e-ISSN 2371-770X

Modern Medical Laboratory Journal

DOI:10.30699/mmlj17.5.1.14

Oral squamous cell carcinoma, novel methods for early diagnosis and treatment

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KEYWORDS

Oral squamous cell carcinoma;

Biomarkers;

Inhibitors;

Molecular pathways;

Targeted therapy

Article Info

Received 2022/03/20;

Accepted 2022/04/05;

Published Online 2022

ABSTRACT

Oral squamous cell carcinoma (OSCC) represents the most common oral cavity cancer worldwide, being among the 10 most frequent cancers of all types. Only around 50% of patients survive longer than 5 years in view of currently applied medical procedures of diagnosis and treatment. The delay in diagnosis accounts for the shortening of survival despite advances in treatment protocols. The poor prognosis as well as high occurrence rate exerts a burden on both patients and clinicians. Cancer biomarkers may possibly present cancer profiles of different patients and foreseeing each upcoming therapy response and the subsequent outcomes. Identification of the most fundamental biomarkers in OSCC may lead us to precise detection, which can give rise to earlier diagnosis, more effective treatment options, and more patient oriented prognostic decisions, alleviating the current situation regarding the failure in effectual OSCC management. In this review, we have outlined the molecular biomarkers for early diagnosis of OSCC and suggested inhibitors through which metastasis and its molecular pathways could potentially be inhibited.

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Abbreviations

AFP, Alpha-fetoprotein; ATM, Ataxia-telangiectasia mutated; ATR, Ataxia-telangiectasia mutated Rad3 related; CA-125, Cancer antigen 125; CCL18, CC motif ligand 18; CCND1, Cyclin D1; CEA, Carcinoembryonic antigen; CTCs, Circulating tumor cells; ctDNA, Circulating tumor DNA; DNA-PK, the DNA-dependent protein kinase; DSG, desmoglein; E-cadherin, epithelial cadherin; EGF, Epidermal growth factor; EGFR, Epidermal growth factor receptor; EMT, Epithelial to Mesenchymal Transition; FAK, Focal adhesion kinase; FISH, Fluorescence in situ hybridization; GAL, Galanin; G-CSF, Granulocyte colony-stimulating factor; HDAC, Histone deacetylase; HGF, Hepatocyte growth factor; HPV, Human papillomavirus; LOF, Loss-of-function; miRNAs, Micro-RNAs; MMP, Matrix metalloproteinase; MT1-MMP, Membrane type 1 matrix metalloproteinase; N-cadherin, Neural-cadherin; NF-Kb, Nuclear factor kappa B; OLk, Oral leukoplakia; OLP, Oral lichen planus; OSCC, Oral squamous cell carcinoma; p16, p16INK4a; PCR, Polymerase chain reaction; PD-L1, Programmed cell death ligand 1; PMDs, Potentially malignant disorders; PSA, Prostate-specific antigen; RANKL/RANK, Nuclear factor-kB ligand; STAT, Activator of transcription; TME, Tumor Microenvironment; TNM, Tumor, nodes, and metastases; VEGF, Vascular endothelial growth factor.

Introduction

According to the latest statistic published by Cancer Global, lip and oral cavity cancers are the 8th most common type of cancers worldwide. The mortality and incidence of these cancers are the highest in Asia, and they affect more males than females (1, 2). Oral squamous cell carcinoma (OSCC) stands for 90% of tumors affecting the oral cavity (3). The most common localization occurs in the tongue, but other frequent sites for tumor formation are lips and floor of the mouth (4).

The risk factors for OSCC are as following: smoking, alcohol consumption, viral infections (Epstein-Barr virus, human papillomavirus (HPV), and herpes simplex virus), betel nut chewing, occupational exposure to carcinogens, immunodeficiency condition, irradiation, diet, and genetic predisposition (5). Tobacco smoke and alcohol consumption as well as the papillomavirus are associated with 90% of the patients with oral cancer. Interestingly, tobacco and alcohol abuse appear to have a synergistic effect (6). HPV also plays a significant role in the development of OSCC in the posterior parts of the oral cavity including oropharyngeal and tonsillar areas (7). Interestingly, HPV accounts for 31,1% of the infection-related risk factors of all cancers (8). OSCC prevalence and mortality are unevenly distributed throughout the world apparently pertaining to variations in overall contribution of the different risk factor trend in each area (9).

