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miRNA in head and neck squamous cell carcinomas: promising but still distant future of personalized oncology

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ABSTRACT

Head and neck squamous cell carcinoma is one of the most common and fatal cancers worldwide. Lack of appropriate preventive screening tests, late detection, and high heterogeneity of these tumors are the main reasons for the unsatisfactory effects of therapy and, consequently, unfavorable outcomes for patients. An opportunity to improve the quality of diagnostics and treatment of this group of cancers are microRNAs (miRNAs) — molecules with a great potential both as biomarkers and therapeutic targets. This review aims to present the characteristics of these short non-coding RNAs (ncRNAs) and summarize the current reports on their use in oncology focused on medical strategies tailored to patients' needs.

Key words: head and neck squamous cell carcinoma; HNSCC; miRNA; biomarkers; therapeutic targets

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Introduction

Head and neck cancers (HNC) have one of the highest incidences worldwide, reaching approximately 932,000 cases in 2020 [1]. The disease takes its burden, especially in low- and middle-income countries where patients are often diagnosed with tumors in advanced stages [2, 3]. In 2016, 67% of HNC cases and 82% of HNC-related deaths came from these regions [4]. This group of tumors originates from the mucosal epithelium of the upper aerodigestive tract, where it develops in three primary subsites — oral cavity, pharynx, and larynx. Roughly 90% of HNC are squamous cell carcinomas (HNSCC) [5]. The primary risk factors for developing this malignancy are long-term, excessive tobacco use and/or alcohol consumption, as well as environmental carcinogens and human papillomavirus (HPV) infection [6, 7]. The first ones are predominantly linked with tumor formation in the oral and larynx localization, whereas the latter is primarily associated with the oropharynx [8]. Interestingly, undergoing HPV infection was correlated with more favorable outcomes [7]. There is an urgent need for vaccination programs, especially among young men from developing countries, who are increasingly diagnosed with HNSCC [7]. Patients are proposed with therapeutic approaches consisting of chemo- and radiotherapy, surgical resection, and biological medicaments, including immunotherapeutics [6]. However, for late-diagnosed patients with advanced disease, even aggressive multimodal treatment does not bring long-term positive results. Belated detection,

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tumor heterogeneity, and metastasis are the main reasons why the mortality rate of HNSCC in the first five years from diagnosis is approximately 50% [6, 9]. Necessity to improve the diagnosis process and find more personalized treatments for cancer patients led scientists to search for potential markers or therapeutic targets among some of the most crucial and universal regulators of cell biology — non-coding RNAs (ncRNAs).

One of the most abundant ncRNA subgroups consists of microRNAs (miRNAs) - small (approximately 22 nucleotides long), endogenous ncRNAs with great power. These molecules are crucial for post-transcriptional regulation of gene expression, which is required for maintaining cell homeostasis and normal organism development. Over 60% of human protein-coding genes have conserved one or more miRNA-binding sites, which, combined with numerous non-conserved sites, indicate possible miRNA-based control of most of those transcripts [10]. Inhibition of target messenger RNA (mRNA) expression is caused by miRNA interaction with its 3' untranslated region (3' — UTR) [11]. Dysregulation of this complex molecular machinery is associated with many diseases, including cancers [11, 12]. That is why it is vital to explore the role and possible diagnostic or therapeutic potential of ncRNA.

This review aims to discuss the current knowledge regarding miRNAs in HNSCC and elucidate their possible future usage as molecules in the personalized medicine service.

miRNA biogenesis

The canonical pathway of miRNA biogenesis begins in the nucleus with transcription of miRNA genes, which in the vast majority are located in introns of non-coding or coding transcripts. Sequences residing in the introns of protein-coding genes usually share promoters with the host. On the other hand, intergenic sequences are transcribed separately from the host although controlled by their promoters [13, 14]. Each locus encodes two mature molecules — one on the 5' and the second on the 3' strand. miRNA genes are transcribed by polymerase II (Pol II), which results in the formation of long primary transcripts (pri-miRNA) containing both future miRNAs enclosed in the local stem-loop structure [11]. This process is regulated by transcription factors associated with Pol II and various epigenetic regulators [15]. The pri-miRNA maturation process is initiated by the nuclear RNase III — Drosha and its cofactor DGCR8, which together form the Microprocessor complex that can cleave molecules in a precisely defined position [16]. Complex recognizes pri-miRNA structure consisting of terminal loop, approximately 33-35 bp long stem, as well as single-stranded tails and crops RNA specifically 11 bp from the basal junction (junction of the single-stranded tails turning into stem) and 22 bp from the apical junction (junction below the terminal loop), creating a hairpin-structured RNA called — pre-miRNA [17, 18]. Both described junctions are crucial for determining the split site [11, 17, 18]; however, the mechanism of interaction between the Microprocessor and pri-miRNA is still unknown.

Subsequently, protein exportin 5 (EXP5) and GTP-binding nuclear protein Ran-GTP form a "baseball mitt"-like transport complex to export pre-miRNA to the cytoplasm for the final steps of the maturation process [11, 19, 20]. Translocation through the nuclear pore requires GTP hydrolysis, which leads to complex disassembly [20]. Released into the cytoplasm pre-miRNA is then cleaved close to the terminal loop by RNase III-type endonuclease, called Dicer, resulting in the creation of a short RNA duplex [21]. Said enzyme consists of an N-terminal helicase domain, the PIWI-AGO-ZWILLE (PAZ) domain, two double-stranded RNA (dsRNA) binding domains (DUF283, dsRBD), and a catalytic center formed by two C-terminal RNase III domains [22–25]. The PAZ domain has two spatial pockets, which can bind simultaneously a 5' end and a two-nucleotide-long overhang at the 3' end of the pre-miRNA [24, 25]. Nevertheless, the 5' end binds to the enzyme only when it is thermodynamically unstable due to the lack of strong guanine and cytidine base pairing [24]. The region between the PAZ and RNase III domains may act as a "molecular ruler" [22, 23], which ensures that Dicer cleaves processed RNA 21-25 nucleotides from the 3' end and 22 nucleotides from the 5' end [22, 24]. This process generates small dsRNA, which is then loaded to the Argonaute family protein (AGO) in an ATP-dependent process and becomes the RNA-induced silencing complex (RISC) [11]. The process of miRNA biogenesis is presented on Figure 1.

