MicroRNA profile in the squamous cell carcinoma: prognostic and diagnostic roles

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ABSTRACT

Head and neck squamous cell carcinomas (HNSCCs) are human malignancies associated with both genetic and environmental factors. MicroRNAs (miRNAs) as a group of small non-coding RNAs have prominent roles in the development of this kind of cancer. Expressions of several miRNAs have been demonstrated to be increased in HNSCC samples vs. non-malignant tissues. In silico prediction tools and functional analyses have confirmed the function of some miRNAs in the modulation of cancer-associated targets, thus indicating these miRNAs as onco-miRs. Moreover, numerous miRNAs have been down-regulated in HNSCC samples. Their targets mostly enhance cell proliferation or inhibit apoptosis. miRNAs signature has practical implications in the diagnosis, staging, and management of HNSC. Most notably, numerous miRNAs have been shown to alter response of tumor cells to anticancer drugs such as cisplatin and doxorubicin. Circulating levels of these small transcripts have been suggested as promising biomarkers for diagnosis of HNSCC. In the present manuscript, we sum up the available literature regarding the miRNAs signature in HNSCC and their role as diagnostic/prognostic biomarkers.

1. Introduction

Squamous cell carcinoma has been detected in various regions in the head and neck. These cancers have several risk factors including tobacco and alcohol usage for tumors of the oral cavity, oropharynx, hypopharynx, and larynx. Moreover, oncogenic viruses are among the most important risk factors for cancers of the nasopharynx, palateine, and lingual tonsils. Based on the rapid increase in the frequency of human papillomavirus (HPV)–associated oropharyngeal cancer, the incidence of these cancers are expected to exceed the incidence of cervical cancer [1]. The presence of distant metastasis at the time of diagnosis and high occurrence of inoperable local and regional relapses following the primary therapeutic modalities are associated with high mortality rate of HNSCC [2]. Mutations in tumor suppressor genes such as TP53 are detected in head and neck squamous carcinomas (HNSCCs) triggered by smoking and alcohol consumption. Yet, the HPV-positive HNSCCs have their specific expression signature and DNA methylation profiles [3]. In addition to the recurrent mutations in the tumor suppressor genes and differentiation pathways [1], HNSCCs are associated with dysregulation of several microRNAs (miRNAs) [4]. These transcripts are initially produced as primary miRNAs which are afterward processed into pre-miRNA hairpin configurations. Subsequently, these hairpins are processed into short double strand RNA (dsRNA) structures. Ultimately, one strand of this dsRNA produces the mature miRNA [5]. This endogenous small transcripts control expression of their targets at the post-transcriptional level through binding with the 3′ UTR of the mRNA [6]. Based on the significance of miRNAs in the modulation of cell proliferation, differentiation and apoptosis, these small RNAs influence carcinogenesis process and therefore are putative biomarkers in this regard [7]. In the present paper, we summarize the current literature on signature and function of miRNAs in HNSCC. We investigated the PubMed/Medline and google scholar databases with the key words “microRNA” or “miRNA” AND “head and neck squamous cell carcinoma” to retrieve related articles published until February 2020. We firstly
| Author/ year | microRNA | Cancer subtype | Tissues | Clinical samples | Cell line | Targets/Regulators | Signaling Pathways | Function | Clinical outcome |
|-------------|-----------|----------------|---------|------------------|-----------|-------------------|-------------------|----------|-----------------|
| Kalfert et al., 2015 | miR-200c, miR-34a, miR-21 | HNSCC (oropharyngeal, laryngeal and hypopharyngeal carcinomas) | Tumor and normal tissues | 51 HNSCC patients | - | - | - | Have some potential prognostic significance | - |
| Ganci et al., 2017 | miR-429, miR96-5p, miR-21-5p, miR-21-3p | HNSCC | Tumor and normal tissues | 132 HNSCC patients | Ga27 line | CHK2 and EZH2 | cell cycle pathway | These miRNAs are predictors of recurrence when highly expressed. | - |
| Childs et al., 2009 | miR-21 | HNSCC | Tumor and normal tissues | 104 HNSCC patients | - | PDCD4, ACTA2, BTG-2 | RTG-2 | miR-21 via inhibition of PDCD4, ACT2, and BTG-2 could promote invasion and metastasis. | - |
| Hebert et al., 2007 | miR-98 | HNSCC | - | - | SCC-4, SCC-9, UMB-108 | HMG1C | - | miR-98 diminished mRNA expression of HMGA2 and increased cell survival during hypoxia. | - |
| Lubov et al., 2017 | miR-7, miR-9, miR-15, miR-18, miR-19, miR-21, miR-22, miR-24, miR-93, miR-96, miR-99, miR-130, miR-139, miR-141, miR-155, miR-181, miR-195, miR-196, miR-210, miR-211, miR-214, miR-222, miR-296, miR-302, miR-331, miR-345, and miR-424 | HNSCC | Tumor and normal tissues | A meta-analysis study includes 8,194 subjects with HNSCC | - | - | apoptotic and cell death signaling pathways | Significant elevated expressions of these miRNAs were associated with poor prognosis in HNSCC. | - |
| Hou et al., 2015 | miR-223 | HNSCC | Tumor and normal tissues And plasma samples of patients prior and 6 months after surgical removal of tumor | 16 HNSCC patients and 9 paired plasma samples | - | FBXW7/hCdc4 | FGF cell signaling | Dysregulation of plasma miR-223 is a biomarker for cancer recurrence. | - |
| Summerer et al., 2015 | miR-142-3p, miR-186-5p, miR-195-5p, miR-374b-5p and miR-574-3p | HNSCC (oropharyngeal, laryngeal and hypopharyngeal carcinomas) | Tumor and normal tissues And Plasma | 18 HNSCC patients and 10 out of the 18 patients | - | - | - | These miRNAs are HPV-independent markers for HNSCC prognosis in persons treated with combined radiochemotherapy. Up-regulation of miR-186-5p, miR-374b-5p and miR-574-3p before treatment was correlated with reduced PR and/or OS. Up-regulation of miR-228-3p, miR-425-3p, miR-574-3p after treatment was correlated with poor prognosis. | - |
| GOMBOS et al., 2013 | miR-21, miR-155, miR-191 | OSCC | Tumor and normal tissues | 40 HNSCC patients | - | - | - | These oncomirs are promising genomic biomarkers for early-cancer detection. | - |
| GOMBOS et al., 2013 | miR-221 | OSCC | Tumor and normal tissues | 40 HNSCC patients | - | PTEN, TIMP3 | ART pathway | miR-221 increases TRAIL resistance and promotes cellular migration via activation of the ART pathway and metalloproteases | - |
| Chen et al., 2019 | miRNA-10a | OSCC | Tumor and normal tissues | 52 HNSCC patients | SCO090/SOC25 | Gli1/T1 | - | miRNA-10a up-regulation enhances glucose uptake and cell proliferation. | - |
| Schneider et al., 2018 | hsa-miR-32-5p | OSCC | Tumor and normal tissues And serum | 5 HNSCC patients | - | - | - | Marker for OSCC detection. | - |
| Schneider et al., 2018 | hsa-miR-21-5p | OSCC | Tumor and normal tissues And serum | 5 HNSCC patients | - | PTEN | PI3K/Akt pathway and rapid cell growth | Marker of survival and response to treatment | - |

