ORIGINAL RESEARCH PAPER
Volume-8 | Issue-11 | November - 2019 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# DIAGNOSTIC POTENTIAL OF SALIVARY MICRORNAS (MIRNAS) IN EARLY DETECTION OF ORAL SQUAMOUS CELL CARCINOMA (OSCC): A SYSTEMATIC REVIEW

Oncology

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## ABSTRACT

**OBJECTIVES:** To analyze the available literature to assess the diagnostic potential of salivary miRNAs in the early detection of OSCC.
**MATERIALS AND METHODS:** A systematic review was carried out in the PubMed/ Medline electronic databases with keywords "Salivary microRNAs and Oral Cancer" and articles fulfilling the objective of the study were included.
**RESULTS:** The searches revealed 968 articles out of which 11 articles conducted on isolation of miRNAs from saliva of OSCC patients were included in this systematic review. Evidence from various studies suggests that miRNAs are significantly de-regulated in saliva of OSCC patients compared to healthy controls. Most of miRNAs were under expressed (miRNA125a, miRNA-136, miR-137 and miRNA-147, miR-193a miR-200, miRNA200a, miR-205 miRNA-1250, miRNA-148a, miRNA-632, miRNA-646, miRNA668, miRNA-877, miRNA-503, miRNA-220a, miRNA-323-5p), 2 miRNAs were over expressed (miRNA-24, miRNA-27b), MiRNA-27b levels were significantly higher in OSCC patients.
**CONCLUSION:** OSCC is associated with a range dysregulated miRNA expression patterns particularly under expression which indicates tumor expansion and progression. miRNAs in human saliva may be used as potential biomarkers for early diagnosis of OSCC as well as postoperative follow-up. Saliva based diagnostics offers a promising future as it can be used as a non-invasive and rapid diagnostic tool for detection of OSCC.

## KEYWORDS

Salivary Mirnas, Mir-31, Rt-pcr, Taqman Microrna Assays

## INTRODUCTION

Oral squamous cell carcinomas (OSCC) are the sixth most common malignancies affecting more than half a million people every year.[1] Since, oral cancer begins as a painless lesion, it goes undetected at the early stages and patients usually seek advice when lesion becomes obvious or when normal functions are affected. Around 6,57,000 new cases of oral and para oral cancers are detected each year and more than 3,30,000 deaths are recorded annualy posing as a major public health issue particularly in the South East Asian countries including India.[2-4]

The oral potentially malignant disorders (OPMD) are symptomless in the early stages and therefore are often missed during the routine examinations.[5] Prevention of OSCC becomes essential because of its high mortality rates along with low survival rate of five years. Hence, developing novel strategies for early cancer detection takes a front seat in reducing the mortality and morbidity.[6] Even though, tissue biopsy is the standard procedure for diagnosis, various adjuncts for early diagnosis aids like VelScope, Microlux DX, Vizilite, Brush biopsy and other diagnostic aids are used. Salivary biomarkers are taking a lead among the advanced diagnostic aids as they are simple, noninvasive and often carried out at point of care settings which have a good sensitivity and specificity.[7]

The saliva comprises of a wide array of biomarkers like proteins, peptides, electrolytes, organic and inorganic salts secreted by salivary glands and gingival crevicular fluid.[8] Numerous promising biomarkers based on DNA, RNA, mRNA, microRNA (miRNA) have been investigated for their diagnostic potential.[9] Among these, the microRNAs (miRNAs) in human saliva have become a promising diagnostic tool in early oral cancer detection.

miRNAs are short and noncoding type of RNA molecules that are associated with regulating of a variety of cellular processes and their dysregulation are associated with various diseases including oral cancers.[10] miRNAs are abundantly found in saliva of OSCC patients and can be used as potential biomarkers of oral cancers.[10,11] miRNAs play a significant role in various biochemical mechanisms like carcinogenesis, cell proliferation and embryogenesis.[11] There are numerous promising salivary miRNAs that can be utilized in oral cancer detection. Since there is paucity of data regarding the diagnostic potential of miRNAs, the present systematic review was undertaken with an objective to analyze the diagnostic utility of miRNAs in OSCC detection.

## OBJECTIVES OF THE SYSTEMATIC REVIEW:

1. To assess over-expression (upregulation) and under-expression (downregulation) of miRNAs in Oral Squamous cell carcinomas (OSCC).
2. To analyze the most sensitive and specific miRNAs in detecting OSCC and prognosis after surgical intervention and radiotherapy.