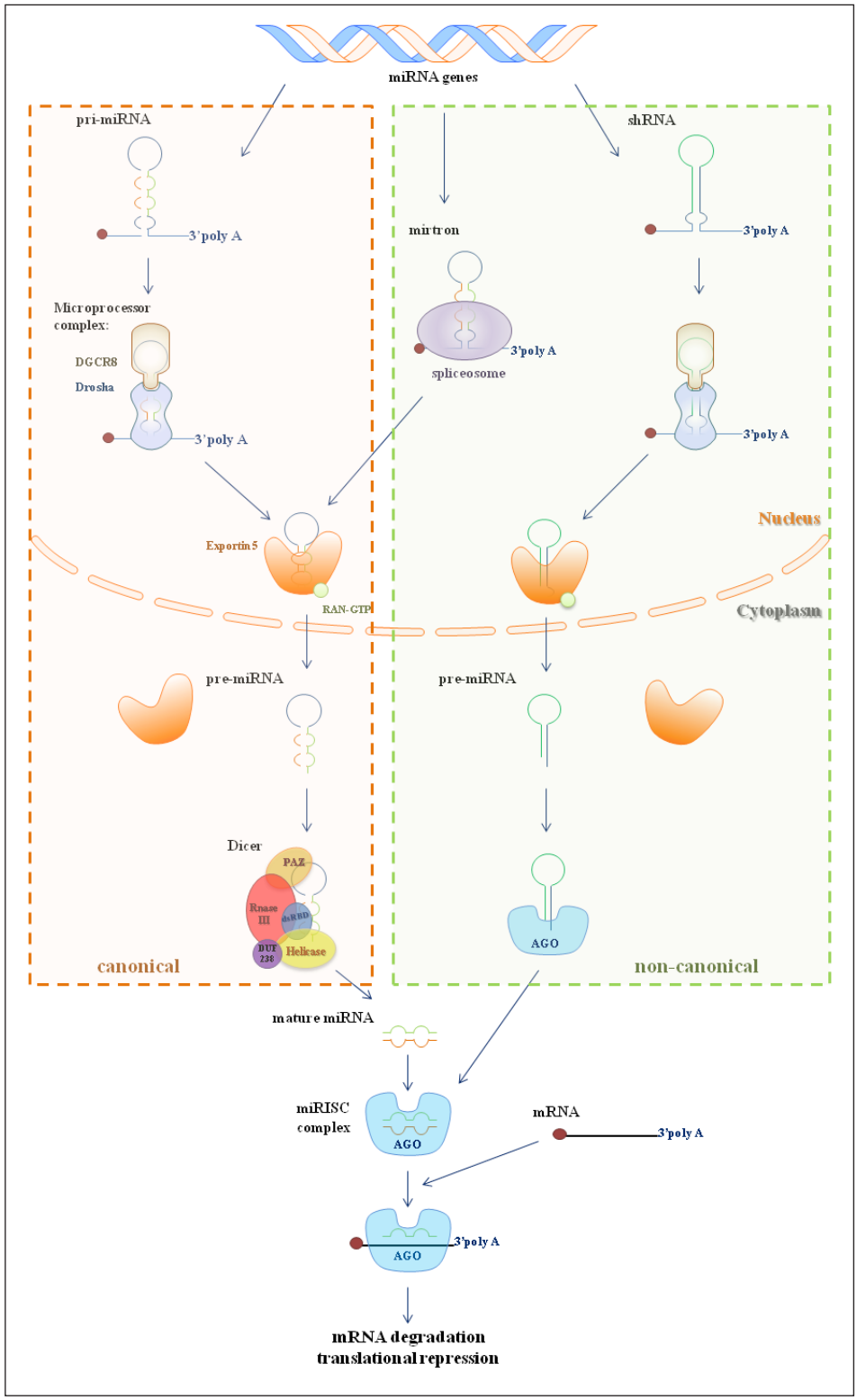

Figure 1. Canonical and non-canonical pathways of microRNA (miRNA) biogenesis. Short RNA transcripts named primary-miRNA transcripts (pri-miRNAs), mitrons, and short hairpin RNAs (shRNAs) shared common and distinct biogenesis steps. Pri-miRNAs and shRNAs are cleaved by the Microprocessor complex in contrast to mitrons, which are trimmed by spliceosomes. All cropped RNAs are stabilized by exportin 5 (EXP5), which, together with Ran-GTP, transfers RNA transcripts from the nucleus to the cytoplasm. Next, pre-miRNAs are cleaved by the Dicer enzyme and, as a mature miRNA, loaded into the Argonaute family protein (AGO) complex in canonical biogenesis. In the case of non-canonical pathways, the Dicer-dependent step is omitted, and pre-miRNAs are loaded into AGO. Finally, in both cases, a functional complex is created with the ability to interact with different types of RNA molecules, creating an RNA interference (RNAi) phenomenon

In humans, there are four AGO proteins (AGO1–4) that can interact with duplex RNA and induce target mRNA degradation causing its translational repression, however, only AGO2 has the ability to cleave perfectly matched transcripts [26]. These proteins contain 4 functional domains — N-terminal domain, PAZ domain, MID domain, and PIWI domain, which are required to bind dsRNA and determine which strand will be further processed. The transcript with high thermodynamic stability and lack of uracil at the beginning of the 5' end isn't preferentially attached to the AGO, resulting in its unwinding from the remaining strand (the "guide strand") and degradation [11, 27]. The above leads to a strong bias toward the "guide strand" generating an imbalance in the mature miRNAs expression levels as well as biological activity. These molecules tend to be more active and abundant than the ones encoded on the "passenger strand". The selection of RNA strands may vary in different tissues due to a phenomenon called "arm switching", which can be generated by alternative Drosha processing [28]. Additionally, these molecular species could be co-expressed in various tissues and display different modulatory roles in tumorigenic processes independently and/or cooperatively [29]. miRNA enclosed in the RISC complex is highly stable because AGO protects both its' ends [30]. That is why small RNAs need to be unloaded to enable exonucleases to access their termini. The process of mature miRNA disassembly from AGO isn't fully described yet.