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Table 1 (continued)

| Author/year | microRNA | Cancer subtype | Tissues | Clinical samples | Cell line | Targets/Regulators | Signaling Pathways | Function | Clinical outcome |
|-------------|----------|----------------|---------|------------------|-----------|--------------------|-------------------|----------|-----------------|
| Schneider et al., 2018 | hsa-miR-375 | OSCC | Tumor and normal tissues And serum | 5 HNSCC patients | - | MMP13 | - | Increases metastatic potential and aggressiveness | - | [19] |
| Schneider et al., 2018 | hsa-miR-31-3p | OSCC | Tumor and normal tissues And serum | 5 HNSCC patients | - | Nanog/OCT4/Sox2/ EpCAM | - | hsa-miR-31 is an important regulator of tumor suppressor genes, and associated with decreased survival, and increased cell proliferation. | - | [19] |
| Meekkanan et al., 2016 | miR-144 | OSCC | Tumor and normal tissues | discovery cohort (n = 29), validation cohort (n = 61), 9 independent normal oral specimens | - | PTEN | PI3K/Akt signaling pathway | Associated with regional lymph node invasion | - | [20] |
| Liu et al., 2012 | miR-31 | OSCC | Salivary | 45 patients with OSCC and 24 controls | SAS | HIF | hypoxia pathways | Biomarker for early detection and postoperative follow-up | - | [21] |
| Lu et al., 2016 | miR-31 | HNSCC | Tumor and normal tissues | 58 HNSCC patients | SAS, OECD1, Fabu and HSC HNSCC cells, 293T cell | ARID1A | Nanog/OCT4/Sox2/ EpCAM | miR-31 suppresses ARID1A and enhances the oncogenicity and stemness of HNSCC | - | [22] |
| Rock et al., 2019 | HNnov-miR-3 | OSCC | Tumor and normal tissues | 25 tumor and 5 non-malignant tissue samples | - | - | - | Prognostic marker for recurrence-free and overall survival | - | [23] |
| Rock et al., 2019 | HNnov-miR-2, HNnov-miR-30 | OSCC | Tumor and normal tissues | 25 tumor and 5 non-malignant tissue samples | - | - | - | Significantly associated with HPV status | - | [23] |
| Salazar-Bules et al., 2018 | miR-122-5p | HNSCC | saliva samples | 108 HNSCC patients and 108 controls | - | - | - | A specific biomarker for the diagnosis of HNSCC | - | [24] |
| Salazar-Bules et al., 2018 | miR-146a-5p | HNSCC | saliva samples | 108 HNSCC patients and 108 controls | - | kinase-1 associated with the interleukin-1 receptor NF-κB pathway | inhibits the expression of the kinase-1 associated with the interleukin 1 receptor, participates in the NF-κB pathway | - | [24] |
| Schneider et al., 2018 | miR-21-5p | OSCC | Tumor and normal tissues and serum | five patients | - | PTEN | PI3K/Akt pathway | Regulates cell growth and proliferation by targeting PTEN, biomarker for survival and response to treatment | - | [19] |
| Schneider et al., 2018 | miR-375 | OSCC | Tumor and normal tissues and serum | five patients | - | MMP13 | - | Predictor of prognosis | - | [19] |
| Schneider et al., 2018 | hsa-miR-32-5p | OSCC | Tumor and normal tissues and serum | five patients | - | - | - | Marker for non-invasive diagnosis of patients with OSCC | - | [19] |
| Hu et al., 2015 | miR-223, miR-142-3p, miR- 16, miR-23a | laryngeal SCC | Tumor and normal tissues | 46 patients | - | - | - | Monitoring biomarkers for laryngeal SCC | - | [25] |
| Hu et al., 2015 | miR-21 | laryngeal SCC | Tumor and normal tissues | 46 patients | - | PDCD4 | - | Suppresses tumor growth through decreasing the tumor suppressor tropomyosin 1 | - | [25] |
| Victoria Martinez et al., 2015 | miR-103/miR-307 | HNSCC (oral, oropharyngeal, laryngeal) | Serum | 7 males with HNSCC and 7 healthy - control males | DAPK, KLF4, and NF1 | - | - | An oncomiR that promotes cell proliferation and migration | - | [26] |
| Victoria Martinez et al., 2015 | miR-320 | HNSCC (oral, oropharyngeal, laryngeal) | Serum | 7 males with HNSCC and 7 healthy - control males | CDKN2A and PTEN | - | - | Promotes proliferation by suppression of the cell cycle inhibitors p57 and p21 | - | [26] |
| Ries et al., 2017 | miR-3651 and miR-494 | OSCC | Whole blood | 21 patients with recurrence of OSCC and 21 patients without recurrence | - | - | - | Prognostic factor, useful in design of a minimally invasive strategy for the | - | [27] |
| Author/year | microRNA | Cancer subtype | Tissues | Clinical samples | Cell line | Targets/Regulators | Signaling Pathways | Function | Clinical outcome | Ref |
|-------------|-----------|----------------|---------|------------------|-----------|-------------------|-------------------|----------|-----------------|-----|
| Huang et al., 2016 | miR-21 and miR-31 | OPMD | Tumor and normal tissues and saliva | 20 saliva samples and 46 tissue samples from patients with OPMD | - | - | - | Salivary miR-21 and miR-31 are useful for cancer screening. Epithelial dysplasia and miR-31 up-regulation are markers for recurrence and/or malignant transformation. | [28] |
| RES et al., 2014 | miR-3651 and miR-494 | OSCC | Whole blood | 50 patients and 33 healthy controls | - | - | - | Suppress cell-cycle arrest, - cell senescence, and apoptosis | [29] |
| Xiao et al., 2015 | miR-93 | Laryngeal SCC | Tumor and normal tissues | 59 patients | HEK293 and Hep-2 | cyclin G2 | CCNG2-MMP-9 pathway | Enhanced cell proliferation, reduced apoptosis rate, induced cell cycle arrest and enhanced cell migration and invasion | - | [30] |
| Geng et al., 2016 | miR-365a-3p | Laryngeal SCC | - | - | Human Hep-2 | p-AKT (Ser473) | PI3K/AKT signaling pathway | Promotes cell cycle progression, migration, invasion, tumor growth and metastasis, and suppresses cell apoptosis in laryngeal squamous cell carcinoma | - | [31] |
| Xu et al., 2016a | miR-483-5p | OSCC | sera samples | 101 OSCC patients | - | - | - | Prognostic factor | High serum miR-483-5p expression predicted poor overall survival. Elevated miR-483-5p was predictive for nodal metastases, late cancer stage, and poor prognosis. | [32] |
| Baba et al., 2016 | miR-155-5p | OSCC | Tumor and normal tissues | 73 patients | HaCaT and HSC-3 | SOCS1 | STAT3 signaling pathway | miR-155-5p enhanced OSCC cell migration rather than enhanced proliferation; may act as an EMT activator that decreases SOCS1 level and promotes STAT3 signaling. High levels of miR-155-5p were associated with a poor prognosis. | - | [33] |
| Zahran et al., 2015 | miR21, miR-184 | OSCC | Salivary | 80 subjects with HNSCC and 20 healthy controls | - | - | - | Diagnostic biomarkers for oral malignant transformation. There was a remarkable increase in salivary miRNA-21 and miR-184 in OSCC and potentially malignant disorders | - | [34] |
| Ren et al., 2014 | miR-21 | tongue SCC | Tumor and normal adjacent tissue | 24 patients | Tca8113 and CAL-27 | PDCD4 | mitochondrial apoptosis pathway | Regulate chemosensitivity to cisplatin by targeting PDCD4. Inhibition of miR-21 or PDCD4 can enhance or decrease cisplatin induced apoptosis, respectively, through modulation of | - | [35] |