## MATERIALS AND METHODS:

A systematic literature survey was carried out to provide regarding the utility of miRNAs in the diagnosis of oral squamous cell carcinoma.

## SEARCH STRATEGY

In this systematic review, MeSH terms/keywords were used to search the PubMed data base, SCOPUS, EMBASE, COCHRANRE library, Science Direct and a manual search was also done, and studies from 2000 to 2019 fulfilling the objectives of the study were included in this study.

Searches was carried out in the electronic data bases in "English Language" with key words such as "saliva and microRNA" "microRNA and cancer" "miRNA and oral cancer" "salivary miRNA and oral cancer" "miRNA and oral squamous cell carcinoma, "miRNA and tongue cancer"

## SELECTION CRITERIA

### INCLUSION CRITERIA

1. Studies on expression of salivary miRNAs in Oral squamous cell carcinoma (OSCC)
2. Studies on expression of salivary miRNAs after oral cancer treatment.
3. Studies carried out on humans.
4. Clinical trials, randomized controlled studies, case control study.

### EXCLUSION CRITERIA

1. Studies on expression of miRNAs in serum, plasma, or tissues of OSCC or any other medium.
2. Studies done on carcinoma other than OSCC.
3. Animal based studies.

4. Reviews.

The searches revealed 968 articles out of which 54 were selected after reading the titles and abstracts.4 articles were added from hand searching to obtain a total of 58 articles. After applying the inclusion and exclusion criteria, 27 were excluded. 31 articles were obtained after screening full text articles and after quality assessment, 20 studies carried out on isolation of miRNAs from serum and tissue biopsies were excluded. In the end, 11 articles conducted on isolation of miRNAs from saliva of OSCC patients were included in this systematic review.

## DATA EXTRACTION

The selected studies were evaluated by two reviewers after quality assessment and a data extraction table was developed. It comprised miRNAs panels, number of samples, population, cases and healthy controls, expression of miRNAs, sensitivity and specificity, year of study and author's name. The resultant data was analyzed interpreted.

## MICRORNAS

miRNAs are small single-stranded RNA molecules, about 19 to 24 nucleotides (nt) long, that regulate gene expression and perform various other important functions.[12] miRNAs are derived from polymerase II controlled transcriptional regions. The primary transcript forms one or several bulging double stranded hairpins which are processed by Drosha and Dicer into hetero-duplexes.[13] miRNAs are secreted by various body cells and present in body fluids like blood, urine and saliva which can be easily quantified and used as diagnosis of various diseases, mainly cancers.[12-16] miRNA is useful for characterizing solid tumor types as compared to mRNA. miRNAs have the ability to precisely discriminate poorly differentiated tumors from mRNA.[17] A wide panel of miRNAs can therefore be used in oral cancer diagnosis.[15,17]

## PROFILING OF MIRNAS

miRNAs are relatively stable and easily found in salivary samples. Draining, spitting, and suction methods are some of the most common approaches for saliva collection. Successful miRNA profiling can be done using RNA isolation kits and detected with Reverse transcriptase- polymerase chain reaction (RT-PCR), Taqman microRNA assays, Northern blotting, Real-time RT-PCR microRNA arrays and In situ hybridization (ISH).[18-20]

## SALIVARY MIRNAS AND ORAL CANCER DIAGNOSIS

Unlike other bio-signatures like transcriptomic and proteomic markers, salivary miRNAs play an important role in diagnosis of various diseases especially potentially OSCC. [11,17,20] miRNAs have a significant function in controlling various intracellular mechanisms such as cell growth, differentiation, apoptosis, and immune response and a single miRNA can possibly bind to over 100 different mRNAs because of its imperfect complementary binding mechanisms.[15,21,22]

The human genome is found to be composed of more than 1,000 different types of miRNAs and over 30% of human mRNAs are regulated by miRNAs.[14,21] miRNAs dysregulation is known to affect cell growth. It can function as tumor suppressors or oncogenes and affect cell proliferation, apoptosis, and chemotherapy resistance in OSCC patients.[21,22]The miRNAs expression is hence different in OSCC cases when compared to healthy controls and therefore used in cancer diagnostics.[23]