Interestingly, approximately 1% of conserved miRNAs are produced in processes deviating from the canonical pathway. For example, molecules residing in short introns called 'mirtrons' after co-expression with their host genes don't undergo Drosha/DGCR8 cleaving but are trimmed by spliceosome instead, and then exported directly into the cytoplasm (Fig. 1)[13]. Experiments studying cells deficient in DGCR8, Drosha, or Dicer showed that some of the small RNAs could be generated in Microprocessor-independent or Dicer-independent (e.g. shRNA, Fig. 1) ways [11, 31]. This suggests the need for evolutionary flexibility in the biogenesis process of these short RNA molecules.

Function and interactions with molecules

miRNAs are known for their wide scope of functions and the great variety of molecules they interact with [10–12]. In general, these small RNAs bind with the specific sequence at the 3' UTR of mRNAs leading to its translational repression, causing deadenylation, decapping, and, consequently, degradation [32]. However, miRNAs could also bind to the 5'UTR and coding region of target mRNA, which results in silencing of the gene expression. They can also interact with the promoter, which on the other hand, may induce the transcription [33].

Gene silencing can be promoted by the minimal miRNA-induced silencing complex (miRISC), which is the AGO with the loaded "guide strand" [34]. Target mRNA has miRNA response elements (MREs), whose sequence is to a different extent complementary to a particular short RNA, conditioning the choice of one of the two possible paths. The first one is activated when miRNA:MRE complementarity is 100% and leads to target cleavage by AGO2 endonuclease activity [35], while the second pathway occurs when miRNA:MRE binding contains mismatches and uses the ability that all AGO proteins have – to mediate RNA interference, causing translational inhibition and target degradation [33, 35, 36]. miRNA can affect transcriptional and post-transcriptional gene regulation by shuttling from cytoplasm to nucleus through importin-8 or exportin-1 in the form of miRISC via interaction with TNRC6A protein [37].

Principally, functional miRNA:MRE interaction happens via the miRNA "seed region" located at the 5' end and consisting of nucleotides 2–8 [33, 36]. One miRNA can interact with numerous mRNAs, and one mRNA can have many MREs incorporated into its sequence [38]. On the cellular level, the relation between all molecules of a particular small RNA and the total number of their available response elements is described by the term "MRE load". This relation can be manipulated by elevating the level of a specific gene or a competing endogenous RNA (ceRNA), e.g. long non-coding RNA (lncRNA) or circular RNA (circRNA), causing sequestration of miRNA, as well as whole miRISC, from their target transcript leading to its derepression [39]. Additionally, MREs have different af-

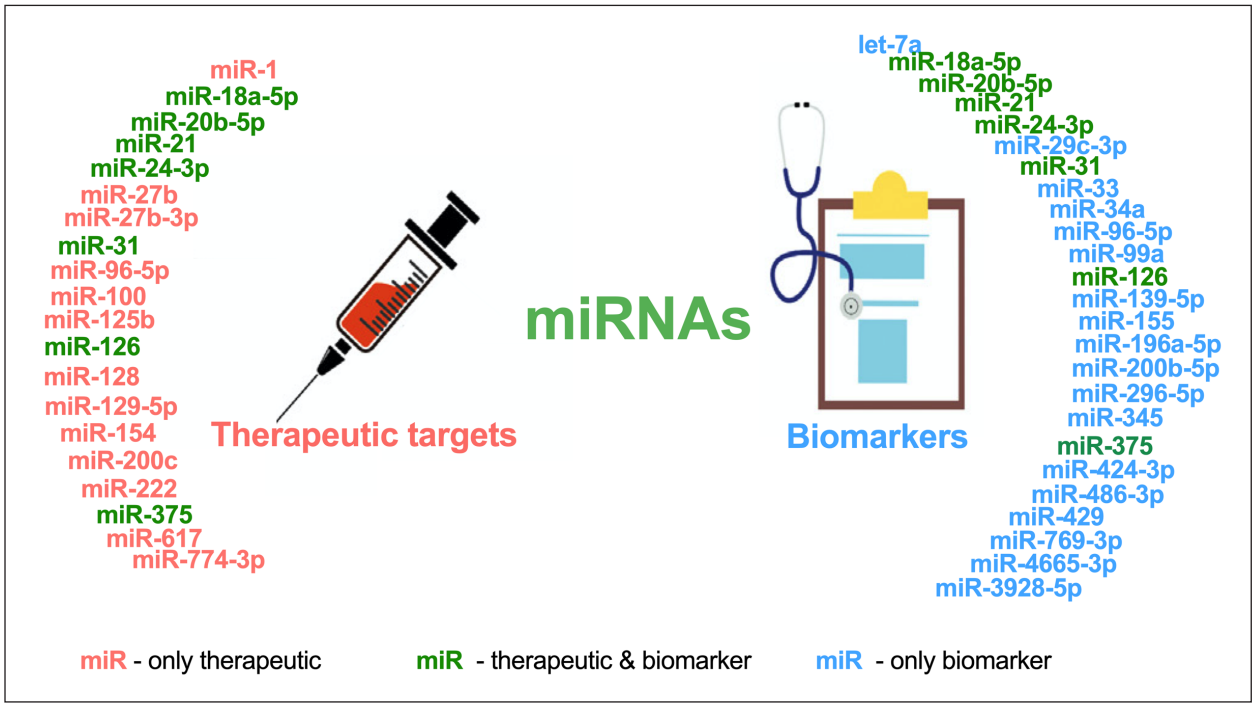

Figure 2. miRNAs as potential biomarkers and therapeutic targets in head and neck squamous cell carcinomas (HNSCC)

finity degrees – ones with the higher affinity will bind miRNAs for a longer time and lead to mRNAs' increased sensitivity for post-transcriptional repression. The above process might provide a stable gene expression by controlling the high mRNA ratio and reducing the expression noise [38]. Interestingly, the study by Tian et al. determined that miRNA-mediated regulation is more strict for tumor suppressor genes than oncogenic ones [40].