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| Author/year | microRNA | Cancer subtype | Tissues | Clinical samples | Cell line | Targets/Regulators | Signaling Pathways | Function | Clinical outcome | Ref |
|-------------|----------|----------------|---------|-----------------|-----------|-------------------|-------------------|----------|-----------------|-----|
| Supic et al., 2018 | miR-183 and miR-21 | tongue SOC | fresh-frozen tissue of tongue carcinomas | 60 patients | - | - | - | miR-183 and miR-21 - tumor tissue are markers of clinical stage and poor survival of patients and may be associated with high alcohol use. | [36] |
| Weng et al., 2017 | miR-373-3p | tongue SOC | tumor and adjacent normal tissues | 63 patients | SOC-9, SOC-15, SCC-25, UM1, UM2 | DKK1 | Wnt/β-Catenin Pathway | miR-373-3p targets DKK1 - to increase EMT-associated metastasis. | [37] |
| Fu et al., 2017 | MiR-155 | OSOC | oral mucosa | 46 cases of OSOC and 25 control | Tca8113 cells | p27Kip1 | - | miR-155 induced cell cycle in G1 phase, weakened cell proliferation and blooded cell apoptosis. | [38] |
| Wang et al., 2017a | miR182 | OSCC | tissues and adjacent noncancerous tissues | 10 patients | Tca8113 cells | RASA1 and SPRED1 | Ras-MEK-ERK pathway | miR-182 enhances cell proliferation and cell-cycle progression, inhibits OSCC cell apoptosis and enhances invasive capacity of OSCC cells. | [39] |
| Zhao et al., 2016 | miR-24 | tongue SOC | paired tumor and corresponding non-tumor control tissues | 84 patients | UM1, UM2, Ga227, SCC1, FRXW7 | SCC15 and SCC25 | FRXW7 pathway | miR-24 enhances proliferation, migration and invasion. | - [40] |
| Liu et al., 2018 | MiR-1275 | HNSCC | paired HNSCC and corresponding non-tumor control tissues | 15 patients | PC1-4A/B and PC1-37A/B | IGF-1R and CCR7 | PI3K/AKT pathway | miR-1275 promotes cell migration, invasion and proliferation. | - [41] |
| Yeh et al., 2015 | miR-372 | HNSCC | paired HNSCC and corresponding non-tumor control tissues | 66 patients | FaDu, OC3, OECM1, SAS | p62 | mTOR pathway | miR-372 promotes the migration of HNSCC cells by targeting p62. | - [42] |
| Wong et al., 2008 | miR-184 | tongue SOC | paired tongue SOC and the normal tissues, and plasma from 38 normal individuals and 30 tongue SCC patients | 20 paired tongue SOC and the normal tissues, and plasma | Ca227, HN21B, and HN96 | - | - | miR-184 has antiapoptotic and proliferative effects. | - [43] |
| Lu et al., 2012 | miR-10b | OSCC | plasma samples | 54 patients with oral cancer | SOC25, 8AB, OECM1, OEC3, OECNH8, OECNH9, OECNH4, OECNH4, OEC1, OEC5, OEC6 | - | - | miR-10b increases cell migration and invasion. Plasma miR-10b may be a novel less-invasive biomarker for the early detection of oral cancer. | - [44] |
| Tu et al., 2015 | miR-372 and -373 | OSCC | paired oral SCC and the normal tissues | 50 patients | OECM-1, SAS and normal IAT52 oral keratinocytes | - | - | miR-372 and miR-373 enhance cancer cell migration and invasion in vitro and in vivo. High miR372 and miR-373 expression associated with worse prognosis tumor size, nodal status. | - [45] |
| Sakha et al., 2016 | miR-342-3p and miR-1246 | OSCC | - | - | HOC313 | DENND2D | - | miR-1246 increases cell migration but not cell growth. | - [46] |
| Zhang et al., 2017 | miR-218 | OSCC | paired oral SCC and the normal tissues | 61 patients | UM1, UM2, Ga227, MiH13864a, SCC1, SCC15, SCC25, Tca8113 | PPP2R5A | PPP2R5A/Wnt signaling pathway | miR-218 induced cell survival and resistance to cisplatin, and inhibits apoptosis by targeting PPP2R5A. | - [47] |
| Du et al., 2017 | miR-221 | OSCC | - | - | SCG4 and SCC9 | TIMP3 | - | miR-221 protects cancer cells from apoptosis. | - [48] |
| Zhou et al., 2016 | miR-221/222 | OSCC | - | - | 293T, CALZF and HCC6 | PTEN | - | - | - [49] |
| Author/year | microRNA | Cancer subtype | Tissues | Clinical samples | Cell line | Targets/Regulators | Signaling Pathways | Function | Clinical outcome | Ref |
|-------------|----------|----------------|---------|------------------|-----------|-------------------|-------------------|----------|-----------------|-----|
| Zheng et al., 2015 | miR-24 | tongue SCC | paired tumor and normal tissues | 79 patients | 8 TSCC cell lines | PTEN | PI3K/Akt signaling pathway | miR-221/222 promotes cell proliferation, induces invasive ability of cells and inhibits cell apoptosis. | miR-24 induces cell survival, cell invasion and migration and cisplatin resistance through targeting PTEN. |
| Cheng et al., 2016 | miR-455-5p | OSCC | paired tumor and normal tissues | 40 patients | CGH9K2, OEC-M1, SCC15, TW26 | U828B/TGF-β | TGF-β/SMAD pathway | miR-8-5p enhances the proliferation and growth of cells. |
| Guo et al., 2015 | miR-96 | tongue SCC | paired tumor and normal tissues | 50 patients | Tca8113 and hNOK | MT81 | - | miR-9-6 mediates cell proliferation and migration. |
| Liu et al., 2019 | miR-31-5p | OSCC | paired match tumor tissues and adjacent, and sera | 11 patients, sera from 82 oral cancer patients and 53 normal subjects | HaCaT, NOK-168, SCC4, SCC9, SCC16, SCC25, CAL27, UMI/UMZ2, 1386Tu/1386Tu, 686Tu/686Ln | AKT and PTEN | PE3K/AKT pathway | miR-31-5p enhances the tumor growth and proliferation of oral cancer cells. hsa-mir-98-5p plays a diagnostic role in OSCC. |
| Akob et al., 2019 | miR-99b-3p | OSCC | paired match tumor tissues and adjacent, and sera | 36 tumor tissue and 17 healthy oral mucosal tissue | - | - | - | miR-21 can be used as a potential diagnostic marker to evaluate very early malignant changes. |
| Shi et al., 2019 | miR-626 and miR-5100 | OSCC | Serum samples and tissue specimens | 218 patients and 90 healthy controls | - | - | - | These miRNAs strongly relate to the prognosis for OSCC. |
| Li et al., 2018 | miR-182-5p | OSCC | paired tumor and normal tissues | 35 patients | DOK and SAS cells | TMEM182/TNFα | ERK and NF-kB pathways | miR-450a mediates cellular adhesion and invasion in OSCC. miR-450a increases OSCC cells invasion ability. |
| Lin et al., 2016b | miR-187 | OSCC | paired tumor and normal tissues | 56 patients and 19 control subjects | HSC3, OKM5 L, SAS, 293FT | BARX2 | - | miR-187 increases oncogenicity and metastasis. |
| Liu et al., 2015 | miR-92b | OSCC | paired tumor and normal tissues | 85 patients | CAL-27, BaDu, SCC9, SCC25 | NIK | NF-κB signaling pathway | miR-92b enhances cell proliferation and suppress the apoptosis. |
| Peng et al., 2018 | miR-134 | OSCC | paired tumor and normal tissues | 42 patients | - | - | - | miR-134 expression was correlated with poor prognosis and lymph node metastasis. |

(continued on next page)
| Author/year | microRNA | Cancer subtype                  | Tissues                                                   | Clinical samples                                      | Cell line | Targets/Regulators          | Signaling Pathways | Function                                                                 | Clinical outcome                          |
|-------------|----------|--------------------------------|-----------------------------------------------------------|-------------------------------------------------------|-----------|----------------------------|-------------------|--------------------------------------------------------------------------|------------------------------------------|
| Qiao et al., 2017b | miR-27a-3p | OSCC                           | -                                                         | -                                                     | SCC-9 and Tca8113 | SFRP1                      | Wnt/β-catenin signaling pathway | miR-27a-3p stimulates EMT via the Wnt/β-catenin signaling pathway by targeting SFRP1. | Patients with high miR-21 and MYCN expression have a poorer overall survival. |
| Zheng et al., 2016 | miR-21    | Tongue SCC                      | paired tumor and normal tissues                           | 44 patients                                           | Tca8113, SCC-25 and CAL-27 | CADM1/MYCN                | -                              | miR-21 increases chemo-resistance via targeting CADM1.                       |                                           |
| Zhao et al., 2017 | miR-24    | Tongue                          | paired tumor and normal tissues                           | 90 patients                                           | -                      | PTEN                       | -                              | miR-24 was associated with tumor progression.                              | Clinical stage, differentiation, miR-24 level, and PTEN expression level were correlated with prognosis. |
| Chen et al., 2016 | miR-211   | OSCC                           | paired tumor and normal tissues                           | 50 patients                                           | SAS, ORCMI, HSCC, FaDu, OC4, and SCC25; 293T | TCF12                      | 4NQO-miR-211-TCF12-FAM213A cascade | miR-211 is a regulator of OSCC by targeting the TCF12 tumor suppressor.        |                                           |
| AHMAD et al., 2019 | miR-15b-5p | HNSCC (oropharyngeal, laryngeal and hypopharyngeal carcinomas) | paired tumor and normal tissues                           | 51 patients                                           | -                      | -                          | -                              | miR-15b-5p is a biomarker for radiation response.                           |                                           |
| Hu et al., 2019 | miR-196a  | Esophageal SCC                  | tumor tissues and adjacent normal tissues                 | 25 patients with ISCC                                 | Hct-1A and EC109 | ANXA1                      | -                              | miR-196a promotes the proliferation, invasion and migration by targeting ANXA1. |                                           |
| González-Ariagada et al., 2018 | miR-26 and miR-125b | HNSCC (oral, oropharyngeal, laryngeal) | tumor tissues                                             | 16 primary HNSCC with lymph node metastasis           | -                      | -                          | -                              | miR-26 and miR-125b may be related to the progression and metastasis.        |                                           |
| Zhao et al., 2018 | miR-196b  | Laryngeal SCC                   | tumor tissues and normal laryngeal mucosa samples         | 113 tumor tissue from patients and 34 normal laryngeal mucosa samples | TU212 and TU177 | SOCS2                      | -                              | miR-196b promotes cell proliferation and invasion, and precludes apoptosis. | miR-196b expression was an independent prognostic factor of overall survival. |

HNSCC: head and neck squamous cell carcinoma, OSCC: oral squamous cell carcinoma, OPMD: oral potentially malignant disorder.
assessed the abstract to verify the relevance of articles with the topic of the main narrative review. Then, two authors independently went through the data regarding assessed samples (numbers and characteristics), details of in vitro experiments (cell lines, identified targets and related signaling pathway, functional importance of the miRNA) and association between the dysregulated miRNAs and clinical outcome. Subsequently, we summarized the obtained data in Tables.

