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REVIEW ARTICLE

Biomarkers and common oral cancers: Clinical trial studies

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Summary

Oral cancer (oral squamous cell carcinoma (OSCC)) has been known as the one of the important types of human cancer worldwide. The number of this cancer has been increased in low-income countries and also the therapeutic and diagnostic applications have been improved in recent years.
Many studies show that there is a significant relationship between tissue level changes and molecular level which lead to malignant changes and make an important role in disease progress. Biomarkers are widely categorized as metabolomics, proteomics or genomics. Oncology research and molecular biology studies on biomarkers that involved in oral cancer (OC) focus on identification of pivotal biological markers related to cancer progression, risk assessment, predicting recurrence, screening, showing prognosis, demonstrating metastasis/invasion, and monitoring cancer treatment reactions. The aim of this review is evaluating efficiencies and functions of biomarkers in diagnosis, monitoring, prognosis and therapeutic responses of OCs in the recent decade.

Key words: *biomarkers, oral cancers, OSCC*

Abbreviations: *oral squamous cell carcinoma (OSCC), oral cancer (OC), lysine-specific demethylase (LSD1),Patient-derived tumor xenograft (PDTX), Circulating Immune Complexes(CIC),Polyethylene Glycol 6000(PEG),A disintegrin and metalloprotease , Oral Premalignant lesions (OPL),clusters of intraepithelial inflammatory cells (EIC),Oral leukoplakia (OL),Enhancer of Zeste Homolog 2 (EZH2),Copy number variations (CNVs) ,a1,6-Fucosyltransferase (Fut8), Leucine-rich alpha-2-glycoprotein1 (LRG1), ZengShengPing, a mixture of six medicinal herbs(ZSP), PDZ-binding kinase/T-LAK cell-originated protein kinase (PBK/TOPK), Black raspberries (BRBs), urokinase plasminogen activator(uPA), uPA receptor (uPAR), plasminogen activator inhibitor(PAI)-1, transcription factors (TWIST1, ZEB1 and ZEB2),Parotid gland tumor (PGT),salivary gland carcinoma(SGC), investigator's choice (IC), green tea extract (GTE), World Health Organization (WHO), oral submucous fibrosis (OSF), microRNAs (mRNAs),Photodynamic therapy (PDT), gas chromatography mass spectrometry (GC-MS), polymerase chain reaction (PCR), nuclear magnetic resonance spectroscopy (NMR), high-performance liquid chromatography (HPLC), whole-mouth saliva (WMS),Epidermal Growth Factor Receptor(EGFR), Harvey RasGene (H-Ras), humane microbe identification microarrays (HOMIM), head and neck squamous cell carcinoma (HNSCC)*

Introduction

Oral cancer contains cancers of all parts of the oropharynx [1], oral cavity and lips. OCs has been known as the 15th major cause of death and the 16th most common cancer around the world. Also, the OC incidence (age-adjusted) is one case per 25000 people, with a broad variety that depends on countries, ethnic groups and races, society and economic conditions, gender and age groups [1,2].

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Worldwide, the IARC (International Agency for Research on Cancer) reported OC often occurs individually in lower and middle income countries in about 350000 people, and the OC was the result of approximately 175000 deaths in 2018 from the 350000 people and the prevalence of OC was more than 2-fold in men compared to women. Therapeutic approaches of oral OSCC include surgery, coadjutant therapy (chemotherapy with agents as for instance docetaxel, 5-fluorouracil, paclitaxel, carboplatin, and cisplatin, and radiation therapy (brachytherapy and/or external beam radiation therapy) [3-6], which are known as expensive and extensive harmful alternatives/treatment [4]. Usually, one of the alternatives or combination of the approaches in treated OSCC and the choosing one or combination of treatment are related to the size, location and tumor stages. Also, the selected approach depends on nutritional status, patient comorbidities and tolerance of the therapeutic approach and the desire of patients to deal with treatment [7]. Surgery is the best choice between all alternative approaches in resectable tumors [4,8-11]. PDT comprises three parts: oxygen, light and photosensitizer. The photosensitizer has the selective accumulation feature in infected or abnormal tissues without damaging normal cells. This innovative treatment approach has been adapted successful in various medicine fields, such as gynecology, urology, dermatology, and cancer therapy [12].