## RESULTS:

| miRNA panel | Sources of the samples | Study population: cases, healthy controls, | Sensitivity, specificity, and AUC | Dys-regulation | Author and Year |
|---|---|---|---|---|---|
| miR-139-5p | Saliva | cases =25 (tongue cancer) Healthy controls=25 | Pre-operative (AUC: 0.805) and post-operative TSCC patients (AUC: 0.713) | Down-regulation: of miR-139-5p in the Tongue cancer validation samples compared to the controls. | Duz MB et. al, 2016[24] |
| miR-412-3p, miR-489-3p, miR-512-3p, miR-597-5p,and miR-603, miR-27a-3p, miR-302b-3p, miR-337-5p, miR-373-3p, miR-494-3p, miR-517b, and miR-520d-3p, miR-645 | Saliva | Cases =21 (OSCC) Healthy contrils=11 | | up-regulated: (miR-412-3p, miR-489-3p, miR-512-3p, miR-597-5p, and miR-603)<br><br>Down-regulated: (miR-193b-3p, miR-30e-3p, miR-376c-3p, miR-484, miR-720, and miR-93-3p | Gai C etal, 2018.[25] |
| miR-31 | Saliva | Cases: Patients with oral carcinoma (n = 45), oral verrucous leukoplakia (n = 10), and control healthy individuals (n = 24) | | Up-regulation: Salivary miR-31 After excision of oral carcinoma, salivary miR-31 was remarkably reduced, | Liu CJ et. al 2012.[26] |
| miR-31 | Saliva | Cases: 35 OC and Healthy controls: 20 | | Up-regulation: miR-31was significantly higher in in control group). | Khadim AM et. al 2015.[27] |
| miR-21 and miR-31 | Saliva | Cases: 20 (OPMD) Healthy Controls =20 | | Upregulation: salivary miR-21 and miR-31 expression in OPMD cases. | Hung KF et. al 2016.[28] |
| MiRNA-27b , miRNA-24, miRNA-27b). miRNA-136, miRNA-147, miRNA-1250, miRNA-148a, miRNA-632, miRNA-646, miRNA668, miRNA-877, miRNA-503, miRNA-220a, miRNA-323-5p) | Saliva | Case: 34 ( 4 groups of subjects-including patients with oral squamous cell carcinoma (OSCC), patients with OSCC in remission (OSCC-R), patients with oral lichen planus, and healthy controls (HCs)=34 | | Upregulation: (miRNA-24, miRNA-27b). Down regulation: miRNA-136, miRNA-147, miRNA-1250, miRNA-148a, miRNA-632, miRNA-646, miRNA668, miRNA-877, miRNA-503, miRNA-220a, miRNA-323-5p MiRNA-27b levels were significantly higher in OSCC patients compared to those found in HCs | Momen-Heravi F et. al, 2014.[29] |

| | | | | | |
|---|---|---|---|---|---|
| miR-125a and miR-200a, | Saliva | Cases: 50 oral squamous cell carcinoma patients Controls: 50 healthy matched control subjects. | | Down regulation: miRNAs, miR-125a and miR-200a, were present in significantly lower levels (P < 0.05) | Park NJ et. al 2009.[17] |
| miRNAs, miR-223, miR-191, miR-16, miR-203, and miR-24 | Saliva | Cases: 20 healthy donors | | Upregulation: miRNAs, miR-223, miR-191, miR-16, miR-203, and miR-24 | Patel RS et. al 2011.[30] |
| miRNAs miR-9, miR-134 and miR-191 | Saliva | Cases= 56( Head and neck cancer)<br>Healty Controls:= 56 | under the curve (AUC) values of 0.85 and 0.74 (P < 0.001) and 0.98 (P < 0.0001), | Up regulation: miR-9, miR-134, and miR-191 were differentially expres sed between saliva from HNSCC patients and healthy controls, | Salazar C et, al 2018.[22] |
| miR-93,<br>miR-125a, miR-142-3p, miR-200a, miR-203, miR-213, let-7a,<br>let-7b, let-7g and let-7i | Saliva | 83 saliva samples<br>from 33 patients collected at several time points pre-, during<br>and post-radiotherapy treatment. | | Upregulation: miR-93 and miR-200a were signifi cantly higher expre ssed 12 months postra dioth erapy<br>than at baseline (p=0.047 and p=0.036). | Greither T et al, 2017.[31] |
| miRNA-21, miRNA-184, and miRNA-145 | Saliva | Cases: 40 patients OPMDs) [20 with dysplastic lesions and 20 without dysplasia], 20 with biopsy-confirmed (OSCC),<br>Healthy controls: 20 | specificity 65% and sensitivity 65%, | Upregulation: salivary miRNA-21 and miRNA-184 in OSCC and PMD (with and without dysp lasia) when compared to healthy and disease controls (P < 0.001)<br>Downregulation: miRN A-145 levels showed a hig hly significant decrease in OSCC and PMD overall (P < 0.001). | Zahran F et al. 2015.[32] |