2. Onco-miRNAs in HNSCC

We extracted the data of up-regulated miRNAs in HNSCC tumors compared with non-malignant tissues and constructed a Table. Totally, we included information of 63 articles showing up-regulation of miRNAs in this kind of cancer in Table 1. In silico prediction tools and functional analyses have confirmed the function of some of these miRNAs in the regulation of cancer-associated targets, thus indicating these miRNAs as onco-miRs. For instance, Ramdas et al. have measured expression of miRNAs in HNSCC and their corresponding normal tissues using miRNA bioarrays. They showed differential expression of 20 miRNAs between these specimens. Authors have also shown down-regulation of targets of these miRNAs. Among these targets were adenomatous polyposis coli (APC), programmed cell death protein 4 (PDCD4) and TGf beta receptor 3 (TGFBR3), thus concluding that over-expression of these miRNAs might contribute in the down-regulation of mRNAs that control growth and characteristics, details of in vitro experiments (cell lines, identified targets and related signaling pathway, functional importance of the miRNA) and association between the dysregulated miRNAs and clinical outcome. Subsequently, we summarized the obtained data in Tables.

3. Tumor suppressor miRNAs in HNSCC

Subsequently, we extracted data of 88 articles which demonstrated down-regulation of miRNAs in tissue/plasma samples of patients with HNSCC compared with controls. Potential targets of these miRNAs have been identified through in silico analyses or functional studies in the original articles. These miRNAs mostly regulate expression of pro-proliferative or anti-apoptotic genes. Lo et al. have shown down-regulation of miR-200c in the regional metastatic lymph node of HNSCC tissues, while BMI1 expression was up-regulated as compared to parental tumors. Their functional investigations demonstrated direct interaction between miR-200c and the 3’ UTR of BMI1 in HNSCC cells. They also reported down-regulation of this miRNA in isolated HNSCC-derived ALDH1+/CD44+/CD133+ cells which had cancer stem cell (CSC) features. Forced over-expression of miR-200c could suppress the malignant CSC-like features of these cells. Notably, miR-200c over-expression decreased expressions of ZEB1, Snail and N-cadherin, while increased E-cadherin expression in ALDH1+/CD44+ cells. The role of miR-200c up-regulation in decreasing malignant phenotype was verified in a xenograft model as well [72]. Using next generation sequencing (NGS) technique, Allen et al. have studied the effect of serum from HNSCC patients on expression of miRNA in exposed cells in vitro. Their results showed induction of a specific miRNA expression profile in the exposed cells following treatment with patients’ serum samples. The analysis of gene ontologies and pathway analysis showed involvement of these miRNAs in cancer-related pathways such as cell cycle and apoptosis. Most importantly, P53 and SLC2A1 were direct targets of these miRNAs [73]. Table 2 displays the list of down-regulated miRNAs in HNSCC samples and their functions.

4. Association with therapeutic response

A number of studies have assessed associations between expression amounts of miRNAs and patients’ response to chemotherapeutic agents. For instance, Hebert et al. have shown that transfection of pre-miR-98™ into HNSCC cells during normoxia decreases expression of HMGA2. As HMGA2 expression promotes selective sensitivity to the topoisomerase II inhibitor, miR-98 confers resistance to doxorubicin and cisplatin [13]. Ren et al. have shown that transfection of miR-21 inhibitor into the tongue SCC cells enhances sensitivity to cisplatin. miR-21 inhibitor also enhances PDCD4 protein level as well. Besides, inhibition of miR-21 or PDCD4 could remarkably increase or decrease cisplatin-induced apoptosis, respectively. Thus, miR-21 has been suggested as a critical factor in modulation of chemosensitivity to cisplatin [35]. Table 3 shows the list of miRNAs that modulate response to doxorubicin or cisplatin.

Moreover, miRNA profiles can also predict response of patients to radiotherapy. Chen et al. have retrieved expression profile of 56 differentially expressed miRNAs between HNSCC tumors and adjacent normal specimens from the Cancer Genome Atlas (TCGA). Then, they compared expression of miRNAs in HNSCC patients getting adjuvant radiotherapy in relation with clinical outcomes. Based on the expression profile of five miRNAs namely miR-99a, miR-31, miR-410, miR-424, and miR-495, authors recognized that only low-risk group would profit from radiotherapy [146]. MI RNAs might also modulate response to targeted therapies such as monoclonal antibodies. Bozec et al. have shown that over-expression of miR-223 in SCC cells not only makes these cells more resistant to cisplatin, docetaxel, and 5-fluorouracil but also aggravates their response to the anti-EGFR monoclonal antibody cetuximab. This
Table 2. List of down-regulated miRNAs in HNSCC.

| Author/year | microRNA | Cancer subtype | Tissues | Numbers of clinical samples | Assessed cell line | Targets/Regulators | Signalling Pathways | Function | Patient's prognosis | Ref |
|-------------|----------|----------------|---------|-----------------------------|-------------------|-------------------|-------------------|----------|-------------------|-----|
| Kalfert et al., 2015 | miR-375 | HNSCC (oropharyngeal, laryngeal and hypopharyngeal carcinomas) | paired tumor and control tissue | 51 patients | - | - | - | Down-regulated in oropharyngeal, laryngeal and hypopharyngeal carcinomas, potential prognostic significance | - |
| Childs et al., 2009 | miR-205, let-7d | HNSCC | paired tumor and control tissues | 104 patients | DHFR, KRAS | PI3 | miR-205 and let-7d could prevent tumor growth by negatively regulating DHFR and p53 pathway as well as KRAS. | Shorter time to death and loco-regional recurrence in patients who have combined lower absolute levels for miR-205 and let-7d. |
| Lo et al., 2011 | miR-200c | HNSCC | paired tumor and control tissue | 5 patients | Isolated ALDH1+CD44+ cell subsets from HNSCC tissue from five patients | BMI1 | ZEB1 and ZEB2 pathways in EMT signaling | miR-200c inhibits self-renewal, radioresistance, high in vivo tumorigenicity, invasion, and distant metastasis in ALDH1+/CD44+ HNSCCs by negatively modulating BMI1. | - |
| Lubov et al., 2017 | miR-17, miR-26, miR-29, miR-31, miR-34, miR-125, miR-126, miR-137, miR-138, miR-143, miR-152, miR-200, miR-203, miR-205, miR-206, miR-218, miR-224, miR-363, miR-375, miR-451, miR-489, miR-491, miR-506, miR-519, miR-639, and let-7d | HNSCC paired tumor and control tissue | A meta-analysis study includes 8,194 subjects with HNSCC | | | | Decreased expressions of these miRNAs were correlated with lower survival and metastasis in HNSCC. | |
| Hou et al., 2015 | miR-99a | HNSCC | paired tumor and control tissue and plasma | 16 paired tissue samples from patients with HNSCC and 9 paired plasma samples prior and 6 months after surgical removal of tumor | - | MTMR3, IGF1R, mTOR, SMARCA5 | | Dyregulation of circulating miR-99a is involved in the therapeutic response. | - |
| Kuo et al., 2014 | miR-99a | oral cancer | paired tumor and normal tissues | 26 patients | NO8s, DOK, CAL-27, SCC-9, SOC-15, SCC-25, OC-2, OC-3, OEC-M1, HSC-3, HMEC-1 | MTMR3 | | | mir-99a has anti-metastatic effect. | - |
| Greither et al., 2017 | miR-93 and miR-200a | HNSCC (oropharyngeal, oral, laryngeal squamous cell carcinomas) | saliva samples | 83 saliva samples from 33 patients collected at numerous times pre-, during and post-radiotherapy treatment. | - | ZEB2 and CTNNB1 | | Biomarkers for the treatment monitoring post-radiation of HNSCC | - |
| Yen et al., 2014 | miR-99a | OSCC | paired tumor and normal tissues | 40 patients | CGHNN5, OC3, OEC-M1, TW26, Fad6, KR, SOC-4, SGC15, SGC29, SGC25, UT-MSCC1, YD-15, DOK, Tel183, UM-D1, HSC-3 | | | | mir-99a acts as a metastasis suppressor and regulates KGF1R expression. | - |
| Yuan et al., 2019 | microRNA-545 | OSCC | paired tumor and normal tissues | 20 patients | HSC2, HSC4, S55, KXN | RIG-1 | | | Human papilloma virus (HPV) infection pathway | tumor suppressive role of miR-545 in OSCC. | - |
| Hudcova et al., 2016 | hsa-miR-375-3p | HNSCC | biopsy samples of tumor from male patients | 42 patients | | | | Down-regulation of hsa-miR-29c-3p in tumor tissue was associated with higher tumor grade. Down-regulation of hsa-miR-29c-3p in tumor-adjacent tissue was associated with worse overall and disease-specific survivals. | - |
| Hudcova et al., 2016 | hsa-miR-29c-3p | HNSCC | | 42 patients | | | | Down-regulation of hsa-miR-29c-3p in tumor tissue was associated with higher tumor grade. Down-regulation of hsa-miR-29c-3p in tumor-adjacent tissue was associated with worse overall and disease-specific survivals. | - |
| Hudcova et al., 2016 | hsa-miR-200b-5p | HNSCC | | 42 patients | | | | Down-regulation of hsa-miR-200b-5p in tumor tissue was | - |