Histologically, the lesion passes through various phases (preneoplastic damage) before the ultimate formation of cancer. This carcinogenesis may be due to precancerous lesions (such as leukoplakia, erythroplakia, and mixed). However, not all active/progressive or potentially malignant lesions result in development of malignant neoplasms (6). The most frequent premalignant lesions which can progress to OSCC are oral leukoplakia (OLK), oral lichen planus (OLP), and erythroplasia (4). OSCC is usually diagnosed via clinical assessment along with histopathological analysis of the tissue (10).This type of visual assessment may bring about dismissing some lesions and failure in determining whether a tumor is malignant or benign. Therefore, the disease is mostly detected in the late stages (11).

Surgical approaches, chemotherapy, and radiotherapy constitute the main conventional OSCC treatment protocols, which are costly and leaves considerable burden and probably certain side effects (12). Resecting surgery is the chief choice of treatment for OSCC, though it brings on diminished life-quality afterwards. Later recurrence might also take place owing to endured tumor cells (13). Metastatic OSCC apparently inflicts a short survival of 4 months if left untreated (14).

Despite the advancements in the therapeutic strategies towards OSCC, not much remarkable enhancement in survival rate has been observed during the previous decades (12). Its early diagnosis remains a great challenge for physicians. The majority of OSCC cases are identified in the advanced stages (i.e., III or IV), which gives rise to a great deal of morbidity and mortality. Metastasis after primary treatment is found in more than half of the patients (80% within the first 2 years of diagnosis) and the five-year survival rate is still lower than 50% (3). Early-stage OSCC eventuates in the survival of 81% of patients (15) in comparison to the progressed disease, reflecting the predictive importance of its prognostics (16).

Biomarkers and Diagnosis

As it has been declared in Robbins Basic Pathology Chapter 6, the methods by which we could characterize and diagnose tumors are categorized in two groups: Molecular and Histopathological. Histopathological methods consist of biopsy, aspiration with a needle, cytologic smear (Papanicolaou), immunohistochemistry, and flow cytometry, while the molecular mean is based on fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) results. Molecular-based methods can identify the tumor, its behavior, minimal residual disease, the genetic potential to develop cancer, and can also accelerate the determination of the right choice of treatment. Molecular profiling of the tumors seems to enhance recognition of the changes in DNA copies, yet histopathological methods have the advantage of indicating anaplasia, aggression, and tumor heterogeneity (17).

Molecules generated by the cancerous cells or other cells in reaction to the existing tumor in the body are called cancer biomarkers (18).

According to the Cancer Medicine,6th Edition, an ideal cancer biomarker has the following characteristics: (1) generated specifically by premalignant or malignant tissues early in the progression of disease; (2) produced at detectable levels in all patients with a specific malignancy; (3) expressed in an organ site-specific manner; (4) present in bodily fluids obtained noninvasively or in easily accessible tissues; (5) being in levels related quantitatively to tumor volume, biological behavior, or disease progression; (6) having relatively short half-life, reflecting temporal changes in tumor burden and response to therapy; and (7) having a standardized, reproducible, validated, objective, and quantitative assay (19).

The biomarkers of OSCC could be classified into the following groups: biomarkers in genomics, transcriptomics, proteomics, and epigenomics (20).

Biomarkers assessment can be of value in various clinical contexts, from predicting the risk of the disease to estimation of the prognosis and treatment response (21). Lately, a great deal of attention has been paid to biomarkers quantification, which can possibly play a crucial role in disease diagnosis (22). In spite of existence of numerous published papers on biomarkers detection, few biomarkers have been exhibited to bring about approved applications in routine medical practice (23). To administer the fitting targeted therapy options, it is crucial to properly perceive these biomarkers. In the following paragraphs, we delineate each group of biomarkers in detail.

Biomarkers in Genomics

Potentially malignant disorders (PMDs) are proven to be correlated with several biomarkers such as an inhibitor of cyclin-dependence p16INK4a protein (p16), nuclear protein ki67, and the tumor suppressor p53. Wnt pathways promote PMDs development and progression (24).

Certain molecular pathways are related to OSCC pathogenesis. These encompass nuclear factor kappa B (NF-kB), PI3KAKT, Wnt pathways, Cyclin D1 (CCND1), Rb, p53, FLJ10540, and TC21. NF-kB and PI3KAKT are commonly mutated in all the mentioned pathways. The pathway which is frequently associated with the pathogenesis of OSCC is the Wnt pathway, which could make it a target for anti-cancer therapy.

