

Functional landscape of dysregulated micrornas in oral squamous cell carcinoma: c...

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Introduction

Oral squamous cell carcinoma (OSCC) is the second most common cancer reported in India. According to recent Globacon-2018 data, ~120, 000 new cases of OSCC are detected every year in India ([1](#), [2](#)). It is the leading cause of cancer-associated death in the Indian male population. Annually, more than 72, 000 deaths are attributed to this disease in this country ([3](#)). OSCC originates in mucosal epithelial cells of the oral cavity ([4](#), [5](#)). Tobacco (smoking/smokeless) and alcohol are the primary risk factors for OSCC. Chewing of areca nut, betel leaf, poor oral health hygiene, and human papillomavirus (HPV) infection are also important risk factors for OSCC. Treatment in the early stages of the disease offers the best chance of cure ([4](#), [5](#)). Surgery is the first line of treatment, whereas radiotherapy and chemotherapy are used as adjuvant therapies ([6](#), [7](#)). Treatment strategies mainly depend on the location of the primary tumor, identification of high-risk features by histopathology, stage of tumor, and comorbidities. The 5-year survival rate of patients with oral cancer is around 50%. Poor outcomes are attributed to disease recurrence (both second primaries and locoregional recurrence) and distant metastasis. Despite availability of risk information from histopathology, the pattern and timing of relapse and metastasis are difficult to predict. About 86% of the recurrence occurs within 24 months after primary treatment ([7](#)). Prognostic information is mainly derived from anatomic location; tumor stage; tumor thickness; and histological characteristics like cellular heterogeneity, degree of differentiation, depth of invasion, presence of nodal metastases, margin status, neural invasion, and pattern of invasion ([6](#)).

Biomarkers are quantifiable indicators associated with the specific disease conditions that facilitate decision-making by clinicians with respect to the most effective clinical interventions. In conventional practice, extra nodal extension (ENE), perineural invasion (PNI), and lymphovascular invasion (LVI) are considered histopathological biomarkers associated with poor disease prognosis ([6](#), [7](#)). Given that the genetics of OSCC is highly heterogeneous and complex, so far, no known molecular biomarker (except HPV positivity) has been used to subclassify OSCC accurately. Currently, only one epidermal growth factor receptor (EGFR)-specific targeted-immunotherapy with cetuximab antibody is available for the management of this cancer. Therefore, in the current scenario, early detection of the disease with identification of distinct prognostic subgroups to facilitate advanced treatment strategies is required for effective management of OSCC. Genomic, epigenomic, proteomic, and metabolomic high-throughput approaches have recently been used to discover and validate tumor biomarkers individually and/or in panels ([8](#) - [13](#)). Since microRNAs (miRNAs) are highly stable in tissues as well as in circulation, they are considered potential biomarkers for cancer detection and prognostication ([14](#) - [18](#)). Here, we review potential candidate miRNAs for their possible use as molecular biomarkers to improve the diagnosis and prognostication of OSCC and to stratify such patients into distinct prognostic subgroups. In this review, we have voyaged through various dysregulated miRNAs reported to be responsible for the pathogenesis, progression, and specific outcomes of OSCC. Their functional associations with overall therapeutic management,

responsiveness, recurrence, and metastasis of OSCC are also elaborated upon.

Basics of MicroRNAs: Altered miRNA Function can Fine-Tune Cell-Fate Decision via Altered Gene and Protein Expression

Mature miRNAs are endogenous, single-stranded, evolutionarily conserved, non-coding RNAs ~19-26 nucleotides long; discovered by Lee et al. ([19](#)). miRNAs preferentially interact with complementary seed sequences in the 3' untranslated regions (UTRs) of their target mRNAs. miRNA binding sites may also be present in the 5' UTRs and coding sequences of target mRNAs ([20](#)). miRNA-mediated gene silencing is a fundamental biological process for cellular homeostasis, executed through translational inhibition followed by mRNA deadenylation and decay ([21](#) - [23](#)). Circulating cell-free miRNAs also play an important role in intracellular/intercellular communication through miRNA-mediated gene silencing ([17](#) , [24](#)). As a result, miRNA expression profiles in tissues and circulation are associated with several pathophysiological conditions, including cancers ([17](#) , [25](#)). Dysregulation in miRNA expression profile was first reported in leukemia ([26](#)). Therefore, a distinct miRNA expression signature that distinguishes normal tissues from cancer tissues could be a new “ hallmark of cancer,” which regulates almost all other cancer hallmarks defined earlier ([18](#) , [27](#) , [28](#)).

