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Biomolecular Markers for Early Diagnosis of Tongue Carcinoma-Review Article

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ABSTRACT

Tongue carcinoma is an aggressive malignant type of tumor that has a poor prognosis. Since the etiological factors of the condition are largely unknown, the study of biomolecular markers is helpful for the early diagnosis of the condition and the evaluation of prognostic factors, and the selection of treatment. Based on the literature review, IL-6, IL-8, and HPV have been found to assist in an early diagnosis. High expression of vimentin, HIF-1α, MALAT-1, and SOX-2 and low E-cadherin expression are associated with low survival rates due to tongue carcinoma due to metastasis progression. We present a mini-review of the biomolecular markers that help to detect tongue carcinoma.

Keywords: Biomolecular markers, Metastasis, Progression, Tongue carcinoma

INTRODUCTION

The head and neck cancer incidence is rapidly rising in the world and the United States, especially for tongue and oropharyngeal carcinoma [1]. Individuals under 50 years of age are primarily at risk of oral cancer, making it a significant cause of concern due to its low five-year survival rates [1-3]. Tongue carcinoma is anatomically defined as cancer located within the anterior two-thirds region of the tongue that majorly consists of mutations within the squamous cells [2,3]. It has been acknowledged to have the worst prognosis rate among other oral SCC types because of its silent pathogenesis without alarming signs or symptoms. The specific etiological factors for the Squamous Cell Carcinoma (SCC) of the tongue remain unknown with broad risk factors such as tobacco smoking, chewing of betel quid, alcohol, poor nutrition, oral thrush, radiation, viruses, ethnicity, familial and genetic predisposition, immunosuppression, ethnicity, genetic and familial predisposition, syphilis being the significant risk factors [1-9].

The knowledge of risk factors for oral cancer is insufficient since it assists in an early diagnosis until SCC symptoms have already manifested, although it does help identify patients at elevated risk [2,3]. To overcome these drawbacks, the study of biomarkers associated with SCC of the tongue is crucial since it reveals the genetic and epigenetic patterns, including gene inactivation or amplification processes. This helps identify the primary alterations that can lead to derangements in the molecular pathways that alter normal cell behaviors leading to mutations [10-12]. This enables an early diagnosis of tongue cancer, which is instrumental for improving the quality of life of patients as well as their five-year survival rates [3]. This review aims to provide a detailed analysis of the biomarkers associated with tongue cancer to institute an early preventive approach in clinical practice.

LITERATURE REVIEW

Biomarkers in Tongue Carcinoma

Several types of biomarkers have been discussed in the literature for facilitating an early diagnosis of oral SCC, such as tongue cancer. A generalized over-expression of Epidermal Growth Factor Receptor (EGFR) has been noted along with other growth factors such as vascular endothelial growth factors [12,13]. Factors responsible for cell motility and apoptosis were generally under-expressed, leading to the uninhibited mutated cells [10]. Wnt-5a, fibronectin, and N-cadherin are generally up-regulated in the cancerous areas at the protein level, whereas E-cadherin, the catenins, claudin-7, and connexin are downregulated. Besides predicting the early stages of cancer, the detection of biomarkers also facilitates an analysis of the cancer stage, with membrane proteins such as Glucose Transporter (GLUT-1) being

closely related to the nodal stage of metastasis of tongue cancer [10]. This review will elaborate on the biological markers specific to tongue carcinoma while closing the gap in existing literature where more generalized factors responsible for oral SCC have been identified with a lack of particular attention to tongue SCC.

Salivary Biomarkers for Tongue Carcinoma

The study of salivary biomarkers entails a promising approach for the early diagnosis of SCC of the tongue through non-invasive methods and easy collection processes [12]. Salivary transferrin levels strongly correlate with the stage, size, and progression of cancer, with migration inhibitory factor-related protein (MRP-14) being elevated in cases of tongue carcinoma [14,15]. The cluster of differentiation factor 34 is a potential salivary biomarker that identifies the recurrence of SCC and can be crucial for diagnosing patients who have previously been diagnosed with other types of oral SCC [11]. Thus, salivary biomarkers can be used to assess the stage and size of the tumor to assess its prognosis in new and recurring cases.