(continued on next page)
| Author/year | microRNA   | Cancer subtype | Tissues                     | Numbers of clinical samples | Assessed cell line | Targets/Regulators | Signaling Pathways       | Function                                      | Patient's prognosis | Ref |
|-------------|------------|----------------|-----------------------------|-----------------------------|--------------------|--------------------|------------------------|-----------------------------------------------|---------------------|-----|
| Ren et al., 2020 | miR-7109-5p | OSCC           | tumor and normal tissues    | six metastic tumor samples, six nonmetastic tumor samples, and six normal tissues | HeLa               | MMP7              | TGFB-beta signaling pathway | Prognostic and diagnostic indicator or potential cancer therapeutic target | -                   | [79]|
| Allen et al., 2018 | miR-33-5p⁶ | HNSCC (oropharyngeal, oral, laryngeal squamous cell carcinoma) | serum samples               | 7 HNSCC patients and 4 healthy individuals | HeLa               | MDM2, Sirt1       | P53 pathway            | Down-regulation of this miRNA could enhance p53 inhibition in the treated cells. | -                   | [73]|
| Wang et al., 2017d | miR-195-5p | OSCC           | paired tumor and normal oral epithelial tissues | 40 patients | 40 patients Tca83 and Cal27 | TRIM14 | NF-kB signaling pathway | In overexpression promotes apoptosis and reduces cell growth, migration, and invasion | -                   | [82]|
| Zhang et al., 2017 | miR-375   | OSCC           | paired tumor and normal oral epithelial tissues | 44 patients | SCC-4 | IGF-1R signaling pathway | Overexpression of miR-375 suppresses growth, induces cell cycle arrest in G0/G1 phase, induces apoptosis and | -                   | [83]|