Carcinogenesis is one of the complex procedures detected at the genotype and phenotype levels. The progress of cancer is caused by epigenetic and genetic changes accumulation that disarrange the balance between death of cells and cell proliferation [13]. Changes of the molecular level occurring in carcinogenesis include (I) proliferation of cancer cell without any external stimuli, lack of sensitivity to the inhibitor growth signals, (III) avoiding apoptosis mechanisms and/or anti-apoptotic genes activation, (IV) infinite replicative potential, (V) consistent angiogenesis, (VI) metastasis and invasion ability, (VII) instability of genomes, and (VIII) proto-oncogenes conversion due to defects in DNA restore. A study on cancerous tissues has shown that it may detected between the molecular level and changes of tissues which causes malignancy and play an important role in disease development [14]. Biomarkers are also defined by the National Cancer Institute as molecules found in body fluids, blood, or tissues detected in normal and unusual procedures of several diseases such as OC [15]. These biological molecules have pivotal role in diagnosing absence or presence of disorder. Changes of tissues in disorder process may be classified as metabolomics, proteomics or genomics expressions. Biomarkers generally derive from combination of the serum, plasma, blood, body secretions, or excretions-involved peptides, proteins, nucleic acids, lipids, antibodies, carbohydrates, metabolites, and enzymatic changes. Sampling body fluids for evaluating biomarker may be acquired noninvasively or minimally invasive methods [16]. DNA/RNA derived from saliva, exfoliative oral cells, cells of buccal smear or blood are important in determining cancers'diagnosis, control the disorder development, or perform as prognostic signs in therapeutic approaches [17].

The aim of this review was the evaluation of efficiencies and functions monitoring, prognosis and therapeutic responses of OCs.

Oral cancer

Oral squamous cell carcinoma

More than 90% of OCs include OSCC which has appeared as a worldwide health issue caused by high prevalence and death. OSCCs are crucially correlated with using alcohol and tobacco products, periodontal disorders, genetic alterations, exposure to papillomaviruses in high-risk humans, and poor nutrition [18].

Melanoma

Melanoma incidence is growing faster than the other seven most common malignancies annually despite public health attempts to suppress ultraviolet radiation and protect against sun exposure. Recently, melanoma has been known as the 6th most often identified cancer in the United State of America [19]. Melanoma includes 4% of skin cancer patients accountable for 80% of death-related skin cancers [20]. The presence of atypical (dysplastic) nevi is the major risk factor for melanoma with abundant melanoma clinical features such as border abnormality, larger size (usually ≥ 0.6 cm) and color changes [21,22].

Salivary gland carcinoma

Salivary gland carcinoma (SGC) is a scarce cancer responsible for 0.2-0.3 % of total malignancies and about 8% of neck and head cancers [23,24]. Advanced SGC are especially unresponsive in traditional chemotherapies. SGC overwhelmed broad-spectrum of histologic types with much more variety than the other [25]. Biological behaviors vary considerably between different histologic types, but the surgical resection is the commonly approved therapeutic approach for all kinds and also radiotherapy after operation is generally accomplished for malignancies with high-

grade [25,26]. Various chemotherapies and therapies based on molecular targeting have been examined as systemic therapies for SGC but the standard regimen has not been fixed yet [25,27].

Parotid gland tumor

Recently, it seems parotid gland tumors are a remarkably crucial challenge in medicine, often because of significant rise-up in the prevalence [28]. The surgery of the parotid gland is challenging, despite surgery processes developed technically from 70 years ago when the procedures had been widely known [29-31]. Iatrogenic injury of nerve total paralysis or partial paralysis of the face mimic muscles in each side is related to damages of a branch of nerve or the main trunk [32].

Oral submucous fibrosis

OSF is a chronic inflammatory disorder, also known as a premalignant condition by WHO [33]. Furthermore, OSF is one of the collagen metabolism disease. The prevalence rate of OSF progression is crucially correlated with fibroblasts (especially myofibrolasts) [34,35]. OSF usually appear in people who are accustomed to chewing betel quid. About 600 million people mostly in the southeast and south parts of Asia chew different types of betel quid [36] and the incidence of OSF is around 6 to 10% among this group of people [34,35].