In determining patients' survival rate, CCND1, Rb, p53, FLJ10540, and TC21 are thought to be more accurate than others. CCND1 can be targeted through the inhibition of cyclin-dependent kinase 4. The Rb protein increases CCND1 and reduces p16 expression. The poor survival rate is concurrent with overexpression of CCND1 and underexpression of p16 (25).

Matrix metalloproteinase (MMP) 2 and 9 play major roles in the development of lymph node metastases (6). FLJ10540 and FOXM1 upregulate the expression of MMP-2. TC21 expression happens early in the carcinogenesis of OSCC; therefore, it can be a promising prognostic factor. An increase in NF-kB may be related to the reduction of the survival rate. Activation of the PKB/AKT pathway inhibits growth, angiogenesis, metabolism, survival, proliferation, protein synthesis, apoptosis, and transcription (25).

In a study carried out in December 2019, it was concluded that p53 and programmed cell death ligand 1 (PD-L1) are correlated in OSCC. Moreover, there is a significant correlation between p53 expression and tumor stage and tumor, nodes, and metastases (TNM) stage in OSCC (26).

DNA of dead cells, circulating tumor DNA (ctDNA), is thought to increase in many malignancies. Research have concluded that there is a correlation between ctDNA levels and OSCC progression. High preoperative plasma ctDNA concentrations are associated with neck lymph node prognosis and poor prognosis (27). CtDNA concentration is proved to be associated with genetic and epigenetic alterations found in tissue samples of malignant neoplasms, tumor size, cellular turnover, stage, vascularity, and drug response (3).

Extracellular vesicles, such as exosomes and microvesicles are implicated in OSCC. Exosomes with oncogenic biomarkers are released in OSCC. The qualitative and quantitative features of salivary extracellular vesicles can improve the diagnosis and prognosis of OSCC (3).

Micro-RNAs (miRNAs) involvement in tumor carcinogenesis has been widely investigated. Tumor development or inhibition is a result of deregulation of oncosuppressors, which is linked to the expression of miRNAs. The differentially expressed miRNAs in OSCC include: miR-125, miR- 200a, miR-21, miR-145, miR-93, miR-375, and miR-184.

Salivary marker miRNA-139-5p is suggested to be downregulated in OSCC samples. Increase in expression of miR-708, miR-10b, miR-19a, miR-30e, miR-26a, and miR-660 and decrease in expression of miR-99, miR-15a, miR-197, miR-145, and miR-150 in the saliva of OSCC patients have been reported (3).

Twenty-one genes that were involved in antioxidant metabolism were differentially expressed in OSCC as well. Four were up-regulated (ATOX1, PRDX4, PRNP, and SOD2), and seventeen were down-regulated (ALOX12, CAT, CSDE1, DHCR24, DUOX1, DUOX2, EPHX2, GLRX2, GPX3, GSR, GSTZ1, MGST3, PRDX1, OXR1, OXSR1, SOD1, and SOD3) (28). Another study, on the other hand, suggests that in the process of OSCC, thirty-two genes are down- and forty-six are up-regulated, which play a major role in transcription, apoptosis, anti-apoptosis, RNA metabolism, stress, and so on (29). Frequently mutated genes in OSCC include TP53, CDKN2A, EPHA2, FAT1, NOTCH1, CASP8, and PIK3CA (30).

CXCL10, IFI6, IFI27, ADAMTS2, COL5A1 are involved in co-expression network (29). CXC chemokine ligand, which is also called inducible interferon protein, is responsible for the regulation of immune response, angiogenesis, cell apoptosis, cell cycle, and cell proliferation. CXCL10 is a novel candidate oncogene, with a dual effect on tumor inhibition and promotion, which may be a therapeutic target for cancers. It can directly be combined with CXCR3 and can have biological effects on cancer behavior such as anti-proliferation influences. The inhibition of expression of HPV oncogenes E6 and E7 and promotion of p53 can also be done by CXCL10 (29). Although the role of abnormal expression of CXCL10 has not been addressed before, these findings suggest that it plays an important role in OSCC tumorigenesis (29). Also, the expression of the RASSF-1A gene has been proven to be decreased in OSCC (31).