Genomic Biomarkers for Tongue Carcinoma

The study of genomic biomarkers is used for the early diagnosis of tongue carcinoma through fluid or salivary samples. The only difference between genomic and salivary biomarkers is that other techniques such as proteomics, epigenomics, transcriptomics, glycomics, and metabolomics can understand the pathogenesis, signaling pathways, and other characteristics of the tumorous cells through salivary samples being limited in genomics [15-19]. Integrin α3, β4, αvβ3 are other important genomic biomarkers that have been useful for evaluating the risk of regional and hematogenous spread in malignant cases of SCC [16,20].

Genomic biomarkers such as micro ribonucleic acid (miRNAs) are negative regulators of gene expression and have been associated with chemoresistance to cisplatin in cases of SCC of the tongue. miR-214 and -23a are the chemoresistant types of tongue carcinoma, whereas miR-21 is a sensitive type [12]. Besides genomics, omics-based studies, as elaborated above, are helpful for the differentiation of tongue carcinoma from the stage of precancerous lesions such as Oral Submucous Fibrosis (OSMF), leukoplakia, and oral lichen planus and erythroplakia [19]. Hence, the genomic analysis will facilitate timely diagnosis of SCC metastatic progression and help determine suitable treatment agents in resistant cases, thereby having an essential role in treatment.

Viral Biomarkers for Tongue Carcinoma

Viral infections due to Human Papilloma Virus infections (HPV) and Epstein-Barr Virus (EBV) have commonly been associated with the etiopathology of tongue cancer, especially in carcinoma of the base and mobile regions of the tongue. HPV subtype-16 and 18 have been identified as biomarkers for these locations and are estimated to increase carcinoma risk by 3 to 5 times. HPV has been isolated in 40% of the cases of mobile and base tongue carcinoma and is said to be an important biomarker for young adults because of the possibility of its transmission through cunnilingus. EBV, which is transmitted through saliva, is not significantly associated with an increased risk of tongue cancer and is not an important biomarker in most cases [10]. Thus, viral biomarkers are used for the early diagnosis of tongue cancer.

Practical Utilization of the Knowledge of Biomarkers of Tongue Carcinoma

Biomarkers are helpful from the stages of detection of the risk of tongue cancer to its actual diagnosis and assessment of grade or severity of metastasis depending upon the choice of biomarkers. Among the many biomarkers for tongue carcinoma that have been discussed across the various meta-analytical and clinical trial studies that have been published so far, the ten most promising biomarkers for practical use have been outlined by Hussein et al. According to their research, interleukin-6 (IL-6), IL-8, prolactin, Hypoxia-Inducible Factor α (HIF-1α), SRY (Sex-Determining Region Y) Box Transcription Factor 2 (SOX2), E-cadherin, vimentin, Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1), Tumor Protein 53 (TP53), and NOTCH1 are the most eminent biomarkers for tongue carcinoma with the former three identified in liquid samples and the remaining seven as tissue biopsies [21].

IL-6 and IL-8 are elevated during tongue cancer and become evident at the time of progression of patients from a high-risk stage to having an actual neoplasm. IL-6 has been found to have excellent sensitivity for analysis. Thus, the combination of the two is used for early detection in new or recurring cases of tongue SCC. Prolactin is relevant for assessing the prognostic factors for the patient, and it is also elevated in positive cases [21].