Oral premalignant lesions

OC is often caused by OPLs with an overall 2 - 3% risk for progression into cancer [37]. Risk of developing cancer increases about 17% during 8 years for high-risk OPLs or dysplastic [38]. OPLs cancer risks generally expand in correlation with proliferative verrucous hyperplasia and erythroleukoplakia (erythroplasia), early chromosomal alterations (17p, 9p, and 3p) [39-41], polysomy, no smoking history [42], and p16INK4a inactivation [43].

Biomarkers

All biomarkers

Biomarkers are generally used as signs in the evaluation of the patient in various clinical backgrounds. Also, biomarkers are utilized for measuring risks of diseases, occult primary malignancy screening, determining any type of cancers from another, distinguishing prognosis, displayed as monitoring, screening/predictors disorder situation. In addition, biomarkers assessment are usually used for identifying response/development of treatment approaches. Identification of OC risk progression is useful to manage the appropriate strategies for reducing the risk and improvement of screening. These strategies are much more effective if used for high-risk groups than widespread applications for the entire patients [44,45]. Saliva

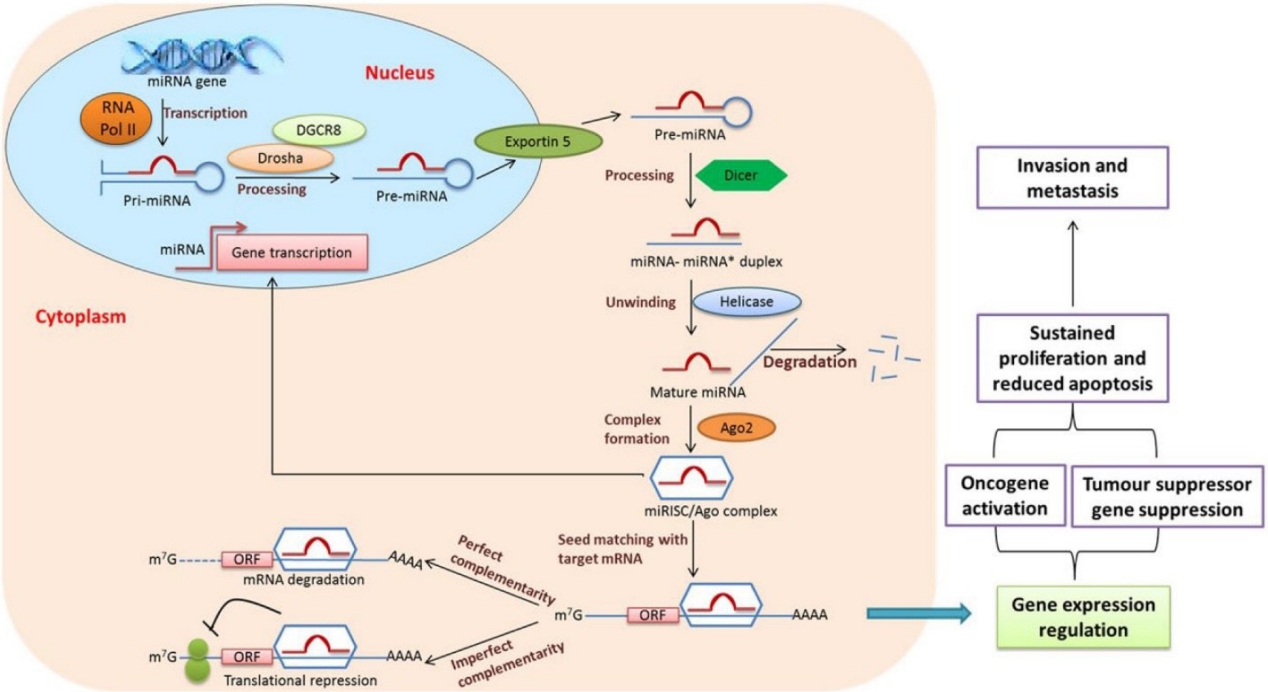

Figure 1. Diagram demonstration of miRNA function and biogenesis [47].