One of the most recent studies carried out in this field, on mice, suggested Mob1a/b deletion in mouse tongue epithelium causes extremely rapid OSCC onset. It also suggested that the onset of OSCC depends on activation of YAP1 rather than TAZ. Therefore, inhibition of YAP1 could slow the progression of OSCC.

Many recent reports have correlated YAP1 activation to either loss-of-function (LOF) mutations of key genes such as TP53 and FAT1, or the triggering of pathways related to PI3K/AKT or epidermal growth factor receptor (EGFR). Accumulation of YAP1 activity can relate to various combinations of these alterations. Both losses of function and gain of function of TP53 can enhance YAP1 activation. YAP1 and TAZ are activated independently in SCC content. Selective targeting of YAP1 may be an effective new method of OSCC treatment (28, 32).

Biomarkers in transcriptomics

TP53 has been proved to be the most common (65-85%) mutated gene in HPV-negative OSCC patients. It is directly related to poor survival and tumor resistance to radiotherapy and chemotherapy, which makes it a potentially useful prognostic marker (5).

Biomarkers in proteomics

Several classic specific tumor proteins are assessed for clinical diagnoses, such as alpha-fetoprotein (AFP), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), and cancer antigen 125 (CA-125). However, none is regarded as an OSCC biomarker (20). Salivary markers are hugely applied as a complementary adjunct for the early detection of oral OSCC. They consist of IL-1β, IL-6, IL-8, MIP-1β, eotaxin,IFN-γ, TNF-α, CD59, M2BP, MRP14, catalase, and profilin. Additionally, CyclinD1 expression has been proven to be elevated in OSCC (31).

Regarding tumor progression evaluations, plasma eotaxin, granulocyte colony-stimulating factor (G-CSF), and IL-6 assessment may assist the detection of advanced OSCC (20, 28).

Biomarkers in epigenomics

In dysplastic cancer tissues such as in OSCC, both hypo- and hypermethylation are significantly increased. Notably, three genes (TRHDE, ZNF454, and KCNAB3) with a high frequency (90–100%) of methylation-specific to OSCC have been discovered. Besides, one study suggested that detecting the methylated state of ZNF582 and PAX1 from saliva and OSCC tissue could also achieve similar diagnostic efficiency (20).

It has been proven that WT1 gene promoter methylation indicates a better prognosis and that MSH6 and GATA5 gene promoter methylation serve as predictors of a worse prognosis. GATA5 gene promoter methylation is said to be significantly associated with a shorter survival rate. Furthermore, PAX5 gene promoter methylation is significantly associated with tongue tumors (33).

Circulating tumor cells

Another biomarker that is widely investigated but not categorized in these four groups is circulating tumor cells (CTCs). Their presence is associated with metastasis, recurrences, and a worse prognosis. Since they are more likely to be detected in the late stages of OSCC, their levels can help with prognosis estimation more than diagnosis applications (3).

Biomarkers related to Metastasis and treatment

The aggressiveness of OSCC is directly associated with its ability to invade other tissues and originate metastasis (34). The clinical significance of invasive properties is affected by both the local region and regional lymph node metastasis with extracapsular invasion. The invasion of OSCC cells is characterized by abnormal regulation of cell adhesion molecules, (e.g., epithelial cadherin (E-cadherin), neural-cadherin (N-cadherin), claudin, and desmoglein (DSG)) (35).

One of the processes, by which metastasis can be accompanied, is a phenomenon named “Epithelial to Mesenchymal Transition” (EMT). It is a highly dynamic and reversible process, through which epithelial cells gain the characteristics of mesenchymal cells. It occurs during normal embryogenic development, wound healing, organ fibrosis, and tissue generation, though it plays a major role in tumor progression. It occurs via down-regulation of E-cadherin, a molecule in the cadherin family, responsible for cell-cell adhesion and cellular polarity, and up-regulation of N-cadherin, a molecule responsible for motility and invasion. Although recent studies have shown expression rate of N-cadherin between 37%-52,4%, its role in tumor progression still remains unclear (24, 36).

This process is triggered by SNAI1 and SNAI2, ZEB1 and ZEB2, Twist, and E12/E47 among transcriptional factors, non-coding RNAs (miRNAs and long non-coding RNAs), chromatin remodeling and epigenetic modifications, alternative splicing, post-translational regulation, protein stability, and subcellular localization. EMT is studied by many scientists over the past few years; however, in order to fully use this process in means of treatment, more research has to be done in this area (36). Increase in the expression of Vimentin, a molecule which maintains cellular integrity and provides resistance against stress, has been reported. TCF/LEF transcription factors that up-regulate Vimentin, are triggered by β-catenin, whose transformation is stimulated by Wnt pathway (24). Enhanced glycolytic metabolic program in OSCC cells can affect the process by which epidermal growth factor (EGF) induces EMT progress (37).