(continued on next page)
| Author/year | microRNA | Cancer subtype | Tissues | Numbers of clinical samples | Assessed cell line | Targets/Regulators | Signaling Pathways | Function | Patient's prognosis | Ref |
|-------------|-----------|----------------|---------|----------------------------|-------------------|-------------------|------------------|---------|---------------------|-----|
| Feng et al., 2019 | miR-532-3p | tongue squamous cell carcinoma (OSCC) | paired tumor and paratumor tissues | 23 patients | TSCCA, TCA8113, CAL-27, and SCC-25 | ORR7 | - | Up-regulation of miR-532-3p inhibits cell proliferation, migration, invasion, and induces apoptosis. | [84] |
| Harandah et al., 2016 | miR-375 and miR-494 | OSCC | paired tumor and non-tumor tissues | - | - | - | - | - | Increased radiosensitivity in OSCC cells, and it is potential therapeutic target. | [94] |
| Shi et al., 2018 | miR-486 | OSCC | paired tumor and non-tumor tissues | 20 TSCC tissues and 10 their adjacent non-cancerous tissues | U81, TCA8113, Cal27, SCI, and SCC25 | ATF3 | SACC, JAK/STAT pathway | Micr-486 suppresses cell invasion and EMT by direct downregulation of ATF3. | [86] |
| Shang et al., 2018 | miR-9 | OSCC | tumor tissues and adjacent normal tissues | 21 patients | Tca8113 | CDK4/6 | G1/S transition pathway | miR-9 decreases cell proliferation and migration. | [87] |
| Lin et al., 2017 | miR-485-5p | OSCC | - | SCC25 and SCC25-r | PAK1 | - | Micro-485p reverses EMT and enhances cispation-induced cell death by targeting PAK1, and significantly inhibited invasion and migration in oral tongue squamous cell carcinoma. | [88] |
| Yu et al., 2011 | let-7a | HNCC | - | HNCALDH1(+) cells relative to HNCALDH1(-) cells | Nanog/Oct4 | - | Let-7 suppresses tumor metastasis and improves survival time. | [89] |
| Alajer et al., 2012 | let-7a | HNSCC (laryngeal and hypopharyngeal carcinoma) | tumor tissues and adjacent normal tissues | Paired tissues from 20 patients NOE and HNSCC FaDu | Nanog/Oct4 | - | Micro-205-5p, micro-130-5p and micro-5p | Micro-205-5p, micro-130-5p and micro-5p | [90] |
| RIES et al., 2014 | miR-186 | OSCC | Whole blood | 50 patients and 33 controls | - | - | IGF2BP2/lin28a as regulator of let-7 | Induced cellular senescence and regulate apoptotic response | [91] |
| Lu et al., 2011 | miR-26a | nasopharyngeal carcinoma | tumor tissues and normal tissues | 18 tumor samples and 16 normal nasopharyngeal epithelial tissues | - | - | - | Partly due to a G1-phase arrest | [92] |
| Tang et al., 2014 | miR-205-5p, miR-130b-5p | nasopharyngeal carcinoma | tumor tissues and normal tissues | 67 fresh NPC and 25 normal control tissues | - | - | - | - | Diagnostic value | [93] |
| Koshimizu et al., 2017 | miR-199a-5p, miR-199a-3p, miR-199b-5p, miR-199b-3p | HNSCC (floor of the mouth and tongue) | tumor tissues and normal tissues | 22 tissue specimens from patients with HNSCC and 22 normal epithelial tissues | SAS and HJC3 | ITGA3, PXN | focal adhesion pathway | Micro-199 family suppresses cell migration and invasion. | [94] |
| Islam et al., 2014 | miR-138 | HNSCC (floor of the mouth and tongue) | primary tumor | 18 patients | UMC-SCC-1 and -47 | RhoA, FAK, Src and Erk(1/2) | Erk1/2 signaling pathway | Micro-138 is a tumor suppressor miRNA that reduces cell motility, colony and stress fiber formation. | [95] |
| Koshinohara et al., 2013 | miR-29a | HNSCC (Tongue, Oral floor, Oropharynx, Larynx and Hypopharynx) | paired tumor and normal tissues | 23 patients | SAS and Fafu | LAMC2 and ITGA6 | Focal adhesion pathway | Micro-29 suppresses cancer cell migration and invasion by targeting laminin-integrin signaling. | [96] |
| Shah et al., 2014 | miR-329 and miR-410 | OSCC | Paired tumor specimens and their adjacent nonneoplastic epithelia | 40 patients | DOK, Fafu, OC-3, OC-5, M2, SCC-4, SCC-5, SCC-15, SCC-25, T2, and TD-15 | Win-7b | Wnt signaling pathway | Micro-29 and Micro-410 inhibit the proliferation and invasion by targeting Win-7b. | [97] |
| Chang et al., 2016 | miR-376c | HNSCC | paired tumor and normal samples | 40 patients | HNRK, 293T, Cal-27, CAL9-22, and SAB | RUNX2 | RUNX2/INHBA axis | Micro-376c suppresses lymph node metastasis by RUNX2/Activin-A axis. Low miR-376c-3p levels predict poor prognosis in HNSCC. | [98] |
| Xu et al., 2015a | miR-143 | OSCC | paired tumor and normal samples | 49 patients | SCC-4, Tca8113, CAL-27 | CD44 v3 | Phospho-c-Met signal pathway | Micro-143 suppresses migration and invasion. | [99] |
| Zahran et al., 2015 | miR-145 | OSCC | saliva | 80 subjects with HNSCC and 20 healthy controls | - | - | - | Non-invasive, rapid diagnostic biomarker | [100] |
| Author/year | microRNA | Cancer subtype | Tissues | Numbers of clinical samples | Assessed cell line | Targets/Regulators | Signaling Pathways | Function | Patient's prognosis | Ref |
|-------------|-----------|----------------|---------|-----------------------------|-------------------|-------------------|-------------------|---------|---------------------|-----|
| Cao et al., 2015 | miR-26b | Tongue SCC | tissues of tongue SCC and the matched normal counterparts | 30 patients | HCC-3, SCC-4, Ca127, bNOX6 | PTGS2 (COX2) | VEGF-C pathway | miR-26b serves as a tumor suppressor by targeting COX-2. Low miR-26b expression is correlated with advanced clinical stage, lymph node metastasis, and poor prognosis. | [99] |
| Wu et al., 2017a | miR-802 | Tongue SCC | paired tumor and normal samples | 20 patients | SCC1, SCC4, Ca127 and U1M | MAP2K4 | MAPK signaling pathway | miR-802 suppresses cell viability and invasion through targeting MAP2K4. | [100] |
| Sun et al., 2016a | miR-137 | Tongue SCC | paired tumor and normal samples | 25 patients | SCC4, SCC1, U1M and Ca127 | SP1 | - | miR-137 suppressed TSCC cell proliferation, colony formation, EMT cell invasion and migration | [101] |
| Wang et al., 2016 | miR-204-3p | OSCC | frozen OSCC patient specimens | 52 patients | Human OSCC cell lines | CXCR4 | Wnt/b-catenin and NF-kappaB signaling pathways | miR-204-3p suppressed OSCC cell proliferation and growth. | [102] |
| Sun et al., 2016b | miR-9 | OSCC | Serum | 104 OSCC patients, 30 OUL patients, and 40 healthy volunteers | - | - | Serum miR-9 is an independent risk factor for OSCC. Low miR-9 expression level predicts poor prognosis. | [103] |
| Yang et al., 2017 | miR-381-3p | OSCC | tumor specimens and adjacent tissue | 18 patients | SCC-9, Tca-4113 | RGR2 | - | miR-381-3p suppresses cell proliferation and enhances apoptosis by directly targeting FGFR2. | [104] |
| Hashiguchi et al., 2018 | miR-205 | OSCC | - | - | HCC-2, HSC-3, SQU-A, SQU-B, SQU-B, SQU-BC, SAS | ZEB1 or ZEB2 | EMT signaling pathway | miR-205 contribute to EMT suppression. | - [105] |
| Shi et al., 2015a | miR-375 | OSCC | paired tumor and adjacent non-tumorous mucosa specimens | 17 patients | Ca127, WHU-HN6, HeK-285T, KL18 | - | miR-375 can suppress cellular proliferation and induce cell apoptosis | - [106] |
| Wu et al., 2017b | miR-375 | OSCC | paired tumor and adjacent non-tumorous mucosa specimens | 40 patients | Hi-680-Tg, Rdu, SCC-25, CAL-27 and Tca8113 | - | miR-375 suppresses cell proliferation and invasion through suppressing the expression of EMT marker. | - [107] |
| Ji et al., 2017 | miR-138 | Tongue SCC | tumor samples and normal tissues | 137 tumor samples and 20 normal tongue tissues | U1M and U1M2 | AKT1 | AKT/ERK1/2 pathway | miR-138 directly targets AKT1 and decreases the invasion and metastatic potential of TSCC cells. Low miR-138 levels predict poor prognosis. | [108] |
| Xu et al., 2015b | miR-138 | OSCC | paired tumor and normal tissues | 20 patients | OC3, K8, OE-M1, HSC-3 and SCC-4 | YAP1 | Hippo pathway | miR-138 suppresses the proliferation and growth of OSCC by targeting YAP1. | - [109] |
| Kim et al., 2018 | MiR-203 | OSCC | - | - | YD-38 cells and normal human oral keratinocytes | BMI-1 | - | miR-203 decreases the viability of YD-38 cells and significantly induces apoptosis by directly targeting BMI-1. | - [110] |
| Lim et al., 2017 | miR-203 | OSCC | - | - | YD-38 cells and normal human oral keratinocytes | SMAD6 | - | miR-203 reduces the viability of YD-38 cells and activated the apoptotic signaling pathway. | - [111] |
| Lin et al., 2018 | miR-203 | OSCC | paired tumor and adjacent non-tumorous specimens | 10 patients | Tca8113 | P21 | - | miR-203 induces a cell cycle arrest and increases the apoptotic | - [112] |
| Xie et al., 2018 | miR-203 | OSCC | paired tumor and normal tissues | 32 patients | HOC313 | ZEB1 | EMT pathway | miR-203 significantly suppress cell invasion and migration, and suppressed EMT via negatively regulating ZEB1 expression. | - [113] |
| Zhao et al., 2015 | miR-222 | Tongue SCC | tissue samples for primary cultural cells | 6 patients | U1M and U1M2 | ABG2/ERCC1 | - | miR-222 inhibits migratory/invasive potential. | - [114] |

(continued on next page)
| Author/year | microRNA | Cancer subtype | Tissues | Numbers of clinical samples | Assessed cell line | Targets/Regulators | Signaling Pathways | Function | Patient’s prognosis |
|-------------|----------|----------------|---------|-----------------------------|-------------------|-------------------|-------------------|----------|-------------------|
| Wang et al., 2017 | miR-15b | tongue SCC | - | - | SCC25 and SCC25-res cells | TGFβ1 | TRIM14 | Inhibits TRIM14 and suppresses cancer-initiating cell phenotypes, and enhances MET thus sensitizing cisplatin-resistant SCC25 cells to cisplatin. | | |
| Li et al., 2017 | MiR-124 | OSCC | paired tumor and normal tissues | 6 patients | SCC-9 and CAL-27 | CCL2 and IL-8 | - | miR-124 suppresses tumor growth. | | |
| Lin et al., 2014 | miR-639 | tongue SCC | paired tumor and adjacent non-tumorous specimens | 92 patients | SCC9 and CAL27 | POXC1 | TGFβ-induced EMT pathway | Inhibits TGFβ-induced EMT | Low levels of miR-639 correlate with lymph node metastasis and poor prognosis. | |
| Liu et al., 2017 | miR-27b | OSCC | - | - | Tca8113 and SCC-4 | PTEN | Wnt signaling pathway | miR-27b suppresses cell proliferation by targeting PTEN and Wnt signaling pathway. | | |
| Min et al., 2016 | miR-148a | OSCC | - | - | NIH and CAPs were isolated from OSCC tumor tissues and SCC-25 cells | Wnt10b | - | miR-148a decreased the migration and invasion through targeting WNT10B mediated signal pathway. | | |
| Qin et al., 2017a | MicroRNA-542-3p | OSCC | paired tumor and adjacent non-tumorous specimens | 108 patients | CRL-1629 | ILK, TGF-β1 and Smad2/3 | ILK/TGF-β1/Smad2/3 Signaling Pathway | miR-542-3p inhibits self-renewal, invasiveness, migration, proliferation and survival. | |
| Qiu et al., 2016 | miR-22 | tongue SCC | - | - | TCA8113 cells | CD147 | - | miR-22 inhibited cell proliferation and motility and down-regulated CD147. | | |
| Rustogi et al., 2017 | miR-277 | OSCC | tissues | 20 patients | UPCI-SCC-16 | HDAC9 | HDAC9/NMA1L/Notch7 pathway | miR-277 inhibits cell growth, induces apoptosis, and decreases cell migration. | | |
| Ruan et al., 2018 | miR-30a-5p | OSCC | oral cancer tissues and adjacent normal tissues | 66 oral cancer tissues and 25 adjacent normal tissues | NH419, SCC-15, SCC-25, SCC-C4, Tca8113 and HCC201 | FAP | Ras/ERK | miR-30a-5p suppresses the cell proliferation, migration and invasion of oral cancer cells via down-regulating FAP. | | |
| Jia et al., 2020 | MiR-148a | OSCC | paired tumor and normal tissues | 110 patients | SCC-15 and HOK | IGF-IR | ERK/MAPK Pathway | miR-148a suppresses OSCC cell proliferation, migration and invasion by targeting IGF-IR and suppressing ERK/MAPK signaling pathway. | | |
| Shi et al., 2015b | miR-146a | OSCC | oral carcinoma tissues and adjacent normal tissues | 40 oral squamous cell carcinoma tissues and 10 adjacent normal oral mucosa tissues | SCC25 and UM1845 | Sox2 | - | Inhibits tumor aggressiveness | | |
| Wang and Liu, 2016 | miR-188 | OSCC | paired tumor and normal tissues | 22 patients | KB, FaDu, and Detroit 562 | SIX1 | cyclin D1/MMP9/p-ERK pathway | miR-188 is a tumor suppressor and suppresses proliferation and invasion by targeting SIX1. | | |
| Wang et al., 2017b | miR-139-5p | OSCC | paired tumor and normal tissues | 40 patients | NOK, SAS, TCA8133, KON | HOXA9 | - | miR-139-5p suppresses the viability, proliferation and migration. | | |
| Wang et al., 2017c | miR-29c-3p | OSCC | paired tumor and normal tissues | 49 patients | SCC-4, SCC-9, SCC-15, SCC-25 | HOXB7 | OSCE | miR-29c-3p inhibits proliferation, viability, migration and invasion and induces G0/G1 arrest and cell apoptosis. | | |
| Wang et al., 2018a | miR-605 | OSCC | paired tumor and normal tissues | 26 patients | Tca8113, CAL-27 and SCC-9 | PTEN | PTEN/AKT pathway | miR-605 suppresses cell proliferation and invasion by targeting PTEN. | | |
| Wang et al., 2018c | miR-1294 | OSCC | paired tumor and normal tissues | 24 patients | HBE2, HBE4, SAS and KON | - | - | | | |