of mouth includes peptides, proteins, electrolytes, RNAs, genes, organic and inorganic salts (by salivary glands), mucosal transudates and fluids of gingival crevicular [46]. Several findings have shown the changed expression of microRNAs (mRNAs/miRs) in OC recently. Different mRNAs play key role in tumorigenesis and mRNA expression level is related to clinical-pathological factors while it is also important in diagnosis and prognosis in OC (Figure 1) [47].

Methodologies of identifying oral cancer biomarkers

Biomarker assessment has a promising effect in early diagnosis that is derived from biological fluids such as saliva, urine and blood. Using saliva fluids displayed potential efficacy in the early detection of malignancy as new clinical markers due to the noninvasive sampling and simple collecting methods. Biomarkers are biological signatures that show the process of pathological and pharmacological response to therapeutic approaches which can give helpful hand for disease diagnosis and prognosis [48]. These markers are detected by different techniques which are based on molecular techniques such as PCR, high-throughput sequencing, DNA and gene expression arrays, ribonucleoprotein immunoprecipitation-gene chip, restricted fragment length polymorphism, mass spectroscopy, NMR, cross-linking immune-precipitation, liquid chromatography, immunohistochemistry, and enzyme assays [44]. Furthermore, these techniques can be effective in the detection of OC (especially OSCC) [49]. Also, some techniques such as GC-MS, NMR and HPLC are used for metabolic evaluations that are useful in OSCC diagnosis [45,50]. Similarly, in the identification of salivary microbiota, methods of salivary microbiome investigation such as PCR, oligonucleotide microarray (based on 16S rRNA), HOMIM, and bacterial microarrays are used [46].

Screening, Treatment and Prognosis

In patients with negative OC results of histological and clinical assessment and healthy people, biomarkers are also known as screening factors for malignancy. OC early diagnosis and screening are effective and important in strategies that are reducing risks. Changing lifestyle, cessation of habits and malignancy prevention through the prophylactic approaches are other strategies increasing patient's survival. Also, these biological markers are generally used in post-therapeutic approaches (chemotherapy, radiation therapy or surgery) of OC patients as determining factors in recurrent potential and the prognosis. In addition, biomarkers play crucial role in distinguishing treatment targets and evaluation of therapeutic efficacy. Biomarkers that detect germ-line mutations are remarkably pivotal in prognosticating risk of OC progression, and which possibly have side effects due to the specialized cancer treatment. Risk of malignancy, apoptosis and cell cycle are also linked to H-Ras , polymorphism in p73/53, CCND1 and MDM2 [51]. In patients who receive treatments for malignancy metastases, biomarkers are an important tool in determining invasion, monitoring responses of therapeutic approaches and metastasis. In 2014, Huang et al studies have shown potential of GIT1 and miRNA-459-51-5p in OSCC tissues as helpful biomarkers for phenotypes of metastasis and invasion. Also, they found that miRNA-491-51-5p and GIT1 expression levels are associated inversely in OSCC. These findings also revealed that miRNA-491-51-5p and GIT1 biomarkers also act as intervention targets and prognostic markers in OSCC metastasis [52].

Recurrence

Distinguishing the potential of recurrent cancer in patients who are treated by adjuvant therapy is another advantage of using biomarkers. In 2013 Sulzyc-Bielicka et al have found that colorectal malignancy patients with high expression of thymidylate synthase gene showed significantly great risk of OC early recurrence in post-treatment (receive 5-fluorouracil as adjuvant) duration [53]. Evaluation of EGFR in third phase clinical studies of HNSCC revealed that biomarkers assessment had a vital influence in OSCC treatment examination for evaluating toxicity and effectiveness of adjuvant therapies [54]. Some importance of clinical OC biomarkers are summarized in Table 1.