The following molecules are considered to be Invasion-Related Molecules in Tumor Microenvironment (TME) in the EMT process: MMPs, periostin, hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), galanin (GAL) (35). Moreover, some molecules in the invasion process are involved in the cell signaling pathway, such as receptor activator of nuclear factor-kB ligand (RANKL/RANK), EGFR, signal transducer, and activator of transcription (STAT), focal adhesion kinase (FAK) (35).

Chemokine CC motif ligand 18 (CCL18) overexpression is also associated with advanced clinical stages in OSCC. It increases cell migration and invasion and induces cell EMT. A study has shown a positive correlation between CCL18 expression and Bmi-1 (38). Additionally, Lymphogenesis is promoted by the Wnt pathway, which is activated by snail upregulation (24).

Hypermethylation of the CDH1 promoter region correlates with loss of E-cadherin expression in the most invasive and metastatic area of OSCC. In cells undergoing EMT, the downregulation of the miR-200 family induces expression of ZEB1/ZEB2, which further causes E-cadherin suppression (35).

Overexpression of claudin-1 is associated with local recurrence and poor survival by a high probability of perineural and lymphatic invasion in OSCC. Furthermore, knockdown of claudin-1 has been proven to decrease the invasion of OSCC cells. Previous reports suggest that claudins may be involved in cancer progression through the complex interaction with several extracellular matrix elements.

The inhibition of claudin-1 expression in OSCC cells diminished invasion and decreased degradation of laminin-5, an important component of the basal membrane, through inactivation of MMP-2 and membrane type 1 matrix metalloproteinase (MT1-MMP). These findings declare that claudin-1 seems to be a potential biomarker of the more progressive lesions and as a result poor clinical outcome of OSCC patients (35).

Surprisingly, overexpression of DSG3 enhance membrane protrusions, and cell spreading and rounding, being the necessary prerequisites for cell migration/invasion. As a result, it could be a candidate for therapeutic purposes (35).

One study suggests that the increase in NLRP3 expression leads to tumor growth and metastasis in OSCC, and can act as an appropriate option for targeted therapy (39).

KRT16 expression is correlated with weaker pathological differentiation, advanced stages, increased lymph nodes metastasis, and decreased survival rate in several Taiwanese OSCC patient cohorts. Mir-365-3p can target ETS homologous factor (EHF), a KRT16 transcription factor, to decrease migration, invasion, metastasis, and chemoresistance in OSCC cells via inhibition of KRT16. Targeting a novel miR-365-3p/EHF/KRT16/β5-integrin/c-Met signaling pathway could improve treatment efficacy in OSCC (40).

HMGA2 has also been proved to play a significant role in the regulation of angiogenesis and might be a potential biomarker to predict distant metastasis and prognosis in OSCC (41). Further studies suggest that BAP18 is involved in the modulation of CCND1/2 transcription and promotes OSCC progression. BAP18 could act as a potential target for OSCC treatment and diagnosis (42). Based on previous studies, it has been proven that TNF-α enhances the invasion and metastasis ability of OSCC cells via the NF-kB sig¬naling pathway (43). LINC01116 silencing may inhibit the progression of OSCC through miR-136-mediated FN1 inhibition, highlighting another promising therapeutic strategy for OSCC (44).

In the absence of functional p53, the cell cycle arrest and DNA repair rely mostly on Ch1 and Ch2, kinases activated in response to diverse genotoxic insults. In a related study, they inhibited Ch1 and Ch2 with AZD7762 and declared that AZD7762 sensitized these cells to cisplatin through induction of mitotic catastrophe, which is a form of cell death that shows the appearance of multinucleated cells and polyploidy. Wee1 kinase inhibitor has also been suggested to target cancer cells undergoing replication (5).