In recent years many reports emphasized the relevance of lncRNA and miRNA, as well as their interactions in cancer biology, treatment, and diagnosis [41-48]. Apart from acting as a "molecular sponge" sequestering miRNA, lncRNAs can compete with them by binding to target mRNAs and preventing transcriptional repression. Additionally, some lncRNAs can be processed into miRNAs, which is another argument corroborating the fascinating joint work of these ncRNAs to control gene expression through numerous complex post-transcriptional mechanisms [41–43, 48].

miRNAs potential — biomarkers or therapeutic targets?

High mortality rates and rising incidence of HNSCC dictate the necessity for developing therapy tailored to each patient. The first step to personalized medicine is to discover therapeutic targets, affecting processes crucial for carcinogenesis or further tumor progression, and diagnostic biomarkers, which could determine not only the occurrence of the disease but also assess individuals' response to the applied treatment. miRNAs can be used as potential biomarkers and therapeutic targets in HNSCC, Figure 2.

Promising biomarkers

A growing number of studies describe miRNAs' potential in diagnostics, emphasizing their specificity, stability of extracellular RNAs in various biological fluids, their relatively concise isolation process from acquired material, and simple analysis of obtained results [46, 49–53]. Importantly, these molecules can be successfully acquired via "liquid biopsy", which is a non-invasive alternative to traditional tumor sampling [51]. Umu et al. determined that serum contains significant amounts of ncRNAs, and approximately 45.7% is miRNA [54]. Biopsy often doesn't fully reflect tumor heterogeneity [55] or can't be obtained at all, i.e., when neoadjuvant therapy reduces the volume of the neoplastic lesion to an undetectable size [56]. Developing a specific panel of diagnostic, prognostic,

or predictive biomarkers would be an innovative approach leading to improvement of the HNSCC detection rate, patients' life quality, and expectancy.

Head and neck squamous cell carcinoma (HNSCC)

Fadhil et al. described two miRNAs with significant specificity and sensitivity to distinguish between patients and healthy individuals. let-7a-5p and miR-3928-5p were significantly downregulated in cancer patients' saliva compared to controls, and their expression levels could be associated with the clinical T stage. Interestingly, low let-7a-5p levels were linked with the more advanced stage as well as the presence of lymph node metastasis, suggesting its prognostic properties [57]. The panel of salivary-based biomarkers will be a useful non-invasive tool for HNSCC prophylaxis and early detection. The study by Ganci et al. focused on determining whether tumor, peritumoral and healthy tissue samples collected from HNSCC patients differ in gene expression alterations. Despite the lack of histopathological evidence, peritumoral mucosa often presents an abnormal molecular landscape that could predict recurrence development. Out of 35 deregulated miRNAs found in the peritumoral tissue, authors identified a signature consisting of miR-21-3p, miR-21-5p, miR-429, and miR-96-5p, which upregulation was linked with significantly shorter local recurrence-free survival (RFS) [58]. Furthermore, Vahabi et al. examined the last of mentioned miRNAs and discovered that it additionally correlates with the most frequently detectable genetic alteration – mutation in *TP53*, as well as increases HNSCC cell lines' resistance to chemotherapeutics and irradiation [59]. Hudcova et al. studied the expression profile of miR-29c-3p, miR-200b-5p, and miR-375-3p in tumor and paired healthy margin tissue samples. The first molecule was downregulated in cancer, and its low levels were associated with worse overall survival (OS) and less favorable outcome. Decreased expression of miR-200b-5p was linked with advanced tumor grade, and its reduction in adjacent healthy tissue was observed in patients with nodal metastasis. These molecules seem to have prognostic properties worth further exploring. Finally, miR-375-3p was significantly upregulated in control samples compared to cancer tissue, and ROC analysis indicated its sensitivity and specificity as a biomarker reaching 87.5% and 65%, respectively, which implies the great ability to distinguish tumor samples from normal tissue [60].

Esophageal squamous cell carcinoma (ESCC)

Qi and Fan described miR-18a-5p as an interesting potential diagnostic molecule in the ESCC. Its high expression was linked with more advanced disease and worse OS. The ROC analysis indicated that miRNAs' sensitivity and specificity as peripheral blood-based biomarkers was 80.7% and 71.9%, respectively. Moreover, the authors have emphasized the promising prognostic and therapeutic potential of the interplay between miR-18a-5p and ATM in ESCC [61]. A different molecule that might be helpful in ESCC diagnosis is miR-20b-5p. The authors demonstrated that serum levels of said miRNA could distinguish controls from cancer patients with 87.1% specificity and 76.3% sensitivity. In addition, its expression levels were positively associated with lymph node metastasis (LNM), advanced stages of ESCC, and poor survival rates [62]. These findings were corroborated by Xue et al. study, which indicated that miR-20b-5p expression level might predict LNM in patients with T1 stage of ESCC better than lymphovascular invasion, invasion depth and tumor differentiation grade, indicating its tremendous prediction potential [63].

Laryngeal squamous cell carcinoma (LSCC)

The study by Lucas Grzelczyk et al. revealed three miRNAs with exceptional diagnostic potential. Based on let-7a, miR-31, and miR-33 serum levels, patients could be distinguished from healthy individuals with nearly 100% accuracy [64]. A biomarker panel consisting of these molecules could become a helpful tool in LSCC prophylaxis. Whereas Hu et al. proposed the molecular signature of two other molecules — miR-21 and miR-375, which may serve as detection biomarkers. Authors indicated that, except for the diagnostic properties of mentioned miRNAs interplay, miR-21 alone could be an independent patients' OS predictor [65]. Wang et al. compared miR-155 expression levels in serum and tissue samples from LSCC patients. miRNA derived from both sample types had significant diagnostic potential, especially in the early stages of the disease. However, miR-155 detected in tumor specimens manifested higher accuracy compared to serum, not only in the whole patient group but also

in individuals at the early stages of cancer development [66]. The above serves as a promising basis for further investigation, which could lead to the creation of a routine screening panel for LSCC patients.