## DISCUSSION

Among the emerging trends for advanced diagnostic tools in oral cancer detection, the salivary miRNAs have risen as potential biomarkers which plays a vital role of a marker in the prognosis of oral therapeutic interventions aswell.[33] The innate advantage of using a miRNA profile is that there are only about 200 miRNAs discovered in the cell which can be profiled for identifying a good marker.[34-36] Saliva based diagnostics offers a promising future as it can be used as a non-invasive and rapid diagnostic tool for detection of OSCC.[30] The salivary mRNAs appear to enter the oral cavity through various sources, including the three major saliva glands, gingival crevice fluid, and desquamated oral epithelial cells.

Many recent studies have reported regarding abnormal miRNA expression, associated with initiation, progression and metastasis. The differential expression of miRNAs in OSCC is used to correlate their expression with the clinico-pathological profile of tumours.[37,38] Researchers have found high miR-155-5p expression in tissue samples from subjects with OSCC that had metastasized to cervical lymph nodes which may suggest its role in metastasis.[39] Gombos K et. al who reported over expression of miR-21, miR-155, miR-191 and miR-221 with sensitivity/specificity of tests were over 90% have concluded the role of these miRNAs in carcinogenesis.[40] The over-expression of miR-191 is a novel finding in OSCC and can be potentially explored for its diagnostic value.[40,41]

Manikandan et al have reported regarding the down-regulation of 10 miRNAs such as let-7a, let-7d, let-7f and miR-16 while miR-29b, miR-142-3p, miR-144, miR-203, and miR-223 were upregulated in OSCC.[42] The association of miR-1275 with nodal invasion and the upregulation of miR-144 in OSCC may provide opportunities for development of novel diagnostic aid.

The articles included for the review showed that most of salivary miRNAs were under expressed such as miR-139-5p, miR-193b-3p, miR-30e-3p, miR-376c-3p, miR-484, miR-720, and miR-93-3p, miR-125a and miR-200a, miRNA-145.[24-32] Significant under expression of miRNA which are associated with tumorogenisis such as miR-125a and miR- 200a were found significantly in the saliva of OSCC patients giving an indication regarding the role played by it in carcinogenisis.[17,31] miRNAs can also be used to diagnose the malignant potential of OPMDS aswell. Many are over expressed or upregulated such as miR-412-3p, miR-489-3p, miR-512-3p, miR-597-5p, and miR-603, miR-31, and miR-181b has been demonstrated in oral leukoplakia that progresses to OSCC, suggesting a miRNA signature has a potential prognostic value in identifying leukoplakias at risk of malignant transformation.[43]

Many researchers have validated the diagnostic potential of miR-31 when compared to other miRNAs as it is associated with tumorogenisis. miR-31 was appreciably superior in all stages of oral cancer, and that salivary miR-31 was more copious than blood suggesting that miR-31 originated from oral cancer.[26-28] Further research is essential to explore the diagnostic potential of miR-31 in developing a point of care device for the detection of oral squamous cell carcinoma. Dysregulation of miR-31 has an important diagnostic value as reported by Siow Y et. al and Gissi B et. al.[44,45]

Salivary miRNAs may play a vital role in the future diagnostics of OSCC. However, more studies are required to validate the findings and isolate a potentially common candidate for diagnosis and prognosis of OSCC. This may be a game changer and it may decrease the high mortality associated with oral cancer. Even though, miRNA based diagnostics may be expensive, still it may open doors for the futuristic point of care devises where oral squamous cell carcinoma can be diagnosed at the early stages so that there a good prognosis and better survival rates.

## CONCLUSIONS:

Salivary miRNAs have a promising diagnostic potential because of their unique expression patterns which are specific to oral squamous cell carcinoma.Salivary miRNAs are an emerging biomarker of oral cancer and potentially malignant lesions. It May become the biomarker of oral squamous cell carcinoma of the 21st century. Further validation studies are required to identify an ideal candidate which has high sensitivity and specificity.

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