Novel molecular targeting with TP53 is achieved by using small-molecule inhibitors of the Ataxia-telangiectasia mutated (ATM), the ATM-Rad3 related (ATR), the DNA-dependent protein kinase (DNA-PK). Histone deacetylase (HDAC), a molecule that acts enzymatically to remove the acetyl group from histones and silence gene expression, may also serve as a target molecule for this therapy. HDAC inhibitors have been suggested to induce growth arrest, differentiation, and apoptosis in various cancer cell lines in vitro and suppress tumor growth in animal xenograft models, including OSCC. As Lindemann has shown, the wtp53 is a known potent inducer of apoptosis and senescence when expressed in tumor cells, reactivation of wild-type function in mutant p53 is an attractive therapeutic approach. Wt53 has no enzymatic function and functions as a sequence-specific transcription factor. Besides, it has been proven that various factors ZMC-1, COTI-2, PRIMA-1, APR-246, and ReAC-p53 can restore wtp53 function (5). The survival rate of patients with recurrent metastatic OSCC cases can be improved by combination of cetuximab as well (5).

At present, given the diversity of the subsets and molecular pathogenesis of OSCC, multimodality therapies are implemented. Multimodality treatments include surgery, chemotherapy, biologic-based therapy, radiotherapy, and intensity-modulated radiotherapy. Early stages of OSCC tend to respond well to monotherapies (surgery and in some cases radiotherapy), though combinational regimens are taken into practice for more advanced stages (III and IV) which account for more than half of the cases (13).

Table 1. summary of potential biomarkers in OSCC.

Name	Type of sample/biopsy required	Nature	Alteration in OSCC	Potential indicative in OSCC	Ref.
p16	Tumor biopsy	protein	Downregulated	Short survival rate	(45)
Ki67	Tumor biopsy	Antigen	Upregulated	Short survival rate Metastasis Advanced tumor	(46)
P53	Tumor biopsy	antigen	upregulated	Advanced tumor	(47)
PD-L1	Tumor biopsy	protein	upregulated	Short survival rate	(48)
CCND1	Tumor biopsy	Gene	upregulated	Short survival rate	(45)
MMP-2	Blood test	protein	Upregulated	Diagnosis Advanced tumor Metastasis	(49)
MMP-9	Blood test	Protein	Upregulated	Diagnosis Metastasis	(49)
TC21	Tumor biopsy	Gene	Upregulated	Early diagnosis Short survival rate	(50)
NF-kB	Tumor biopsy	Nuclear factor protein	Upregulated	Short survival rate tumor recurrence metastasis	(45)
ctDNA	Blood test	DNA	upregulated	Short survival rate Therapy response	(51, 52)
miRNA-139-5p	Saliva sample	Micro-RNA	Downregulated	Short survival rate	(51)
CXCL10 (IP-10)	Blood test	Chemokine ligand	upregulated	Early diagnosis	(53)
IL-6	Saliva sample	cytokine	Upregulated	Early diagnosis	(53)
IL-8	Saliva sample	cytokine	upregulated	Early diagnosis	(11)
Eotaxin	Blood test	Chemokine	Upregulated	Advanced tumor	(53)
IFN-γ	Saliva sample	Cytokine	Upregulated	Early diagnosis	(53)
TNF-α	Saliva sample	Cytokine	upregulated	Early diagnosis	(11)
G-CSF	Blood sample	glycoprotein	upregulated	Advanced tumor	(53)
TRHDE	Tumor biopsy	gene	Methylated	Diagnosis	(54)
ZNF454	Tumor biopsy	gene	Methylated	Diagnosis	(54)
KCNAB3	Tumor biopsy	gene	Methylated	Diagnosis	(54)
Circulating Tumor Cells	Blood sample	cells	upregulated	Metastasis, Advanced tumor Poor prognosis	(51)
E-cadherin	Tumor biopsy	Cell adhesion molecule	Downregulated	Metastasis tumor recurrence	(55)
N-cadherin	Tumor biopsy	Cell adhesion molecule	Upregulated	Metastasis tumor recurrence	(55)
P-cadherin	Tumor biopsy	Cell adhesion molecule	Upregulated	Short survival rate metastasis	(56)
WNT5A	Tumor biopsy	protein	Upregulated	metastasis	(56)
Desmoglein-3	Tumor biopsy	Cell adhesion molecule	Upregulated	Metastasis Tumor recurrence	(57)
MIP-1β	Saliva sample	chemokine	Upregulated	Early diagnosis	(53)
miR-708	Saliva sample	Micro-RNA	Upregulated	Diagnosis	(51)
miR-10b	Saliva sample	Micro-RNA	Upregulated	Diagnosis	(51)
miR-19a	Saliva sample	Micro-RNA	Upregulated	Diagnosis	(51)
miR-30e	Saliva sample	Micro-RNA	Upregulated	Diagnosis	(51)
miR-26a	Saliva sample	Micro-RNA	Upregulated	Diagnosis	(51)
miR-660	Saliva sample	Micro-RNA	upregulated	Diagnosis	(51)
miR-99	Saliva sample	Micro-RNA	Downregulated	Diagnosis	(51)
miR-15a	Saliva sample	Micro-RNA	Downregulated	Diagnosis	(51)
miR-197	Saliva sample	Micro-RNA	Downregulated	Diagnosis	(51)
miR-145	Saliva sample	Micro-RNA	Downregulated	Diagnosis	(51)
miR-150	Saliva sample	Micro-RNA	Downregulated	Diagnosis	(51)
RASSF-1A	Tumor biopsy	gene	Downregulated	Diagnosis	(31)