Future directions

Certainly, distinguishing markers possibility to diagnose primary tumor of oral cavity or recurrence, particularly if it happened early, many lives of patients can be saved. Investigated biomarkers indicate OC risk while easy sampling comprises all patients who have genetic risk (family history or gene predisposition) or environmental risks (smoking, using alcohol, etc.). Nowadays, the major benefit of immunohistochemical biomarkers evaluation is at the early stage of dysplastia. Using an entire panel that display cancer stem cells existence may be essential in the early detection of OC. Also, administration of Cetuximab (anti-EGFR-specific chimeric monoclonal antibody) and Nivolumab (PD-1 receptor antibody inhibitor) as molecular targeted

Table 1. Importance of clinical OC biomarkers

Type	*Method*	*Outcomes*	*Ref/Year*
Clinical Trial Studies			
Melatonin	Evaluation of anticancer effect of using LSD1- overexpressing and investigation of mechanism of melatonin in OSCC with lymphatic metastases (PDTX models) Examining LSD1 overexpression in OSCC with immunohistochemistry tissue arrays	The melatonin beneficial effects in reducing OC cell proliferation are correlated with LSD1 expression reduction (in vivo and in vitro)	[56]/2017
Ras/MEK/ERK pathway activation	Evaluation of Trametinib in patients with Stage II–IV OCSCC prior to surgery (2mg/day for 7days). Immunohistochemistry assessment of ERK1/2 and CD44 in primary tumor samples. Clinical tumor and metabolic activity maximum changes. Investigation of SUVmax (Standardized Uptake Values) by F-18 (fluorodeoxyglucose positron emission tomography/computed tomography), in tumor down staging. Evaluation of drug-related side effects and wound/surgical complications.	Trametinib reduce activation of Ras/MEK/ERK pathway significantly in responses of metabolic tumor in OSCC patients.	[57]/2017
The salivary proteases	Assessment of salivary protease range in OSCC, chronic periodontitis, and oral masses by human protease array kits, western blot, immunofluorescence, and enzyme-linked immunosorbent assay	Analysis of the salivary protease range may be a cost-effective and innovative Enhances in kallikrein 5, ADAM9, and cathepsin V may be beneficial biomarkers in the OSCC diagnosis and screening.	[58]/ 2019
Circulating miRNAs (involving miR-26a, miR-21, miR-223, and miR-126)	Investigation of circulating changes by ultra-sensitive genome-wide miRNA array in OC patients and healthy individuals	miR-223 suppresses tumors by inducing apoptosis and cell proliferation and inhibiting	[59]/2016
DeltaNp63	Evaluation of deltaNp63 expression in induced-OPL patients in comparison with retinyl palmitate alone or plus beta-carotene by immunohistochemistry analysis Investigation of the relation between deltaNp63 expression and other risk factors for OC progression.	Podoplanin, deltaNp63, and EIC may be utilized as identification biomarkers in OPL patients with significant risk of OC	[60]/2009
EZH2	Evaluating EZH2 expression in OLs (oral lesions) in OSCC patients. Relation between EZH2 expression with clinical results and clinicopathologic parameters. Determination of EZH2 role on cell cycle dependent/independent growth, and invasion in OL	EZH2 has a vital role in OL malignant transformation. As a biomarker in estimating OSCC development in OL patients	[61]/2011
CNV of genetic abnormalities	Examination of chromosomal loci and CNVs frequencies by Taqman copy number assays in OLs patient with later development of OC	Genetic abnormalities of the precancer show the risk progression which cannot be determined by recent histopathologic diagnosis	[62]/2016
mRNA levels of FUT8 and core-fucosylated glycoprotein	Evaluating data after affinity chromatography and In-gel digestion of proteins separated by SDS-PAGE for MS analysis (mass spectrometry) and LC-MS (Liquid chromatography–mass spectrometry).	The LRG1/total protein ratio was enhanced while LRG1 levels were not found in plasma to compare between the plasma of OC patients and normal groups	[63]/2019