The increased expression of HIF-1α and SOX-2 is also associated with a poor prognosis of tongue SCC 16. SOX-2 is a biomarker of embryonic stem cell pluripotency and is detected in 62% of the patients with large size of the tumor [22]. On the other hand, E-cadherin depicts the risk of metastasis, with its lower expression being associated with delayed neck metastasis [23]. Downregulation of E-cadherin is associated with over-expression of other biomarkers like SIP1, which has been closely interlinked with delayed metastasis of tongue cancer, explaining the mechanism of this effect [23]. High vimentin expression is associated with poor differentiation of cells and metastasis to near and distant lymph nodes. It is directly linked to poor survival rates in patients and lower disease-specific survival due to higher levels of differentiation of tumorous cells compared with the normal tissue [24]. MALAT-1 is also peculiarly expressed at high levels in patients with lymph node metastasis as detected with the help of PCR techniques in patients with SCC of the tongue [25]. Finally, TP-53 and NOTCH-1 are associated with the pathogenesis of tongue carcinoma and help evaluate the patient's treatment needs. TP-53 has a direct impact on protein function, which leads to pathogenesis [26]. Overall, patients with a high expression of vimentin, HIF-1α, MALAT-1, and SOX-2 and a low expression of E-cadherin will have a poorer overall, cancer-specific and disease-free survival-related prognosis through the involvement of these factors in cancer progression [21-24].

Immunohistochemistry is a common technique used for biomarker analysis that presents a simple and affordable methodology, which can be replicated easily in clinical practice. However, the technique has some limitations, which results in lower validation of its results. Genomic tools such as microassays and the use of Reverse Transcription Polymerase Chain Reaction (RT-PCR) are more reliable tools based on robust quantitative methodologies, which are used more assertively [27]. In addition, new methods based on novel nanomaterials and/or technology providing reliable and also more precise results as compared to RT-PCR for introducing a genomic tool for detection of single nucleotide polymorphisms of DNA molecules resulted in the ultrasensitive detection of cancer [28]. However, it can only be used to assess the patterns of genetic mutations associated with tongue carcinoma, with immunohistochemistry still being needed to analyze molecular biological factors such as proteins. Hence, a combination of these methods is recommended for practical use, with immunohistochemistry being beneficial for the analysis of HIF-1α, SOX2, E-cadherin, and vimentin, and genomic methods can be used for the analysis of other biomarkers such as integrin and miRNA as discussed in the above sections [21]. Besides these two methods, salivary techniques are also used to analyze tongue biomarkers, which have also been elaborated in detail in the former sections.

Limitations of Using Biomarkers for the Diagnosis of Tongue Cancer

Biomarkers serve as potential tools for the early diagnosis and management of tongue SCC helping to make important treatment decisions such as surgical resection of margins or the addition of adjuvant chemo-radiation therapy based on the evaluation of patient prognosis [21-26]. However, the use of biomarkers has certain limitations. Foremost, an increased expression of specific biomarkers such as IL-6 and IL-8 is also observed in various inflammatory states, which can lead to the possibility of a misdiagnosis of cancer that can have severe emotional and psychological impacts for the patient as well his/her family members [21]. This indicates the lack of biomarker-based analysis in reaching a definite or a confirmed diagnosis for the patient, which is one of its drawbacks [29]. Hence, it is imperative to determine the cut-off values for each biomarker for the differentiation of cases of tongue carcinoma at different stages from healthy subjects [21]. It is also eminent that the use of biomarker-based analysis is made in combination with other diagnostic techniques used for the detection of cancer, and the findings of the tests are correlated with the symptomatic profile and history of the patient to rule out the risk of a false positive or a false negative evaluation. Thus, while being a valuable tool for early diagnosis and management of tongue cancer, biomarker analysis has some limitations and must be used to consider the overall clinical situation.

CONCLUSION

Biomarkers assist in the early diagnosis of tongue carcinoma and provide useful treatment insights based on the analysis of the response of cancerous tissue to various types of treatments. Its role has been established for making predictions related to the prognosis of the patient depending upon the size and stage of the tumor as well as the degree of metastasis. Several biomarkers such as vimentin, HIF-1α, MALAT-1, and SOX-2 are elevated in the later stages of the disease and have been associated with poor patient prognosis, including lower overall survival rates and disease-free survival. Genomic or immunohistochemistry methods are used for the process of biomarker analysis, with each of

the techniques having its limitations indicating that clinical decision making related to the choice of methods as well as the accuracy of results must be determined based on the clinical profile of the patient and their previous history.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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