YAP1	Tumor biopsy	gene	Upregulated	Diagnosis Advanced tumor	(32)
TAZ	Tumor biopsy	gene	Upregulated	Diagnosis	(28)
ATOX1	Tumor biopsy	Gene	Upregulated	Diagnosis	(28)
PRDX4	Tumor biopsy	Gene	Upregulated	Diagnosis	(28)
PRNP	Tumor biopsy	Gene	Upregulated	Diagnosis	(28)
SOD2	Tumor biopsy	Gene	Upregulated	Diagnosis	(28)
ALOX12	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
CAT	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
CSDE1	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
DHCR24	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
DUOX1	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
DUOX2	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
EPHX2	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
GLRX2	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
GPX3	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
GSR	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
GSTZ1	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
MGST3	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
PRDX1	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
OXR1	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
OXSR1	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
SOD1	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
SOD3	Tumor biopsy	Gene	Downregulated	Diagnosis	(28)
TP53	Tumor biopsy	Gene	Upregulated	short survival rate chemoresistance radio-resistance	(5)
TP53	Tumor biopsy	Gene	Mutated	radio-resistance Short survival rate	(5)
CDKN2A	Tumor biopsy	Gene	Mutated	Diagnosis	(30)
EPHA2	Tumor biopsy	Gene	Mutated	Diagnosis	(30)
FAT1	Tumor biopsy	Gene	Mutated	Diagnosis	(30)
NOTCH1	Tumor biopsy	Gene	Mutated	Diagnosis	(30)
CASP8	Tumor biopsy	Gene	Mutated	Diagnosis	(30)
PIK3CA	Tumor biopsy	Gene	Mutated	Diagnosis	(30)
CD59	Saliva sample	glycoprotein	upregulated	Early diagnosis	(31)
M2BP	Saliva sample	glycoprotein	upregulated	Early diagnosis	(31)
MRP14	Saliva sample	Protein	upregulated	Early diagnosis	(31)
Catalase	Saliva sample	enzyme	upregulated	Early diagnosis	(31)
Profilin	Saliva sample	protein	upregulated	Early diagnosis	(31)
IL-1β	Saliva sample	Cytokine	upregulated	Early diagnosis	(31)
ZNF582	Saliva sample + Tumor biopsy	Gene	Methylated	Diagnosis	(54)
PAX1	Saliva sample + Tumor biopsy	Gene	Methylated	Diagnosis	(54)
WT1 gene promoter	Tumor biopsy	Gene promoter	Methylated	Long survival rate	(33)
MSH6 gene promoter	Tumor biopsy	Gene promoter	Methylated	Short survival rate	(33)
GATA5 gene promoter	Tumor biopsy	Gene promoter	Methylated	Short survival rate	(33)
PAX5 gene promoter	Tumor biopsy	Gene	Methylated	Diagnosis of tongue tumors	(33)
TRHDE	Tumor biopsy	Gene	Methylated	Diagnosis	(54)
ZNF454	Tumor biopsy	Gene	Methylated	Diagnosis	(54)
KCNAB3	Tumor biopsy	Gene	Methylated	Diagnosis	(54)
SNAI1	Tumor biopsy	Non-coding RNA	Upregulated	Metastasis	(36)
SNAI2	Tumor biopsy	Non-coding RNA	Upregulated	Short survival rate Metastasis	(58)
ZEB1	Tumor biopsy	Non-coding RNA	Upregulated	Metastasis	(36)
ZEB2	Tumor biopsy	Non-coding RNA	Upregulated	Metastasis	(36)
Twist	Tumor biopsy	Non-coding RNA	Upregulated	Metastasis	(36)

