive Protein (CRP)is a functional analogue to immunoglobulin G, which synthesis by pro-inflammatory cytokines	Associatedbiomarker
4. Cycling D1	Cyclin D1, the product of the CCND1 gene located on chromosome 11q13	Associatedbiomarker
5. DCR3	Decoy receptor 3. DcR3 functions as a death decoy inhibiting apoptosis mediated by the tumor necrosis factor receptor family.	Specific biomarker
6. GDF 15	Growth-differentiation factor 15 (GDF 15) is involved in tumor pathogenesis. Its expression is increased in many types of cancers.	Specific biomarker
7. Hb	Heamoglobin level mediates tumor response to radiation through the delivery of oxygen to the tumor.	Associatedbiomarker
8. TNFa	Tumor necrosis factor-alpha	Specific biomarker
9. IL6	Interleukin 6. Proinflammatory cytokines	Associated biomarker
10. MiCB	Major histocompatibility complex class I-related chain A/B (MICA/B), a ligand of natural killer group 2D (NKG2D) immunoreceptors.	Associated biomarker
11. MMP-3	Matrix metalloproteinase-3 is a member of MMP family which is capable to degrade a broad range of substrates. MMP-3 reveals pathological expression in many tumors.	Associated biomarker
12. MMP-9	Matrix metalloproteinase-9. Potent factors involved in angiogenesis. Under physiological conditions MMP are capable of degrading extracellular matrix and basement membrane components.	Associated biomarker
13. Nitric Oxide	Nitric Oxide concentration plays an essential role in the process of lipid peroxidation.	Associated biomarker
14. PDEs	Phosphodiesterases have a fundamental role in the transduction of the intracellular signals and tumor growth by influencing angiogenesis.	Associated biomarker
15. PlGF	Placenta growth factor is a member of the vascular endothelial growth	Associated

	factor (VEGF) family.PlGF stimulates proliferation, differentiation, and survival of endothelial cells.	biomarker
16. SCCAg	Squamous cell carcinoma antigen. A tumor-associated protein, an adjunct in the diagnosis of the disease (associated biomarker)	Specific biomarker
17. Serum fucose	L-fucose, is a monosaccharides that compounds serum glycoproteins.	Associated biomarker
18. Serum Leptin	Leptin is a protein of cytokine family, related to body weight metabolism and reproductive function	Associated biomarker
19. Sialic acid levels	Siacilic acids are acetylated derivatives of neuramic acid. They are attached to the non-reduced residue of carbohydrate chains of glycoproteins and glycolipids.	Associated biomarker
20. Th17 cells	TH17 cells are the third subset of CD4+ T helper cells (T lymphocytes that belong to the CD4+ subset). Important role in inflammation.	Associatedbiomarker
21. TPA	Tissue polypeptide Antigen. TPA is one of the most frequently used cytokine evaluated as a serum marker	Associatedbiomarker
22. VEGF	Vascular endothelial growth factor. VEGF is a multifunctional cytokine that plays a pivotal role in angiogenesis. (induction of angiogenesis in tumour growth)	Associatedbiomarker
23. Visfatin/pre-bcell Colony enhancing factor	Nicotiamide phosphoribosyl transferase or pre-B cell colony enhancing factor, is a pro-inflammatory cytokine. It regulates growth, apoptosis, and angiogenesis.	Associatedbiomarker

Discussion

Biomarkers have been wide accepted in other disciplines but there is no consensus for their use in oral malignancies. Despite recent advances in surgical, radiotherapy, and chemotherapy treatment protocols, the survival of patients with OSCC still lacks significant improvement. This unsatisfactory treatment may be explained by the fact that OSCCs frequently present with extensive local invasion and advanced stages.[15,16] That makes necessary the development of new tools for the diagnosis and prognosis.

Tumor growth, invasion and metastasis are multiple step processes in which many genes and molecules are involved. The molecular biology of OSCC is complex and OSCC develops from the dysfunction of several interrelated pathways.[17]

Our literature review shows how several authors in the last years have looked for the best marker for diagnose oral cancer at earlier stages, establish the prognosis and increase the survival of patients with this disease – Adiponectine. Adiponectin is an adipokine produced predominantly by adipocytes that circulates abundantly in plasma and functions as an anti- diabetic, anti-atherogenic, anti-inflammatory and anti-angiogenic hormone .[18]

In a study by Guo *et al.* [20] showed that serum adiponectin level was reduced in tongue squamous cell carcinoma (TSCC), and inversely associated with histological grade and lymph node metastasis of TSCC. They suggested

that hypoadiponectinemia is correlated with histopathologic features of TSCC, and could be a new biomarker of aggressive phenotype in TSCC. But they still reckon the underlying mechanisms of adiponectin in potential cancer suppression are not fully elucidated - Annexin A1 mRNA. Annexin A1 an anti-inflammatory and calcium-dependent protein of the superfamily of annexins, may have important regulatory roles in tumor development and progression.[20] The Annexin A1 gene expression was investigated in peripheral blood samples of patients with oral squamous cell carcinoma and control subjects and Annexin A1 mRNA was expressed in all of them. Comparative analysis of OSCC blood patients showed significantly lower Annexin A1 expression when compared to blood sample of control individuals. However, there were no significant differences between patients' subgroups in relation to smoking, drinking, recurrence, TNM staging histopathological grading. This present study revealed the Annexin mRNA as new possible transcript biomarker for early detection of OSCC in the peripheral blood of patients.