Functional dysregulation of mature miRNAs is associated with various kinds of pathological conditions. Dysregulation of miRNA expression and function may be due to one or more of the following: (1) altered miRNA biogenesis process: (a) epigenetic (methylation and histone modifications) alterations of <https://assignbuster.com/functional-landscape-of-dysregulated-micrnas-in-oral-squamous-cell-carcinoma-clinical-implications/>

miRNA genes, (b) altered activities of transcription factors, and (c) altered expression of miRNA-processing enzymes (Drosha, Dicer, etc.); (2) chromosomal instability, genomic instability, and presence of mutations in miRNA genes; (3) single-nucleotide polymorphisms (SNPs), deletions, and duplications in miRNA genes (pri-, pre-, and mature miRNA regions) as well as in the binding sequences on target mRNAs; (4) loss of miRNA-binding sites on target mRNAs; and (5) redirecting of the miRNA-induced silencing complex (miRISC) to multiple competitive miRNA-binding sites present in competing endogenous RNAs (ceRNAs), which act as miRNA sponges and inhibit their functions ([17](#), [23](#), [28](#) – [30](#)). All ceRNAs are naturally occurring, endogenous regulatory molecules, like long non-coding RNAs (lncRNAs), circular RNAs, pseudogenes, and some protein-coding mRNAs ([29](#), [30](#)). Notably, in miRNA-mediated regulatory networks, one miRNA can regulate many genes and a single gene can be regulated by many miRNAs ([23](#)).

The above-described processes ultimately lead to activation of some oncogenic genes/proteins and, at the same time, deactivation of some tumor suppressor genes/proteins. They also direct cellular signaling cascades toward making the cell fate verdict ([23](#), [28](#)). Eventually, these distinct alterations in miRNA expression profile drive a normal cell to transform into a cancer cell and dictate its progression, metastasis, stemness, and responsiveness to therapy (radiotherapy/chemotherapy) ([17](#), [18](#)).

Distinct MicroRNA Signatures as Hallmarks of Oral Squamous Cell Carcinoma

The utility of miRNAs as diagnostic and prognostic biomarkers of OSCC has not been convincingly established. Previous studies on miRNA expression <https://assignbuster.com/functional-landscape-of-dysregulated-micrnas-in-oral-squamous-cell-carcinoma-clinical-implications/>

profiling mainly focused on differential expression of miRNAs in normal and tumor tissues and body fluids (blood, saliva, serum, or plasma) from OSCC patients ([10](#), [12](#)). These studies have yielded a plethora of dysregulated (upregulated/downregulated) miRNAs in OSCC. Here, we used the miRCancer database, PubMed, and Google to search for relevant data and reevaluate miRNAs as potential biomarkers for the diagnosis, prognosis, and therapeutics of OSCC. miRCancer is an online, up-to-date database (last updated on August 27, 2019) that provides a comprehensive collection of miRNA expression profiles in various human cancers extracted from published literature available in PubMed ([31](#)).

MicroRNA Profiling in Oral Squamous Cell Carcinoma

Dysregulated miRNA Expression in Tumor Tissues

Tran et al. ([32](#)) performed the first high-throughput miRNA profiling in OSCC using nine OSCC cell lines. Subsequently, several investigators have studied miRNA profiles as prognostic biomarkers using primary tumor and paired control tissues from patients with head and neck squamous cell carcinoma (HNSCC) ([33](#)- [35](#)). The differential expression analysis revealed sets of mature miRNAs that were either upregulated or downregulated in the tumor tissues. Childs et al. ([35](#)) showed that miR-21, miR-155, miR-191, and miR-221 were upregulated, whereas miR-1, miR-133a, miR-205, and let-7d were downregulated in primary tumors at diagnosis ([35](#), [36](#)). Another retrospective study on 51 formalin-fixed HNSCC tumor samples revealed consistent expression of mature miRNAs in malignant tissues; miR-21, miR-155, let-7i, miR-142-3p, miR-423, miR-106b, miR-20a, and miR-16 were overexpressed, whereas miR-125b, miR-375, and miR-10a were