EB12	Tumor biopsy	Non-coding RNA	Upregulated	Metastasis	(36)
EB47	Tumor biopsy	Non-coding RNA	Upregulated	Metastasis	(36)
Vimentin	Tumor biopsy	Intermediate filament protein	Upregulated	Metastasis	(59)
claudin-1	Tumor biopsy	tight junction protein	Upregulated	Local recurrence Short survival rate Metastasis	(55)
DSG3	Tumor biopsy	Gene	Upregulated	Metastasis	(55)
CCL18	Tumor biopsy	Gene	Upregulated	Advanced tumor Metastasis Short survival rate Tumor recurrence	(60)
CDH1 gene promoter	Tumor biopsy	Gene promoter	Hypermethylated	Metastasis	(55)
Chemerin	Blood sample	protein	Upregulated	Advanced tumor Metastasis	(61)
IL-6	Blood sample	Cytokine	Upregulated	Advanced tumor	(53)
Eotaxin	Saliva sample	Chemokine	Upregulated	Early diagnosis	(53)
hsa_circ_0009128	Tumor biopsy	circRNA	upregulated	Metastasis Advanced tumor	(62)
Periostin	Tumor biopsy	Protein	upregulated	metastasis	(55)
HGF		Growth factor	upregulated	metastasis	(55)
VEGF	Tumor biopsy	Growth factor	upregulated	metastasis	(55)
GAL	Tumor biopsy	Nucleopeptide	upregulated	metastasis	(55)
BAP18	Tumor biopsy	protein	upregulated	Advanced tumor	(42)
miR-483-5p	Blood sample	Micro-RNA	Downregulated	Metastasis	(63)
miR-200	Tumor biopsy	Micro-RNA	Downregulated	Metastasis	(55)
NLRP3	Tumor biopsy	Protein	Upregulated	Metastasis Tumor growth	(39)
KRT16	Tumor biopsy	Intermediate filament protein	Upregulated	Advanced tumor Metastasis Short survival rate	(40)
HMGA2	Tumor biopsy	gene	upregulated	Metastasis Short survival rate	(41)
cyclin A1	Tumor biopsy	protein	upregulated	Metastasis Short survival rate	(64)

AFP, alpha-fetoprotein; CCL18, CC motif ligand 18; CCND1, Cyclin D1; ctDNA, Circulating tumor DNA; DSG, desmoglein; E-cadherin, epithelial cadherin; GAL, galanin; G-CSF, granulocyte colony-stimulating factor; HGF, hepatocyte growth factor; MMP, Matrix metalloproteinase; N-cadherin, neural-cadherin; NF-kB, nuclear factor kappa B; OSCC, oral squamous cell carcinoma; p16, p16INK4a; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor.

Conclusion

OSCC stands for the most common malignant tumor of epithelium that dentists encounter. The belated detection of the disease substantially aggravates its prognosis. The expense and side effects of its typical treatments poses another obstacle for the patients to utterly combat OSCC. On the contrary to advanced OSCC, 81% of patients survive if they are diagnosed in early stages. Unfortunately only few biomarkers have validated medical employment despite the large number of studies investigating biomarkers detection. The diversity in patients' characteristics and outcomes necessities further biomedical research to yield a meticulous understanding of biomarkers, leading researchers to design and perform the appropriate clinical trials of OSCC personalized therapy.

Declaration

Acknowledgments

Authors would like to express their gratitude to their colleagues in regenerative medicine department, Royan institute and experimental cancer research, Karolinska institute.

Funding

No funding was provided related to this work.

Conflicts of interest/Competing interests

The authors declare no conflict of interest.

Authors' contributions

MZM and AT drafted manuscript. RG, PA, and MH edited manuscript. NM, NHK and MV edited manuscript and did final approval.

Ethics approval

Not applicable.

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How to cite this article: Zangeneh Motlagh M, Tamimi A, Golroo R, Hossein-khannazer N, Aminishakib P, Mahdavi N, Hassan M, Vosough M. Oral squamous cell carcinoma, novel methods for early diagnosis and treatment. Mod Med Lab J. 2022;5(1): 14-25.