Nasopharyngeal carcinoma (NPC)

Ye et al. analyzed exosomes present in serum samples from NPC patients and controls. Obtained results indicated that vesicles acquired from the first group are significantly more enriched in miR-24-3p. Additionally, the high expression level of said miRNA was correlated with shorter disease-free survival (DFS), implying its potential diagnostic value [67]. Wen et al. identified two miRNA-based molecular signatures crucial for NPC diagnosis. The first combination consisted of 8 miRNAs: miR-4465-3p, miR-4433-5p, miR-3935, miR-188-5p, miR-513b, miR-3196, miR-1908, and miR-4284, and enabled to distinguish healthy individuals from NPC patients with 88.9% specificity and 86.1% sensitivity. The second one was the combination of 16 miRNAs: miR-296-5p, miR-361-3p, miE-4665-3p, miR-4439, miR-155-5p, miR-5091, miR-4706, miR-4436b-5p, miR-4284, miR-1224-3p, miR-4740, miR-425-5p, miR-1973, miR-513b, miR-1908, and miR-1280, and allowed to differentiate NPC patients from patients with other head and neck cancers and controls with 72.2% specificity and 94.4% sensitivity. These 2 signatures could become powerful biomarker panels in the future [68]. Recently, Wei et al. identified molecules with substantial diagnostic potential, miR-34a and Ki67 protein. This miRNA was proven to be downregulated in the cancer tissue compared to the healthy samples, and its decreased levels were associated with more advanced disease (stage III and IV in TNM staging) and bone metastasis. The diagnostic value of both molecules was examined with the ROC analysis, which indicated that joint detection exceeded the specificity and sensitivity of miR-34a and Ki67 alone, reaching 82.9% and 73.3%, respectively. Furthermore, survival analysis determined that patients with low expression of studied miRNA and high levels of Ki67 had significantly better OS than the group with the opposite expression pattern. Authors underlined not only diagnostic but also prognostic properties of the above signature in NPC [69].

Oral squamous cell carcinoma (OSCC)

Scholtz et al. described a promising molecular signature consisting of three miRNAs, which could distinguish healthy individuals from OSCC patients with a high accuracy. The combination of miR-31-5p, miR-345, and miR-424-3p detected from saliva samples could become a very precise non-invasive diagnostic tool [70]. Interestingly, Lee et al. determined that miR-769-3p could be strongly associated with specific subtypes of OSCC. Its high expression levels were linked with better treatment response, more favorable OS, and less invasive phenotype of the tumor [71]. Whereas low levels of miR-126 were associated with poor outcomes and shorter DFS in cancer patients [72]. Analysis of miR-99a presence in serum samples demonstrated that individuals with OSCC had significantly lower expression levels than the control group and could be distinguished with specificity and sensitivity reaching 83.6% and 80.2%, respectively. Furthermore, decreased miRNA amounts were associated with shorter OS and RFS as well as more advanced TNM stage and histological grade. Analysis of said miRNAs level in blood samples obtained from patients before and after surgery indicated post-treatment increase in the studied molecule level. The authors emphasized that miR-99a could serve as an independent prognostic biomarker of OSCC [73].

Tongue squamous cell carcinoma (TSCC)

Chen et al. proposed a diagnostic signature consisting of 3 miRNAs: miR-21, miR-139-5p, and miR-486-3p, which had exceptional potential in TSCC detection. These molecules differentiated tumors from healthy tissue with specificity reaching 86.7% and 100% sensitivity. However, it is worth mentioning that these results require validation on a larger cohort [74]. Interestingly, an earlier study by Duz et al. also underlined the diagnostic properties of miR-139-5p. This miRNA was downregulated in saliva from cancer patients compared to controls and post-operative TSCC individuals. Detection of miR-139-5p allowed it to differentiate these groups with significant accuracy, which suggests its possible role as a reliable non-invasive TSCC biomarker [75]. Another molecule with high diagnostic accuracy is miR-196a-5p, whose upregulation was identified in TSCC tissue samples. Moreover, its high levels were associated with shorter lymph node metastasis-free survival and early stages of the disease, confirming its importance for cancer screening and prophylaxis [76].

Although much work remains to be done in the field of miRNA-based diagnostic tools, there are many tremendous candidates which might become useful biomarker panels in the future. It is worth mentioning that a few such assays are currently in use, e.g. for distinguishing molecular subtypes of breast cancer [77], forms of lung malignancies [78], or even identifying primary tissue of origin for different tumor types [79]. Among the molecules described above, let-7a, miR-21, miR-29c-3p, miR-31, miR-96-5p, miR-375, miR-429, and miR-3928-5p, can be considered the most universal for detecting the HNSCC tumor group. However, it should be emphasized that most of the miRNAs proposed in this review are currently being investigated for association and possible diagnostic or therapeutic use in more than one type of cancer. More analysis needs to be done to precisely identify molecules specific to a given malignancy, or on the other hand, propose a panel that detects cancer in general. Potential diagnostic biomarkers and their role in the HNSCC are summarized in Table 1.

Beneficial therapeutic targets

miRNAs affect numerous different molecules modulating a variety of pathways and cellular processes, which can lead to astounding therapeutic results as well as severe off-target consequences. Carefully designed small RNA-based drugs have the potential to target not only the multitude of proteins that aren't influenced by any common medicaments but also many compensatory mechanisms participating in the development of therapy resistance [80]. However, the above is inevitably linked with the so-called "too many targets for miRNA effect" (TMTME), which leads to a wide range of difficult-to-predict results. Among others, that is why miRNA-based therapeutics don't enter phase III of clinical trials [81]. On the other hand, bioinformatic tools predicting potential targets and interactions become more and more accurate, giving us hope for designing a new drug which would revolutionize modern medicine.