underexpressed) ([37](#)). Lu et al. ([38](#)) showed that miR-10b, miR-196a, miR-196b, miR-582-5p, miR-15b, miR-301, miR-148b, and miR-128a were upregulated, whereas miR-503 and miR-31 were downregulated in six oral cancer cell lines compared with those in normal keratinocytes. Specific miRNAs related to the clinicopathological features of site-specific OSCC were investigated, which demonstrated a significant difference in let-7a, miR-200c, miR-34a levels between oropharyngeal and laryngeal cancers ([39](#)). In addition, miR-21, miR-200c, and miR-34a were upregulated, and miR-375 was downregulated in tumor tissues of all subsites when compared with those in paired control tissues ([39](#)). Studies also suggested that genes associated with the phosphoinositide 3-kinase (PI3K)/AKT and p53 signaling pathways, which are involved in the OSCC carcinogenesis process, were regulated through a set of dysregulated miRNAs, such as let-7a, let-7d, let-7f, miR-16, miR-29b, miR-142-3p, miR-144, miR-203, and miR-223 ([40](#)). Lamperska et al. ([41](#)) suggested that miR-21 and miR-205 could be used to analyze the clarity of surgical margins, but they failed to find a correlation between miRNA expression and clinical outcome and the course of illness. Here, we considered only those studies that reported targeted or genome-wide miRNA profiling either in cell lines or in tumor samples.

These studies make it obvious that malignant OSCC tumors have distinct miRNA expression profiles. Subsequently, the regulatory network composed of these distinct miRNAs in the malignant cell causes key downstream molecular alteration, which ultimately leads to a distinct patient outcome ([17](#), [28](#), [42](#)). It is evident from the above studies that the results are not always consistent. The source of the problem could be found within and

among the studies. Variations are observed in study design, end point objective, selection of cell lines, use of appropriate controls (in most of the cases, adjacent normal tissues were used which could harbor genomic alterations), methodology, protocol or treatment strategies, and localized patient pools in these studies. Further, purity and availability of tumor tissue, stromal cell contamination, and small sample size may impact study results. In most of the studies, intra/inter tumor heterogeneity, variable etiopathogenesis, and heterogenous genetic constitution of each patient are important factors that lead to variations in results. Despite these limitations, the results of individual studies demonstrate that miRNAs may be useful as potential biomarkers to predict OSCC outcome. The present quantum of knowledge lays the groundwork for logical implementation and execution of large-scale studies with improved, standardized study protocols in the future.

miRNA Expression Signatures Associated With Risk Factors of OSCC

One miRNA profiling study comparing smoker and non-smoker patients reported high miR-155 expression in 58% of OSCC cases and 83% of dysplasia cases and subsequently suggested miR-155 as a driver of oral tumorigenesis in non-smokers ([43](#)).

The association of OSCC with betel quid was also analyzed in OSCC specimens by another investigator who discovered 84 betel quid-associated mature miRNAs, of which 19 were located on chromosome 14q32. 2 ([44](#)). In this context, Hou et al. ([45](#)) established that specific polymorphisms in miR-499a are associated with OSCC progression. They discovered that the T/C+C/C genotypes of miR-499a increased the risk of betel quid-associated oral submucosal fibrosis (OSF) but decreased the risk of OSCC. Further, miR-
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499a T> C (rs3746444) influences the expression of miR-499-5p during OSCC carcinogenesis ([45](#)).

Several investigators have also conducted miRNA expression profiling to compare HPV-positive and -negative OSCC tumors and revealed that miR-127-3p, miR-363, miR-20a, miR-34a, let-7c-5p, and miR-9 could effectively distinguish between the two groups ([39](#), [46](#) - [49](#)). Different etiological factors causing distinct patterns of miRNA expression have also been well-established by several investigators. Most of the work has been done on HPV-associated OSCC. The studies reveal little effect of tobacco and betel quid on miRNA expression in OSCC compared with that in HPV-associated OSCC.

Dysregulated miRNAs in Tumor Cells Collected Through Non-invasive Brush Biopsy

Recently, the more advanced brush biopsy or other related scraper-based methods have offered non-invasive ways to identify OSCC-specific miRNA biomarkers for diagnosis and prognostication of the disease. Gissi et al., using brush biopsy samples from OSCCs and from regenerative areas after surgical resection and from their respective normal distant mucosa, revealed that miR-146a and miR-191 were significantly altered in the regenerative areas after OSCC resection ([50](#)). Studies also claim that brush biopsy samples may be superior to surgically dissected samples ([51](#), [52](#)). In brush biopsy, sampling sites within lesions that are not ulcerated and are non-necrotic and minimally friable make the samples homogeneous, with viable epithelial cells. It must be noted, however, that in case of smaller tumors (T1, T2), there is a chance of normal epithelial cell contamination in brush

biopsy samples ([51](#), [52](#)). For high-throughput technology (next-generation sequencing), obtaining high quality and quantity of total RNA (or enriched miRNA) from brush biopsy samples is the main challenge ([51](#)). Quantitative real-time PCR (qRT-PCT) is a reliable method in this case. miRNA profiles in individual brush biopsy OSCC samples show ~50% overlap with miRNAs enriched in surgically obtained tumor tissue profiles ([51](#)). The non-invasive rapid brush biopsy methods are useful in obtaining homogeneous tumor cells. Over the years, given all the limitations, the accuracy in predicting OSCC-associated miRNA expression signature is still to be improved for clinical applications.