(continued on next page)
| Author/year     | microRNA | Cancer subtype | Tissues                                      | Numbers of clinical samples | Assessed cell line | Targets/Regulators | Signalling Pathways | Function | Patient's prognosis | Ref |
|---------------|----------|----------------|---------------------------------------------|-----------------------------|--------------------|--------------------|--------------------|----------|---------------------|-----|
| Weng et al., 2016 | miR-494-3p | OSCC           | paired tumor and normal tissues             | 45 patients                | SAS cells          | Bmi1               | -                  | miR-1294 inhibited cell growth and cell migration. | -   |
| Chang et al., 2015 | miR-494 | HNSCC          | pairs of tumor and adjacent noncancerous matched tissues | 45 patients | S-4-6 human gingival epithelial cell line, SAS | Bmi1 and ADAM10 | - | miR-1294 inhibits tumor aggressiveness. | -   |
| Xu et al., 2016b | miR-340  | OSCC           | paired tumor and normal tissues             | 3 patients                 | SAS and HER293 T cells | Glit1             | -                  | miR-340 inhibits growth, induces a metabolic shift | -   |
| Zeng et al., 2016 | miR-27a-3p | OSCC         | paired tumor and normal tissues             | 50 patients               | Tca8113, CAL-27, SCC-A, SCC-9, SCC-25, HN-6 and hNOK | YAP1             | YAP1-OCT4-Sox2 signal axis | miR-27a-3p downregulates the EMT-related molecules effectively and suppress EMT process, invasion and metastasis. | -   |
| Li et al., 2018b | miR-218-5p | OSCC         | -                                           | -                          | UM-SCC6            | CD44               | CD44-ROCK pathway | miR-218-5p suppresses cell invasion. | -   |
| Gao et al., 2019 | miR-145-5p | Laryngeal SCC | paired tumor and normal tissues             | 40 patients               | human 293T and LSOC cell line, 2, T1177 | FSCN1             | EMT pathway     | miR-145-5p inhibits migration, invasion, and growth by suppressing EMT. | Low miR-145-5p/high FSCN1 levels predict poor prognosis. | -   |
| Chou et al., 2019 | miR-486-3p | OSCC         | paired tumor and normal tissues             | 46 patients               | OKF4/3TER, OEC-M1 and TW2.6 OSCC | DDR1/ANK1         | -                  | miR-486-3p inhibits proliferation and activates apoptosis. | -   |
| Jakub et al., 2019 | miR-100-5p | OSCC         | tumor tissue and healthy oral mucosal tissue | 36 tumor tissue and 17 healthy oral mucosal tissue | - | - | - | prognostic impact | -   |
| Ding et al., 2019 | miR-145 | OSCC          | tumor tissues and adjacent normal tissues.  | 48 patients               | SCC-9              | HOX1A              | ERK/MAPK signaling pathway | miR-145 inhibits cell viability, invasion, and migration. | -   |
| Cao et al., 2017 | miR-375  | OSCC          | -                                           | -                          | Tca8113, UM2, UMI and CAL-27 | PDGFA-A          | -                  | miR-375 suppresses the migration and invasion of OSCC. | -   |
| Du et al., 2015 | miR-98   | OSCC          | paired tumor and normal tissues             | 19 patients               | SCC-25 and Tca-8113 | IGFR1             | -                  | miR-98 inhibits tumor cell growth and metastasis by targeting IGFR1. | -   |
| Fadhil et al., 2020 | miR-let-7a-5p and miR-3928 | HNSCC (glottis, buccal sulcus, buccal mucosa, tongue, and floor of the mouth (FOM)) | saliva | 150 HNSCC patients and 80 healthy controls | - | - | - | Biomarkers for diagnosis and prognostic indicators | -   |
| Herzi et al., 2018 | miR-9   | HNSCC         | -                                           | -                          | H357, HNS, HN30, HER293T, HSC3 and HSCIM3 | CXCR4             | -                  | miR-9 expression has a significant tumor suppressor role in HNSCC cells, potentially through inhibition of cellular proliferation, cell cycle progression, migration and colony formation. | -   |
| Gonzalez-Antiqueada et al., 2018 | miR-203 | HNSCC (oral, oropharyngeal, laryngeal) | primary HNSCC with lymph node metastasis and their matched lymph node, without metastasis | 16 primary HNSCC with lymph node metastasis 16 their matched lymph node, without metastasis | - | - | - | miR-203 is associated with good prognosis. | -   |
| Wang et al., 2018b | miR-200  | OSCC          | -                                           | -                          | SOC25 and SSCI5    | EZH2               | STAT3 signaling pathway | miR-200 mediates antitumor functions by targeting STAT3 signaling. | -   |
| Kang et al., 2018 | miR-300  | OSCC          | specimens of OSCC                           | 120 patients              | Tca8113, Cal-27 and HaCaT | - | - | miR-300 could suppress metastasis by inhibiting EMT. | -   |
| Dong et al., 2018 | miR-876-5p | HNSCC (Buccal, Palate, Gingiva, Oropharynx, Tongue) | tumor tissues | 40 patients | CAL27, HER293T, WSU-HN4, WSU-HN6 | vimentin         | -                  | miR-876-5p inhibits cell migration and invasion. | -   |

HNSCC: head and neck squamous cell carcinoma, OSCC: oral squamous cell carcinoma, OPMD: oral potentially malignant disorder. *: These miRNAs are down-regulated in cells treated with serum samples of patients with HNSCC.
Table 3. Role of miRNAs in chemoresistance in HNSCC based on up-/down-regulation of miRNAs.

| Response to chemotherapeutic drug | miRNA | Reference |
|----------------------------------|-------|-----------|
| Cisplatin resistance             | miR-21 (up), miR-203 (down), miR-15b (down), miR-218 (up), miR-98 (up), miR-24 (up), miRNA-654-5p (up) | [10,13,47,50,63,112,114,115] |
| Doxorubicin resistance           | miR-98 (up), miR-221 (up) | [13,48] |

Table 4. Summary of results of studies which investigated diagnostic/prognostic value of miRNAs in HNSCC.