Continued on the next page

Type	*Method*	*Outcomes*	*Ref/Year*
IL-8 and IL-6	Serum and saliva univariate and multivariate analyses of OC patients and control cases by using ELISA kits.	Salivary IL-6 as a probable prognostic biomarker.	[64]/2015
ZSP	Histological investigation of DMBA (7, 12 Dimethylbenz[a] anthracene) induced OC in hamster model in 4NQO (Nitroquinoline 1-oxide) –induced oro esophageal cancer in mice model. Clinical evaluation of ZSP (3.6 gr per day) in OPL patients	Using ZSP substantially decreased the tumors number, the volume of tumors, and the prevalence of tongue SCC, and slightly decreased the esophageal cancer incidence	[65]/2010
PBK,TOPK	Investigation of the correlation between expression of PBK/TOPK and clinicopathological characteristics in OC patients	High expression of PBK/TOPK, either alone or in subgroups related to clinicopathological characteristics as an suitable prognostic marker in OC patients	[66]/2016
Hydrophilic metabolites of salivary	Evaluation of metabolomic analysis of saliva samples by Mann–Whitney test and tissue samples by Wilcoxon matched-pairs signed-rank test in OC patients	Combined salivary metabolites could be possible clinical method of noninvasive OC screening	[67]/2016
Profile of gene expression	Investigation of Clinical-pathologic parameters in OSCC and non-developed OSCC patients	Profiles of gene expression may improve the prognosis of OC risk in OPL patients and the important genes identified may serve as promising targets for OC chemoprevention.	[68]/2011
BRBs	Investigating transcriptional biomarkers by changes which are related to BRB powder administration in OSCCs patients and non-involved HARM (high at-risk mucosa).	Molecular biomarkers with anti-apoptotic and pro-inflammatory features are the basis of modifiable OC and represent molecular efficacy of BRB-mediated OC chemoprevention.	[19]/2018
uPA	Investigating the genetic polymorphisms of uPAR, uPA, and (PAI)-1 in OC patients by PCR-RFLP	The combination of uPA system gene polymorphisms and environmental carcinogens was correlated with the OC risk. The PAI-1 genetic polymorphism was related to a low risk to the OC clinicopathological progression	[69]/2011
Lipidome and proteome components	Examination of lipidome and proteome components of patients with tongue lesions by LC-MS, MALDI–MSI, Lilliefors test, and F test	Differences of Molecules between cancerous and normal mucosa were higher in the proteome domain than in the analyzed lipidome subdomain, imaging of lipidome components also authorized discrimination of OC and normal tissues.	[55]/2019
Met Receptor Tyrosine Kinase	Evaluating Met expression in OL patients by using immunohistochemistry. Multivariable analysis of Met expression relation with OC progression. Evaluating pharmacological Met inhibition sensitivity in vitro (OC cell lines) and in vivo (OC chemoprevention)	Activation of Met may display an early prognosis in oral premalignancy and a target for OC chemoprevention	[70]/2018
Co-expression of TWIST1 and ZEB2	Investigation of TWIST1 and ZEB2 expression in OSCC patients by IHC staining	The co-expression of ZEB2 and TWIST1 may have clinical value in determination of patients with poor survival for proper management	[48]/2015