Cell-Free MicroRNA Profiling: Potential Biomarkers for Liquid Biopsy

The most fascinating aspect of miRNA biology is the stable presence of cell-free miRNAs in all biological fluids. Previous studies have demonstrated that the stability of circulating cell-free miRNA results from either internalization of miRNAs into exosomes or other microvesicles or formation of complexes between circulating miRNAs and specific proteins and lipids ([14](#) - [16](#), [53](#)). These cell-free miRNAs are probably released by cancer cells, necrotic cells, and/or apoptotic cells along with their associated proteins or lipids, such as the RNA-binding protein NPM1 (nucleophosmin), AGO proteins (argonaute 1/2), and high-density lipoprotein (HDL), to avoid RNase degradation in blood circulation ([15](#), [16](#), [54](#)). Further, the spectrum of these cell-free miRNAs is altered by various pathophysiological conditions, including cancer ([42](#), [54](#) - [57](#)). In OSCC, saliva is one of the important sources to identify reliable biomarkers for predicting diagnosis and prognosis. Blood (serum and

plasma) is another important sampling source. The sources of these cell-free miRNAs are thought to be directly associated with tumor pathogenesis and/or other related systemic physiological (immune system/metabolic system) conditions ([54](#) - [56](#)).

Dysregulated Cell-Free miRNAs in Biological Fluids of OSCC Patients

Saliva

Studies using human saliva samples have shown that salivary cell-free miRNAs could be potential diagnostic biomarkers in OSCC patients compared with those in healthy individuals ([58](#) - [60](#)). Genome-wide expression patterns of miRNAs have revealed that miRNA expression is significantly altered in the saliva of OSCC patients compared with that in healthy controls. miR-125a, miR-136, miR-147, miR-1250, miR-148a, miR-200a, miR-632, miR-646, miR-668, miR-877, miR-503, miR-220a, and miR-323-5p were downregulated, and miR-24 and miR-27b were found to be upregulated. The studies revealed that miR-27b was significantly upregulated in OSCC patients compared with that in healthy controls, patients with OSCC in remission, and patients with oral lichen planus and served as a biomarker to detect OSCC. Finally, the studies concluded that miR-27b could be a valuable cell-free biomarker in saliva for distinguishing OSCC patients ([60](#)).

Plasma

A study using plasma samples obtained at different time points showed that plasma miR-146a levels were significantly higher in OSCC patients (sensitivity: > 0.72) than in healthy controls, and these levels decreased drastically after tumor resection in these patients ([61](#)). Similarly, higher

plasma miR-187-3p level was found to be another potential marker of OSCC diagnosis, and the plasma levels of miR-187-3p were significantly reduced after tumor resection in patients who had better prognosis ([62](#)). Studies have also suggested that circulating miR-196a, miR-196b, and miR-200b-3p levels in plasma might serve as a panel of plasma biomarkers for the early detection of oral cancer ([63](#) - [65](#)). In a separate study, three plasma miRNAs—miR-222-3p, miR-150-5p, and miR-423-5p—were identified for early detection of malignant OSCC ([66](#)). miR-222-3p and miR-423-5p negatively correlated with T stage, lymph node metastasis status, and clinical stage. A high diagnostic accuracy (area under curve = 0. 88) was demonstrated for discriminating oral leukoplakia from OSCC ([66](#)).

Serum

A miRNA microarray experiment using serum samples from OSCC patients vs. healthy controls revealed 16 miRNAs were significantly upregulated and 10 were significantly downregulated in the patients. miR-483-5p expression was significantly correlated (sensitivity = 0. 853, specificity = 0. 746) with lymph node metastasis and shorter survival, suggesting increased miR-483-5p expression in OSCC and suggesting its potential as a novel diagnostic and prognostic biomarker for OSCC ([67](#)). Further, low serum miR-9 level correlated with poor prognosis of OSCC ([68](#)). Recently, another study compared the circulating miRNA profile with the respective tumor-specific dysregulated miRNA profile and suggested that hsa-miR-32-5p in serum is a potential non-invasive biomarker for OSCC ([69](#)).