| Sample number | Area under curve | Sensitivity | Specificity | Kaplan-Meier analysis | Univariate cox regression | Multivariate cox regression | Reference |
|---------------|------------------|-------------|-------------|------------------------|--------------------------|-----------------------------|-----------|
| Forty samples of OSCC and 40 matched normal tissues | 0.9 | 88% | 99% | Higher levels of miR-191 suggesting a lower survival probability | - | - | [17] |
| Salivary from 45 patients with OSCC and 24 controls | 0.82 for miR-31 | 80% | 68% | - | - | - | [21] |
| Salivary samples from 108 HNSCC cases and 108 controls | 0.73 for miR-122-5p and 0.79 for miR-92a-3p | - | - | - | - | - | [24] |
| 46 laryngeal SCC tumors and non-cancerous tissues | 0.753 for miR-223/miR-375, 0.991 for miR-21/miR-375 and 0.856 for miR-142-3p/miR-375 | - | - | High expression of miR-21/miR-375 in cancerous tissue associates with poor prognosis | - | - | [25] |
| Whole blood of 21 patients with recurrence of OSCC and 21 patients without recurrence | 0.80 for miR-3651 | 81% for miR-3651, 71.4% for miR-494, 71.4% for miR-186 | - | - | - | [27] |
| Whole blood of 50 OSCC patients and 33 controls | 0.81 for miR-3651, 0.72 for miR-494 | 87.51% | 73.73% | miR-31 over-expression and epithelial dysplasia synergistically predict OPMD progression. | miR-31 and epithelial dysplasia were independent factors for OPMD progression. | - | [29] |
| 20 saliva samples and 46 tissue samples from patients with OPMD | 0.82 | 69% | 66% | - | - | - | [27] |
| Serum samples and tissue specimens from 218 patients with OSCC and 90 controls | 0.920 | 0.842 | 0.810 | Patients having elevated serum miR-626 and miR-5100 had significantly decreased DFS and OS. | The two-miRNA signature exhibited greater prognostic performance than one-single-miRNA. | The expression of the two-risk miRNAs (miR-626 and miR-5100) was inversely related to DFS. Significant associations between DFS and grade, serum miRNA signature, and TNM stage were detected. | [36] |
| 11 paired match tumor tissues and adjacent tissues, sera from 82 oral cancer patients and 53 normal subjects | 0.77% for miR-31-5p | 76.8% | 73.6% | - | - | - | [35] |
| 51 Samples of HNSCC cancer tissue and adjacent non-cancerous tissue | 0.719 | 93% | 64% | Patients with increased expression of miR-15b-5p have a significantly longer locoregional relapse-free survival. The predictive value of miR-15b-5p was independent of other clinicopathological factors, including the stage or the pT1 status | Patients with high miR-183 expression have a 5.6 times higher overall mortality rate, and a tendency towards recurrence. | The two-risk miRNAs were significantly associated with LRC. | [38] |
| 60 fresh-frozen tissue of tongue carcinomas | 0.7 for miR-183 | 86.2% for miR-183 | 48.4% for miR-183 | Patients with miR-183 up-regulation had shorter overall survival, miR-21 over-expression had a tendency towards poorer survival. | Patients with high miR-183 expression had a 5.6 times higher overall mortality rate, and a tendency towards recurrence. | The expression of these forty-six miRNAs was significantly associated with LRC. | [38] |
| Salivary samples from 150 HNSCC patients and 80 healthy subjects | 0.77 for miR-let-7a-5p, 0.78 for miR-3028 | - | - | - | - | - | [141] |

5. Diagnostic/prognostic value of miRNAs in HNSCC

Recent studies have shown diagnostic value of miRNAs in HNSCC. They mostly designed receiver operating characteristic (ROC) curves and measured the area under curve (AUC) values to estimate diagnostic power of miRNAs. Such assessments have been accomplished in different biological sources such as saliva, whole blood, serum, and tumor tissue observation implies that expression of miR-223-3p enhances resistance to anticancer modalities [147].
samples. Control samples were obtained from cancer-free individuals except for the latter in which paired non-tumoral samples from the same patients were used as controls. Moreover, a number of studies have assessed power of miRNAs in the differentiation between patients with recurrence and those without recurrence. Although all assays are practically useful, serum, blood and saliva provide non-invasive sources for diagnosis of cancer. Theoretically, miRNAs can be used for early/routine diagnosis of HNSCC as well as patients’ follow-up for observation of relapses. Notably, miRNA signature can even discriminate different stages of HNSCC tumors [24]. Moreover, higher expression of several oncomiRs and lower expression of a number of tumor suppressor miRNAs were correlated with poor patients’ outcome as defined by disease free survival or overall survival. The predictive values of several miRNAs were also assessed in relation with clinicopathological factors such as grade, stage or the p16 status. Table 4 shows the results of studies that investigated this issue in HNSCC. Prognostic value of miRNAs was estimated through Kaplan-Meier or Cox regression evaluation.

6. Discussion

HNSCC is among common human malignancies and affects more than 60,000 individuals yearly [148]. Chemotherapy, radiotherapy and surgical resection are therapeutic modalities that have improved survival of patients; yet, less than half of all patients are rescued [149]. Thus, there is an urgent need for identification of cancer at early stages. Mutations in TP53, proliferation pathways (RAS/Pi3K/mTOR pathway, PIK3CA, HRAS), cell cycle regulating genes, Notch pathway, cell communication and death pathways have been identified in HNSCC [150]. Notably, several targets within these pathways are regulated by miRNAs as well. Thus, aberrant expression of miRNAs is an alternative route for development of HNSCC. Expression profiling has revealed dysregulated expression of several miRNAs in HNSCC in association with clinical determinants of cancer behavior; therefore, miRNAs have prominent roles in the pathogenesis of HNSCC. Some preliminary studies have reported correlations between expression profile of miRNAs and site of the HNSCC tumor [9], which might indicate a site-specific role for these miRNAs. Moreover, miRNAs profile is important in the recognition of minimal residual disease in HNSCC [151]. Consistent with this speculation, altered expression of miRNAs in the tumor-adjacent mucosa has been correlated with the risk of HNSCC recurrence [11]. Decreased expression levels of a number of miRNAs such as HNnov-miR-2, HNnov-miR-30, and HNnov-miR-125 have been associated with the presence of HPV infection [23]. Future studies are required to find a putative panel of miRNAs which specifically correlate with HPV status. Several panels of miRNAs have been suggested as diagnostic panels for HNSCC. Yet, diagnostic power of none of them has been verified in large scales. A recent meta-analyses have shown consistent results about aberrant expression of 22 miRNAs including miR-9 and miR-483-5p in HNSCC. Notably, up-regulation of miR-9 and down-regulation of miR-483-5p have been associated with poor survival of patients [152]. Other miRNAs such as miR-191, miR-21, miR-375, miR-31, miR-626, miR-5100, miR-183 and miR-15b-5p are also involved in determination of patients’ prognosis. Levels of miRNAs in the saliva samples might be used for detection of oral SCC both at the time of cancer diagnosis and after resection of the primary tumor [21]. In a retrospective study, Ahmad et al. have shown that miR-15b-5p is differentially expressed between patients with short and long time of locoregional control in a way that patients with higher levels of this miRNA had a remarkably longer locoregional relapse-free survival [68]. Further prospective studies are needed to verify whether expression level of this miRNAs might be employed for individualized treatment decisions. Moreover, plasma levels of a panel of miRNAs including miR-142-3p, miR-186-5p, miR-195-5p, miR-374b-5p and miR-574-3p has been regarded as an HPV-independent prognostic panel for HNSCC patients who were treated with combined radiochemotherapy [16]. miRNAs might also modulate response of cancer cells to chemotherapeutic agents, radiotherapy or even targeted therapies. Besides, preliminary results from cell line studies indicated that suppression and forced expression of a number of miRNAs could influence cancer cells behavior. Thus, miRNAs have been regarded as therapeutic targets. Delivery of certain pre-miRNAs or siRNAs using nanoparticles has been promising [153,154]. Future studies should assess the efficacy of these methods in combination with routine therapeutic options such as chemotherapy. Taken together, miRNAs signature has practical implications in the diagnosis, staging, and management of HNSCC [155,156]. The most important usefulness of miRNAs in HNSCC is their application as diagnostic markers for primary diagnosis of this type of cancer and patients’ follow-up. Altered expression levels of miRNAs might reflect tumor recurrence after initial response to the therapeutic options. The stability of miRNAs in the serum samples potentiates these transcripts as suitable tools in non-invasive methods of cancer diagnosis. The therapeutic usefulness of miRNAs have been evaluated in xenograft models of HNSCC, yet clinical studies are missing in this regard. Future studies should focus on identification of modalities to restore function of tumor suppressor miRNAs and abolish effects of onco-miRs in animal models as well as clinical settings.

Declarations

Author contribution statement

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