HNSCC

One such future therapeutic molecule might be miR-31 described by Lu et al. This molecule is upregulated in cancer compared to normal samples, and it is directly reducing the expression level of *ARID1A*, a known inhibitor of Nanog/OCT4/Sox2 stemness factors and epithelial cell adhesion molecules (EpCAM) activity. miR-31/*ARID1A* interplay promotes tumorigenesis and could be correlated with a worse prognosis. The authors suggested that therapeutic induction of *ARID1A* expression is a valuable approach for combating HNSCC [82]. Furthermore, the aforementioned miR-96-5p, a promising predictor of local recurrence, was considered a valuable asset in novel therapeutic approach design. Its high levels induced cell migration, strengthened the resistance to irradiation and cisplatin-based chemotherapy, as well as negatively regulated its direct target *PTEN*, the primary inhibitor of the PI3K/AKT/mTOR pathway. Repression of miR-96-5p expression or induced upregulation of *PTEN* might be a beneficial new strategy for individuals with a high risk of local HNSCC recurrence [59]. Chen et al. described different miRNA with oncogenic properties of miR-18a-5p. It promoted a malignant phenotype in cancer cell lines via *SORBS2* expression inhibition, resulting in the induction of cell migration and proliferation as well as suppression of apoptosis. Forced increase in *SORBS2* expression hindered miR-18a-5p negative impact and implied that therapeutic modulation of the described axis could provide interesting new directions in the design of personal medicine [83]. These reports and the aforementioned diagnostic properties in ESCC make miR-18a a fascinating aspect of oncology research [84].

On the other hand, Hauser et al. found that miR-128 might be a promising tumor suppressor. Its direct negative regulation of *PAIP2, BAG-2, H3F3B, BMI-1*, and *BAX* mRNA level was associated with the proliferation inhibition and promotion of apoptosis. Authors implied that miR-128 has a significant clinical value and its artificial induction might be beneficial for the patients [85]. Nohata et al. showed that miR-1 modulated the expression of *TAGLN2*, a protein with oncogenic properties described in different cancers. Induction of miRNA caused a decrease in tumor growth and invasiveness, proving the importance of further studies regarding its possible therapeutic potential [86].

ESCC

miR-20b-5p that was mentioned before is also a potential therapeutic target. Yu et al. showed that its high expression promoted growth, colony for-

Table 1. Potential diagnostic biomarkers in the group of head and neck squamous cell carcinoma (HNSCC)

miRNA		Cancer type	Expression	Role	Sample	Ref.
let-7a	let-7a	LSCC	Upregulated	Discriminates healthy from LSCC patients with almost 100% specificity and sensitivity. In combination with miR-31 and miR-33 create a molecular signature with tremendous diagnostic potential	Serum	[64]
	let-7a-5p	HNSCC	Downregulated	Promising biomarker for early stages of HNSCC	Saliva	[57]
miR-18a-5p		ESCC	Upregulated	Highly sensitive prognostic biomarker in ESCC	Peripheral blood	[61]
miR-20b-5p		ESCC	Upregulated	Specific biomarker for lymph node metastasis prediction in T1-stage ESCC	Serum	[63]
		ESCC	Upregulated	Discriminates healthy from ESCC patients with high specificity and sensitivity; additionally, positively associated with lymph node metastasis and advanced stages of the disease	Serum	[62]
miR-21	miR-21	TSCC	Downregulated	In combination with miR-139-5p and miR-486-3p diagnose TSCC with 86.7% specificity and 100% sensitivity	Tissue	[74]
		LSCC	Upregulated	Specific biomarker of LSCC detection. In combination with miR-375 distinguishes patients from healthy individuals with significantly higher accuracy	Tissue	[65]
	miR-21-3p	HNSCC	Upregulated	Potential biomarker of local recurrence in HNSCC individually, as well as in combination with miR-21-5p, miR-429, and miR-96-5p	Tissue	[58]
	miR-21-5p	HNSCC	Upregulated	Potential biomarker of local recurrence in HNSCC individually, as well as in combination with miR-21-3p, miR-429, and miR-96-5p	Tissue	[58]
miR-24-3p		NPC	Upregulated	Serum-based potential prognostic biomarker in NPC	Serum	[67]
miR-29c-3p		HNSCC	Downregulated	Future potential biomarker of HNSCC progression	Tissue	[60]
miR-31	miR-31	LSCC	Upregulated	Discriminates healthy from LSCC patients with almost 100% specificity and sensitivity. In combination with let-7a and miR-33 create a molecular signature with tremendous diagnostic potential	Serum	[64]
	miR-31-5p	OSCC	Upregulated	Biomarker with great potential to detect early malignant oral lesions	Saliva	[70]
miR-33		LSCC	Upregulated	Discriminates healthy from LSCC patients with 100% specificity and sensitivity. In combination with let-7a and miR-31 creates a molecular signature with tremendous diagnostic potential	Serum	[64]
miR-34a		NPC	Downregulated	In combination with Ki67 creates a highly specific and sensitive molecular signature for NPC diagnosis and prognosis	Tissue	[69]
miR-96-5p		HNSCC	Upregulated	Potential biomarker of local recurrence in HNSCC individually, as well as in combination with miR-21-3p, miR-21-5p and miR-429	Tissue	[58]
		HNSCC	Upregulated	Predictive biomarker for local HNSCC relapse; additionally correlated with TP53 mutation status	Tissue	[59]
miR-99a		OSCC	Downregulated	Highly specific and sensitive potential biomarker with the ability to differentiate cancer tissue from the healthy sample	Serum	[73]
miR-126		OSCC	Downregulated	Potential prognostic biomarker associated with advanced OSCC	Tissue	[95]
miR-139-5p		TSCC	Downregulated	Saliva-derived and highly accurate biomarker for TSCC detection	Saliva	[75]
			Upregulated	In combination with miR-21 and miR-486-3p diagnose TSCC with 86.7% specificity and 100% sensitivity	Tissue	[74]