Whole Blood

Circulating miR-21 level and *PTEN* expression observed in whole blood samples could be possible biomarkers for detection of OSCC ([70](#)). Ries et al. ([71](#) - [73](#)) suggested that whole-blood sample is more reliable than only one specific blood component (serum/plasma/circulating cells) for identifying miRNA biomarkers for OSCC using a minimally invasive method. Microarray-based miRNA expression profiling was performed on 20 whole-blood samples (in a PAXgene blood RNA tube) from OSCC patients and healthy volunteers, and the results were validated through qRT-PCR using another 57 OSCC patient samples and 33 healthy control samples. This study showed that miR-186 was downregulated and miR-3651 and miR-494 were upregulated significantly in OSCC ([71](#)). In further studies, the authors evaluated these circulating miRNA biomarkers with diagnostic and prognostic significance in different patient cohorts ([72](#)). They also showed that the circulating miRNA expression signature (from whole-blood sample) was different from the miRNA expression in OSCC tissues ([73](#)). This is probably because the changes in miRNA expression in circulation occur as a consequence of pathogenic reactions upon immune-pathogenic interactions in response to cancer.

On the basis of all these studies, we can suggest that liquid biopsy would be a reliable, consistent, rapid, easy, cheap, and minimally invasive method to determine miRNA expression signatures to predict OSCC diagnosis and prognosis ([57](#) , [74](#)). Evident challenges persist in terms of quality and quantity (for high-throughput techniques) of RNA and usage of proper endogenous controls for data normalization ([75](#) - [77](#)). To overcome these

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issues, recently advanced instruments (Qubit, concentrator, droplet digital PCR) and advanced modified assay protocols (inclusion of exogenous spike-in-control and newly identified endogenous cell-free control miRNA) have been introduced to obtain reliable, potential predictive biomarkers for OSCC ([75](#), [77](#), [78](#)). We prepared a list of dysregulated miRNAs, in which each miRNA is representative of a particular miRNA expression signature in tumor tissues/cell lines and/or in circulation/other body fluids ([Supplementary Table 1](#)). Individual studies on the effect of one/two miRNAs with clinical significance were also included in this table. Each miRNA is accountable either for sole or cumulative functions related to OSCC pathogenesis, progression, differential tumor behavior, aggressiveness, invasion, and metastasis, resulting in distinct outcome for each patient with OSCC.

Clinical Significance of Dysregulated MicroRNAs in the Diagnosis and Prognosis of OSCC

miRNA Signature for Susceptibility to OSCC

A major goal of precision medicine is to assess disease risk based on the genetic makeup of an individual. SNPs in various miRNAs have also been shown to be associated with different cancers. Dysregulation due to distinct polymorphisms in mature miRNAs, particularly miR-196a2 rs11614913 C> T, miR-146a rs2910164 G> C, miR-149 rs2292832 C> T, and miR-499 rs3746444 A> G, are associated with the risk of OSCC ([45](#), [63](#), [79](#)). In addition, polymorphisms in miR-146a [genotype: CC vs. GG + CG; odds ratio (OR) = 0.874, $p = 0.041$] and miR-196a2 (genotype: TT vs. TC + CC; OR <1, $p < 0.05$) increase the risk of OSCC, whereas the miR-499 polymorphisms (G allele and the GG genotype; OR > 1, $p < 0.05$) exert

protective effects against OSCC risk. In this context, study results on miR-149 polymorphisms are not significant. They are associated with both increased risk of nodal metastasis and poor survival in OSCC, although another research group disclosed that they appeared to have no significant relationship with the risk of OSCC ([80](#), [81](#)).

miRNAs as Early Biomarkers for OSCC Diagnosis

Early detection of OSCC allows clinicians to provide proper administration of curative treatment long before it metastasizes and progresses to the advanced stages. The identification of biomarkers for early detection and prognostication of OSCC through minimally invasive or non-invasive methods acquires major emphasis in current investigative drives. A targeted miRNA expression profiling study (using 22 oral leukoplakia tissue samples with different grades of dysplasia, 17 OSCC samples, and six normal oral mucosa samples) demonstrated the prognostic values of miR-21, miR-181b, and miR-345 in oral leukoplakia with severe dysplasia. Although dysplasia grading is not a very reliable predictor, advanced aggressive dysplasia progresses to OSCC ([82](#)). Other studies using tumor tissues revealed that miR-137 and miR-29a/b/c could be potential biomarkers for early diagnosis of OSCC. miR-29s (miR-29a/b/c) were significantly downregulated in OSCC patients ([83](#)). Consecutively, circulating miR-223 and miR-10b in plasma were proposed to be potential biomarkers for early detection of oral cancer ([38](#), [84](#)). Further, miR-146a, miR-187-3p, miR-196a, miR-196b, miR-200b-3p, miR-222-3p, miR-223, miR-150-5p, and miR-423-5p levels in plasma could also be potential diagnostic markers for early detection of OSCC ([61](#) - [66](#)). A separate study described serum miR-32-5p as a potential biomarker for OSCC ([69](#)).