Continued on the next page

Type	*Method*	*Outcomes*	*Ref/Year*
IL-33 and itsST2 receptor	Evaluation of IL-33 and ST2 in blood of patients with PGT by CRP and ELISA methods	Serum IL-33 level was substantially increased in patients with different types of PGT. ST2 levels were significantly increased in pleomorphic adenoma and acinic cell carcinoma patients	[32]/2018
Metabolites	Evaluation of patient with OSF, OSCC and the healthy individuals by GM-MS and chemometric analysis	GC-MS mechanisms based metabolite profiling and extensive chemometric tissue analysis may be able to determine biomarker metabolites which can remarkably change in OC patients	[71]/2016
Stathimin	Examination of the combination therapy effects of TPF chemotherapy and PI3K-AKT-mTOR inhibitors in vitro and in vivo	Overexpression of Stathimin elevated proliferation of cells and reduced sensitivity of OSCC cell to TPF treatment. Inhibition of the PI3KAKT-mTOR signaling pathway reduced expression of stathmin and phosphorylation. The combination therapy (TPF chemotherapy and PI3K-AKT-mTOR inhibitors) showed a promising antitumor effect both in vivo and in vitro.	[72]/2020
Twist Trastuzumab, Vismodegib, Vemurafenib, or Atezolizumab	Treating Patients with advanced SGC with, Pertuzumab Trastuzumab (HER2 alteration), Vismodegib (PTCH-1/SMO mutation), Vemurafenib (BRAF V600 mutation), or Atezolizumab [high tumor mutational burden (TMB)].	Matched targeted therapy for SGC has potential efficacy, supporting molecular profiling in treatment identification.	[73]/2020
Hospital based case–control study			
CCND1 (Cell cycle regulator cyclin D1)	Evaluation of CCND1 polymorphisms in age- and gender matched controls and OC patients	Cell cycle regulation have important role in OC and CCND1 rs9344 polymorphism may be a helpful biomarker for OC.	[74]/2011
Randomized clinical trial			
Nivolumab	Treating patients with nivolumab to patients or IC (methotrexate, docetaxel, or cetuximab) treatment.	Nivolumab resulted in a higher survival versus IC in patients	[75]/2018
GTE	Evaluating biomarkers in high risk OPL patients after 12 weeks giving GTE	Higher doses of GTE may improve OPL outcome. The results promote longerterm clinical GTE testing for OC prevention.	[76]/2009
EGFR	Assessment of EGFR expression in OPL patients by immunohistochemistry	EGFR inhibitors may prevent OC in patients with OPLs having an increased EGFR expression which is correlated with OSCC progression	[77]/2010
Bleomycin	Measuring Changes in histopathologic features, myofibroblasts, ultrastructure, the collagen types I and III levels, TGF-β1, and INF-γ after therapy with bleomycin in animal models	Bleomycin induces OSF which is similar to human OSF.	[78]/2016

treatment are used in patients with OC. Nevertheless, some targets of OSCC diagnosis and therapy are still unknown and tumor markers progression is required. In the near future, novel tumor biomarkers will be recognized. The major restriction of researches is that no patient is followed up correctly and the serum biomarker assessment has not been repeated. In this study, researchers believe that the limitation is associated with disease development and prognosis. Therefore, future research should focus on the restrictions to provide further information for the usefulness of serum biomarkers. Clinical evidence and scientific findings also support biomarkers for the prognosis and diagnosis of diseases. However, protocols of monitoring should be set up in dentistry teams to ensure proper understanding after choosing a specific biomarker. Advantages of biomarkers involved in detecting malignancies, prediction of malignancies outcome, and choosing proper therapeutic approaches are required. Accordingly, biomarkers investigation has an important place in estimating the cost in the clinical management of cancer. Also, the biomarkers panel generally determines the exact molecular stages in diseases. Providing diagnostic kits which are simple, can predict cancer accurately and use in the clinic.

Conclusion

Saliva is one of the special fluids in humans with abundant capability in clinical assessment and diagnosis. Biomarkers of salivary diagnosis may have promising potential in the future. Human WMS (whole-mouth saliva) is an important factor to clarify OCs pathogenesis and diagnosis that is a non-invasive method for fluid biopsy. Also, this method has more advantages such as sampling without any pain, simple and comfortable to use. Therefore, saliva has been known recently as a main factor due to the surveillance potential of general health and disorders. Findings about saliva features and their correlation to biological markers has been developed and salivary biomarkers are found in various conditions, for instance metabolites, microbes, DNA, proteins, lipids and RNA, which are related to the development, risk or recurrence opportunity of OSCC. Some biological markers are valuable in diagnosis, prognosis or therapy of OCs. An epigenetic and genetic investigation based on saliva provides information related to oral microbiota, virus infection [55], and genome of the host. Finding out the reporting procedures, methods and protocols analysis will facilitate new scientists to decrease bias in researches that are based on biomarkers. Moreover, researches for biomarkers progression help understand the response of the host immune system and heterogeneous cancer cell population.

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Ethical approval

The present study was approved by the Vice Chancellor of Research Affairs at Ardabil University of Medical Sciences, Ardabil, Iran, under report number IR.ARUMS.REC.1400.240.

Conflict of interests

The authors declare no conflict of interests.

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