Conclusion

Recent research has identified a multitude of potential markers that have a significant role in the surveillance of oral squamous cell carcinoma. In this review, despite the inherent limitations, we identified several potential biomarkers of particular interest that appear to carry prognostic significance. Sensitive technology is needed to detect biomarkers in low quantities to be a useful diagnostic medium. Furthermore, serum biomarkers can be used between biopsies to assist in monitoring the disease status of OSCC patients. Taking together all these aspects, it can be concluded that there are abundant possibilities in saliva diagnostics already at present, and the immediate future of this area is even more promising

References

1. Faria PC, Sena AA, Nascimento R, Carvalho WJ, Loyola AM, Sil- va SJ. Expression of annexin A1 mRNA in peripheral blood from oral squamous cell carcinoma patients. Oral Oncol. 2010;46: 25-30
2. Tanaka T, Ishigamori R. Understanding carcinogenesis for fighting oral cancer. J Oncol. 2011;2011: 603740.
3. Mishra R. Biomarkers of oral premalignant epithelial lesions for clinical application. Oral Oncol. 2012;48: 578-84.
4. Kademani D. Oral cancer. Mayo Clin Proc. 2007;82: 878-87.
5. Gupta PC, Murti PR, Bhonsle RB, Mehta FS, Pindborg JJ. Effect of cessation of tobacco use on the incidence of oral mucosal lesions in a 10-yr follow-up study of 12,212 users. Oral Dis. 1995;1: 54-8.
6. Bundgaard T, Bentzen SM, Wildt J. The prognostic effect of tobacco and alcohol consumption in intra-oral squamous cell carcinoma. Eur J Cancer B Oral Oncol. 1994;30B:323-8.
7. Sawant SS, Zingde SM, Vaidya MM. Cytokeratin fragments in the serum: Their utility for the management of oral cancer. Oral Oncol. 2008;44: 722-32.
8. Bijian K, Mlynarek AM, Balys RL, Jie S, Xu Y, Hier MP, et al. Serum proteomic approach for the identification of serum biomarkers contributed by oral squamous cell carcinoma and host tissue microen- vironment. J Proteome Res. 2009;8: 2173-85.
9. Cordes C, Von Lingen J, Gorogh T, Ambrosch P, Gottschlich S, Hoffmann M. Molecular and immunological aspects of p53 and p53-

autoantibodies in head and neck squamous cell carcinoma. Oncol Rep. 2009;22: 1299-303.

10. Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. Cancer. 1977;40: 1621-8.
11. Hoffmann-Fazel A, Hoffmann M, Gottschlich S, Maass JD, Rudert H, Maune S. Cyfra 21-1 in diagnosis of distant metastases of head and neck carcinoma. Anticancer Res. 2003;23: 917-20.
12. Joshi M, Patil R. Estimation and comparative study of serum total sialic acid levels as tumor markers in oral cancer and precancer. J Can- cer Res Ther. 2010;6: 263-6.
13. Doweck I, Barak M, Uri N, Greenberg E. The prognostic value of the tumour marker cyfra 21- 1 in carcinoma of head and neck and its role in early detection of recurrent disease. Br J Cancer. 2000;83: 1696- 701.
14. Clementini M, Morlupi A, Agrestini C, Barlattani A. Immediate versus delayed positioning of dental implants in guided bone regene- ration or onlay graft regenerated areas: A systematic review. Int J Oral Maxillofac Surg. 2013;42: 643-50.
15. Chang KP, Wu CC, Fang KH, Tsai CY, Chang YL, Liu SC, et al. Serum levels of chemokine (C-X-C motif) ligand 9 (CXCL9) are asso- ciated with tumor progression and treatment outcome in patients with oral cavity squamous cell carcinoma. Oral Oncol. 2013;49: 802-7.
16. Chang KP, Chang YT, Liao CT, Yen TC, Chen IH, Chang YL. Prog- nostic cytokine markers in peripheral blood for oral cavity squamous cell carcinoma identified by multiplexed immunobead-based profiling. Clin Chim Acta. 2011;412: 980-7.
17. Inal E, Laçin M, Asal K, Ceylan A, Köybaşioğlu A, Ileri F, et al. The significance of ferritin, lipid-associated sialic acid, CEA, squa- mous cell carcinoma (SCC) antigen, and CYFRA 21- 1 levels in SCC of the head and neck. Kulak Burun Bogaz Ihtis Derg. 2004;12: 23-30.
18. Madsen EL, Rissanen A, Bruun JM, Skogstrand K, Tonstad S, Hougaard DM, et al. Weight loss larger than 10% is needed for ge- neral improvement of levels of circulating adiponectin and markers of inflammation in obese subjects: A 3-year weight loss study. Eur J Endocrinol.2008;158: 179-87.
19. Perretti M, Flower RJ. Annexin 1 and the biology of the neutrophil. J Leukoc Biol. 2004;76: 25-9.
20. Guo XH, Wang JY, Gao Y, Gao M, Yu GY, Xiang RL, et al. De- creased adiponectin level is associated with aggressive phenotype of tongue squamous cell carcinoma. Cancer Sci. 2013;104: 206-13.