miRNAs as Biomarkers for OSCC Prognostication

Lymph Node Invasion and Distant Metastasis in OSCC

Epithelial-mesenchymal transition (EMT) of cancer cells is directly associated with cellular migration/invasion leading to cancer metastasis. In OSCC, ample dysregulated miRNAs have been found to be involved in EMT, invasion, and metastasis, which are primarily responsible for lymph node metastasis and distant metastasis.

In preclinical OSCC cell lines, miR-130b, miR-134, miR-149, miR-181d, miR-146b, miR-491, and miR-27a-3p are associated with EMT and cellular migration through targeting BMI1, MMP9, E-cadherin, and the YAP1-OCT4-Sox2 signaling axis ([85](#), [86](#)). High levels of miR-1275 and low levels of miR-222-3p and miR-423-5p are correlated with induced regional lymph node invasion in OSCC ([40](#)). Similarly, other studies have suggested that upregulation of miR-187, miR-196b, miR-372, miR-373, and miR-483 could be potential biomarkers for nodal metastasis in HNSCC ([38](#), [62](#), [67](#), [87](#) - [90](#)). ZEB1, Twist, and Snail (EMT-related transcription factors) are directly regulated by miR-429 and miR-101 and inversely by let-7d and mediate tumor growth and metastasis in OSCC ([35](#), [91](#) - [93](#)). Downregulation of miR-300 is another requirement for EMT initiation and maintenance, mediated through modulation of Twist expression and the transforming growth factor (TGF) β signaling pathway in OSCC ([94](#)). Bufalino et al. ([95](#)) demonstrated that lymph node metastasis resulted from downregulation of the miR-143/miR-145 cluster and consequent induction of activin-A, which contributed to poor prognosis through induced EMT. Similarly, RUNX2 is directly regulated by miR-376c-3p, which was found to be downregulated

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and to promote lymph node metastasis in OSCC ([96](#)). Other studies also demonstrated that the miR-23b/27b cluster regulates the MET oncogene, whereas miR-29a/b/c regulates the expression of *MMP2*, *LAMC2*, and *ITGA6*, responsible for disease invasion and metastasis in OSCC ([83](#), [97](#), [98](#)). Further, miR-218 is directly correlated with increased invasion and cellular migration mediated through *LAMB3* and *RICTOR* and the focal adhesion and mTOR-Akt signaling pathways ([99](#), [100](#)). *EGFR*, *c-MET*, and *KRAS* are direct targets of miR-1 and miR-206. Both these miRNAs, particularly miR-206, are significantly associated with advanced tumor node metastasis (node positivity in the Tumor Node Metastasis staging system) and shorter overall survival in OSCC ([101](#), [102](#)). Moreover, high expression of miR-196a and miR-149 polymorphisms is associated with increased risk of nodal metastasis ([63](#), [80](#)).

Biomarkers for Locoregional Recurrence in OSCC

The evolution of second primary or locoregional recurrence is unpredictable. In most cases, relapses are detected in late stages, which significantly reduce survival and worsen morbidity. Salvage surgery can cure recurrent tumors effectively if detected early.

Low miR-422a expression in stage III-IV tumors promotes local recurrence *via* targeting oncogenic *CD73* when compared with that in oropharynx stage III-IV tumors, without relapse or with locoregional relapse within 2 years of posttreatment ([103](#)). Other studies have shown that miR-196a, miR-205, and miR-675 are significantly associated with locoregional recurrence at diagnosis and treatment in OSCC ([35](#), [80](#), [103](#), [104](#)). miR-451 was found

to be significantly overexpressed (4.7-fold) in non-relapsed vs. relapsed patients ([37](#)). Furthermore, locoregional recurrence in OSCC is also significantly affected by polymorphisms in miR-196a ([63](#)). All these indicators could be building blocks for developing meaningful biomarkers for early disease prognostication, recurrence, and/or metastasis in the clinical setting.

Dysregulated miRNAs Associated With Response to Chemoradiation Therapy in OSCC

Until date, cetuximab is the only clinically applied targeted drug used to treat patients with OSCC. However, the occurrence of therapeutic resistance or non-responsiveness has been found during chemotherapy/radiotherapy treatment in patients with OSCC. Several studies identified miRNAs as potential biomarkers to predict the sensitivity/resistance of tumors to chemotherapy or a particular drug used in chemotherapy and radiotherapy for OSCC.