→

Table 1. Potential diagnostic biomarkers in the group of head and neck squamous cell carcinoma (HNSCC)

miRNA		Cancer type	Expression	Role	Sample	Ref.
miR-155		LSCC	Upregulated	Serum or tissue-derived biomarker for LSCC detection with the potential to early stage identification	Serum and tissue	[66]
miR-196a-5p		TSCC	Upregulated	Biomarker with the potential to diagnose delayed lymph node metastasis in early stages of TSCC	Tissue	[76]
miR-200b-5p		OSCC	Downregulated	Potential predictor of nodal metastasis in HNSCC	Tissue	[60]
miR-296-5p		NPC	Downregulated	In combination with miR-361-3p, miE-4665-3p, miR-4439, miR-155-5p, miR-5091, miR-4706, miR-4436b-5p, miR-4284, miR-1224-3p, miR-4740, miR-425-5p, miR-1973, miR-513b, miR-1908, and miR-1280 creates valuable diagnostic signature to distinguish NPC patients from other head and neck patients and healthy individuals with 72.2% specificity and 94.4% sensitivity	Whole blood	[68]
miR-345		OSCC	Upregulated	Highly specific molecule for early OSCC diagnosis	Saliva	[70]
miR-375	miR-375	LSCC	Downregulated	Highly specific biomarker of LSCC detection. In combination with miR-21 distinguish patients from healthy individuals with higher accuracy	Tissue	[65]
	miR-375-3p	HNSCC	Downregulated	Distinguishing HNSCC cancer samples from normal tissue with high specificity	Tissue	[60]
miR-424-3p		OSCC	Downregulated	In combination with miR-31-5p and miR-345 distinguish healthy and cancer patients with high sensitivity and specificity.	Saliva	[70]
miR-429		HNSCC	Upregulated	Potential biomarker of local recurrence in HNSCC individually, as well as in combination with miR-21-3p, miR-21-5p and miR-96-5p	Tissue	[58]
miR-486-3p		TSCC	Upregulated	In combination with miR-21 and miR-139-5p diagnose TSCC with 86.7% specificity and 100% sensitivity	Tissue	[74]
miR-769-3p		OSCC	Upregulated	Potential prognostic biomarker for specific OSCC phenotype	Tissue	[71]
miR-3928-5p		HNSCC	Downregulated	Promising biomarker for early stages of HNSCC	Saliva	[57]
miR-4665-3p		NPC	Upregulated	Together with miR-4433-5p, miR-3935, miR-188-5p, miR-513b, miR-3196, miR-1908, and miR-4284 creates powerful diagnostic signature to distinguish healthy individuals from NPC patients with 88.9% specificity and 86.1% sensitivity	Whole blood	[68]

ESCC — esophageal squamous cell carcinoma; HNSCC — head and neck squamous cell carcinoma; LSCC — laryngeal squamous cell carcinoma; NPC — nasopharyngeal carcinoma; OSCC — oral squamous cell carcinoma; TSCC — tongue squamous cell carcinoma

mation, and invasion process in cancer cell lines through negative regulation of *RB1* and *TP53INP1*. Nude mice after injection with cells overexpressing miR-20b-5p developed a stronger metastasis burden than the control group, emphasizing miRNAs' oncogenic character. A therapeutic approach focusing on reducing miR-20b-5p expression level would be a valuable addition to protocols of personalized oncology treatment [62]. Nourmohammadi et al. described an interesting strategy for diminishing the negative impact of miR-200c, a known tumorigenic miRNA. Reduction of miRNAs' expression level through repressing *EZH2* led to a decrease in EMT-related proteins, such as N-cadherin, Zeb2, or Vimentin. This strategy might substantially improve patients' survival rates by attenuating ESCC malignant phenotype [87]. Another miRNA that could significantly repress the process of metastasis is miR-27b-3p. It exerts tumor suppressor function by targeting *Nrf2* and inhibiting N-cadherin, Vimentin, and Claudin-1 expression levels. Upregulation of miR-27b-3p could be beneficial for patients with advanced, metastatic stages of tumor development [88].

LSCC

Niu et al. described miR-154 as one of the potential therapeutic targets in LSCC. Its low ex-

pression levels were associated with an unfavorable prognosis and manifestation of a malignant phenotype. Induced overexpression caused downregulation of *GALNT7*, resulting in decreased proliferation, clonogenicity, and migration of cancer cell lines, as well as promotion of cell cycle arrest. Strategy for miR-154/*GALNT7* regulation could provide beneficial cancer treatment [89]. The study by Li et al. showed that miR-744-3p was significantly upregulated in LSCC patients compared to controls and negatively correlated with PTEN and PDCD4 levels. High expression of of miRNA was linked with cervical LNM and increased invasion, which resulted from *MMP-9* overexpression via activation of AKT and NF-κB. Reducing miR-744-3p could attenuate the LSCC malignancy [90]. A recent article by Tu et al. indicated that miR-129-5p directly regulates *OTX1* oncogene. Overexpression of said miRNA resulted in *OTX1* reduction and, consequently, a decrease in migration and invasion ability of cancer cell lines. A therapeutic approach modulating the described axis could substantially reduce the metastatic character of LSCC [91].

NPC

Ou et al. determined that miR-21 promoted proliferation and suppressed apoptosis in NPC cell lines. It exerts an oncogenic function modulating AKT phosphorylation through regulation of *PTEN* expression level. Authors suggest the significant therapeutic potential of studied miRNA [92]. Xu et al. demonstrated that miR-375 negatively regulates *PDK1* expression, inhibiting tumor progression. Enhancement of *PDK1* expression diminishes miRNas' antitumor effect in NPC cell lines via PI3K/AKT axis, promoting proliferation and migration, and inhibiting apoptosis. Modulating miR-375/PDK1/PI3K/AKT axis might be a promising treatment strategy for NPC patients [93]. A similar interplay between miR-375 and *USP1* was described by the same authors a year later. However, in the case of miR-375/USP1/PI3K/AKT axis, the oncogenic effect of *USP1* overexpression could be reversed by the administration of selective PI3K inhibitor (S2739) [94]. The above indicates the possibility of restoring the positive miR-375 effect in NPC through multiple molecular strategies. A different miRNA with substantial therapeutic potential is miR-24a-3p. It was significantly enriched in serum exosomes of NPC patients compared to controls, leading to repression of *FGF11*, which affected the proliferation and differentiation of various T cells. This mechanism supporting cancer immune evasion is still unclear, however, obtained results lay a valuable foundation for designing an antitumor exosome-based therapy in the future [67].