Henson et al. ([105](#)) showed that the amplification of chromosomal band 11q13, loss of distal 11q, and downregulation of miR-125b and miR-100 are associated with radioresistance and disease progression ([105](#), [106](#)). In our previous study, we identified six cisplatin resistance-specific signature miRNAs—miR-130b, miR-134, miR-149, miR-181d, miR-146b, and miR-491. These miRNAs function in OSCC mainly through modulating the expression of proteins related to cancer stem cells (augmentation of CD44, c-Myc, and Oct-4), drug resistance (upregulation of P-gp and MRP1), and EMT (increase in BMI1 and MMP9 expression and loss of E-cadherin) ([85](#)). Low miR-29a level is reported to be associated with induced drug resistance and invasion ([97](#)).

High miR-196a and miR-21 levels enhance radioresistance through inhibiting annexin A1 and signal transducer and activator of transcription 3 (STAT3), respectively ([107](#), [108](#)). Moreover, low Dicer expression is associated with resistance to 5-fluorouracil-based chemoradiotherapy and shorter overall survival in patients with OSCC ([109](#)). In brief, upregulation of the let-7 family, miR-203, miR-23a, miR-214, miR-518c, and miR-608 and downregulation of miR-21 and miR-342 have been shown to be connected with the manifestation of chemosensitivity/chemoresistance in OSCC ([91](#), [110](#), [111](#)). Moreover, therapeutic resistance is mediated through EGFR and c-MET, which are further alleviated by low levels of miR-1 and miR-206 in OSCC ([102](#)). However, determination of the exact range (single/panel) of these miRNA biomarkers as well as the spectrum of their expression level needs to be extremely accurate, sensitive, and specific in order to predict optimum therapy response in OSCC.

Biomarkers for Prediction of Patient Survival in OSCC

The relation between disease-free survival and overall survival of OSCC patients and aberrant miRNA expression has been studied by several investigators. Early detection and prompt treatment using suitable multidisciplinary protocols could improve survival in OSCC. Earlier evidence has shown that irrespective of tumor size, poor patient survival is significantly correlated with lower expression levels of miR-9, miR-149, miR-150-5p, miR-200b, miR-205, miR-375, miR-483-5p, miR-542-3p, and let-7d ([35](#), [62](#), [68](#), [103](#), [104](#), [112](#) - [118](#)). Concurrently, it was also found that overexpression of miR-1246 and miR-675 and downregulation of miR-187 and miR-134 in plasma are associated with better patient survival in OSCC (<https://assignbuster.com/functional-landscape-of-dysregulated-micrnas-in-oral-squamous-cell-carcinoma-clinical-implications/>

[35](#), [62](#), [67](#), [68](#), [103](#), [104](#), [112](#) - [118](#)). Moreover, other studies discovered that decreased levels of Dicer and miR-206 correlate significantly with lower overall survival in OSCC ([101](#), [109](#)).

Advanced Therapeutics Based on MicroRNA Expression in Oral Squamous Cell Carcinoma

As described above, a variety of tumor-specific dysregulated miRNAs have been identified in OSCC, with either tumor suppressor or oncogenic functions. However, the challenges that remain for therapeutic application of miRNAs in OSCC are as follows: (a) miRNA selection, (b) complex regulatory mechanisms, (c) delivery, (d) pharmacokinetics, and (e) toxicity.

Nevertheless, being endogenous molecules, miRNAs exhibit low toxicity in humans. Further, owing to their small size, miRNAs can be introduced into the system through different delivery methods.

In this context, so far, miRNA sponging, locked nucleic acid-mediated suppression of oncogenic miRNAs, and replacement of tumor-suppressive miRNAs using respective mimics/viral vectors/small compounds have already been used for different cancers ([17](#), [119](#)). To this end, the efficacy and accuracy of the miRNA delivery system are very important. Two main miRNA delivery approaches have been described: local (intra-tumor) and systemic. Systemic approaches would be suitable for metastatic or late-stage advanced cancers. The miRNA could be conjugated with a folate ligand, such as vitamin B9, for selective delivery to treat the cancer ([17](#), [119](#)). In addition, exosome/microvesicle/liposome-mediated delivery of miRNAs could also be used as novel tools for miRNA-based cancer therapy ([53](#)).

Interestingly, therapeutic delivery of miRNA may be possible just through <https://assignbuster.com/functional-landscape-of-dysregulated-micrnas-in-oral-squamous-cell-carcinoma-clinical-implications/>

oral intake of vegetables, since it has been found that humans and animals can acquire plant miRNAs in their sera or body fluids through food intake ([120](#)). The first miRNA-based therapy specifically for cancer is MRX34, wherein a synthetic miR-34a mimic is loaded into liposomal nanoparticles ([121](#)). Quantification of MRX34 in non-human primates has established a satisfactory 7.7 h half-life in whole blood ([122](#)). Currently, only two observational miRNA-based therapies, miR-29b and miR-29, have progressed to clinical trials (Trial ref No.: NCT02009852 and NCT01927354, respectively) for OSCC. Further studies on miRNA-based diagnostics and therapies need to be evaluated extensively for OSCC treatment.

Conclusion

This review highlighted the functional landscape of dysregulated miRNAs in OSCC from a clinical perspective. We identified 17 miRNAs (let-7d, miR-1, miR-125b-5p, miR-138-5p, miR-142, miR-145, miR-155, miR-16, miR-196a, miR-196b, miR-200c, miR-20a-5p, miR-21-5p, miR-218, miR-31-5p, miR-34a, and miR-375) commonly dysregulated in OSCC and that have been found to have clinical significance in three or more extensive studies. We also found 22 miRNAs (let-7d, miR-125b-5p, miR-145, miR-146a, miR-150, miR-16, miR-184, miR-191, miR-196a, miR-196b, miR-21-5p, miR-223, miR-24, miR-26a, miR-27b, miR-29a, miR-31-5p, miR-32-5p, miR-375, miR-451, miR-9 and miR-99b-3p) to be significantly dysregulated in two or more clinical sample types (tumor tissues/epithelial cells and one or more circulating body fluid) collected from OSCC patients. These miRNAs could have the potential for clinical application for disease diagnosis, patient stratification, and therapy in OSCC. Six miRNAs (miR-146a, miR-148a, miR-24, miR-438-5p, miR-9, and <https://assignbuster.com/functional-landscape-of-dysregulated-micrnas-in-oral-squamous-cell-carcinoma-clinical-implications/>

miR-99b-3p) which are common to different types of biological fluid samples (blood/plasma/serum/saliva) from OSCC patients could be potential biomarkers through minimally invasive or non-invasive methods to predict OSCC more accurately. Logical selection, validation, and confirmation of these potential miRNA biomarkers (single/panel) are very important for augmenting their specific clinical applications in OSCC.

The number of human miRNAs (> 2, 600) in miRbase significantly increases in every successive version of the database (recent is v22. 1) due to continuous inclusion of novel miRNAs ([123](#)). In most of the cases, the newer studies came up with new sets of dysregulated miRNA signatures for OSCC detection and prognostication. Therefore, large differences are frequently found in the results of similar older studies and current large-scale data sets. The ethnicity of the recruited patient population is also an important issue in this situation. In the current review, importantly, we summarized the recent progress on elucidating the clinical significance of miRNAs (tumor-associated or circulating), especially with respect to possible ways to develop miRNA-based detection and prognostication methods in conjunction with available techniques. Recent evidence increasingly demonstrates that cell-free miRNAs are evolving as consistent and reliable biomarkers for early detection, disease monitoring, and patient stratification, as well as guides to optimum treatment protocols for patients with OSCC.

In conclusion, a wide variety of dysregulated miRNAs contribute to the OSCC phenotype and differential patient outcomes, including tumor progression, therapy response, recurrence, metastasis, and survival. Moreover, miRNA-

mediated regulatory mechanisms are complex and tangled with numerous interconnected physiological events. Here, one of the biggest challenges is to identify the tailor-made potentially relevant key miRNA candidates (single or in spectrum) along with or without their key targets for detection of disease and stratification of each patient with OSCC. Therefore, on the basis of our previous knowledge, careful, logical selection, and functional characterization of signature miRNAs (mentioned above) are very important. Standardized validation studies must be undertaken to ensure the sensitivity, specificity, and robustness of the signature miRNAs for individual patient conditions. Thus, well-designed, multicentered, prospective trials with large patient cohorts would be necessary to mitigate external variations in data sets. This will provide useful information for molecular diagnostics and determination of prognostic information for improved management of OSCC.

Author Contributions

RG conceived the idea, collected all data, and designed and wrote the manuscript. SR and AP supervised and contributed with their expert comments and views in the logical presentation of manuscript and checked and edited the manuscript. All authors approved the final manuscript.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary Material

The Supplementary Material for this article can be found online at:

<https://www.frontiersin.org/articles/10.3389/fonc.2020.00619/full#supplementary-material>

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