OSCC

Henson et al. demonstrated that simultaneous overexpression of miR-100 and miR-125b affects the growth and development of OSCC cell lines. Moreover, this modification caused alteration in expression levels of numerous direct and non-direct target genes, which were associated with crucial cellular processes. An artificial increase in miR-100 expression level might diminish OSCC radioresistance, emphasizing tremendous therapeutic potential [95]. Sasahira et al. determined that miR-126 is a promising biomarker as well as an interesting target. The significant association of its low expression level with tumor progression, VEGF-A-related angio- and lymphangiogenesis, and unfavorable prognosis of OSCC patients suggest its potential, especially in advanced cases. Further research regarding miR-126 can inspire new treatment approaches [72]. Recently Zhao et al. presented the miR-617/SERPINE axis, which artificial regulation might be beneficial for patients. Mentioned miRNA was downregulated in OSCC, and its low expression level was linked with advanced stages of tumor development. Its induction led to a reduction of *SERPINE1* expression and diminished its oncogenic effect on the proliferation, viability, and apoptosis of cancer cell lines [96].

TSCC

Liu et al. indicated that miR-222 is strongly associated with the migration and invasion ability of TSCC. Identified mechanism of this carcinogenic effect primarily depended on *MMP1* expression regulation which happened directly through miRNA targeting MMP1 mRNA, or indirectly via modulating SOD2 levels [97]. Moreover, miR-222 negatively modulated *ABCG2* expression, which led to enhanced sensitivity to cisplatin [98]. Therapeutic induction of the miR-222/ABCG2 axis might be

profitable for patients burdened with metastatic and chemoresistant cases of TSCC. A different miRNA with substantial therapeutic potential is miR-27b whose direct target for *ITGA5* mRNA was positively associated with poor prognosis, EMT, and advanced stages of the disease. Stimulated high expression of miRNA resulted in suppression of malignant phenotype and could provide another valuable strategy for combating metastatic TSCC [99].

There is a long way from finding the appropriate target to design the suitable drug form, dose, and route of administration. Then comes the last, most crucial step — clinical trials — a stage where only a few molecules are currently at and where many potentially promising miRNAs have failed so far [100]. The list of miRNA-based therapeutic targets in the HNSCC is presented in Table 2.

Conclusions

The above numerous examples underline the potential of miRNAs both in the field of diagnostics and oncological therapy. Unfortunately, along with the wide range of functions comes the challenge of designing a drug modulating the desired pathway without disastrous off-target effects. Lack of standardization, burdensome drug delivery design, and difficult-to-predict results of TMTME are primary reasons why currently, miRNA-based therapy attempts are succeeding mostly in the cell line models and then stop at the early stages of clinical trials [81,100]. Although the above data favors miRNAs utility as biomarkers, we are convinced that finding the suitable molecule, whether with diagnostic or therapeutic potential, will be a significant step towards the oncology treatment

Table 2. Promising therapeutic targets in the group of head and neck squamous cell carcinomas (HNSCC)

miRNA	Cancer type	Expression	Possible therapeutic effect	Target	Ref.
miR-1	HNSCC	Downregulated	Upregulation of miR-1 might lead to a significant decrease in tumor invasiveness and proliferation ability through negative regulation of TAGLN2 expression	TAGLN2	[86]
miR-18a-5p	HNSCC	Upregulated	Induced upregulation of SORBS2 reduces the oncogenic effect of miR-18a-5p high expression level in HNSCC cell lines	SORBS2	[83]
miR-20b-5p	ESCC	Upregulated	Therapeutically decreased miRNA levels could significantly attenuate tumor proliferation, migration, and invasion in ESCC patients	RB1 and TP53INP1	[62]
miR-21	NPC	Upregulated	A decrease in miR-21 level would repress tumor growth and promote apoptosis through modulation of AKT phosphorylation	PTEN	[92]
miR-24-3p	NPC	Upregulated	Reduction of exosomal miR-24-3p levels could inhibit mechanisms of immune evasion via increasing FGF11 levels which promotes T cell proliferation and differentiation	FGF11	[67]
miR-27b	TSCC	Downregulated	Enhancement of miR-27b expression represses the EMT process in TSCC via targeting ITGA5	ITGA5	[99]
miR-27b-3p	ESCC	Downregulated	Upregulation of miR-27b-3p might attenuate the EMT process by inhibiting Nrf2 expression level	Nrf2	[88]
miR-31	HNSCC	Upregulated	Inhibition of miR-31 could promote ARID1A expression leading to a decrease in Nanog/OCT4/Sox2/EpCAM levels diminishing oncogenicity and stemness, as well as improving patient survival	ARID1A	[82]
miR-96-5p	HNSCC	Upregulated	Induced downregulation of miRNA or upregulation of PTEN might lead to a reduction in cell migration ability as well as sensitize cancer cells to irradiation and cisplatin-based chemotherapy	PTEN	[59]
miR-100	OSCC	Downregulated	Overexpression inducement could inhibit cancer proliferation and lead to a decrease in the radioresistance of OSCC cells	ID1, EGR2, MMP13, and FGFR3	[95]
miR-125b	OSCC	Downregulated	Upregulation of this miRNA expression reduces tumor growth and development	KLF13, CXCL11, and FOXA1	[95]

→

Table 2. Promising therapeutic targets in the group of head and neck squamous cell carcinomas (HNSCC)

miRNA	Cancer type	Expression	Possible therapeutic effect	Target	Ref.
miR-126	OSCC	Downregulated	A high expression level of miR-126 could inhibit tumor progression via modulating VEGF-A-related angio- and lymphangiogenesis	VEGF-A	[72]
miR-128	HNSCC	Downregulated	Induced upregulation leads to the suppression of tumor growth and promotion of apoptosis	PAIP2, BAG-2, H3F3B, BMI-1, and BAX	[85]
miR-129-5p	LSCC	Downregulated	Overexpression of miR-129-5p might cause a decrease in migration and invasion ability of cancer cell lines via OTX1 expression reduction	OTX1	[91]
miR-154	LSCC	Downregulated	Enhancement of miR-154 expression attenuates proliferation, and migration, and promotes cell cycle arrest through a decrease in GALNT7 expression	GALNT7	[89]
miR-200c	ESCC	Upregulated	Inhibition of miR-200c expression through EZH2 might significantly reduce EMT in ESCC	EZH2, CDH1, FN1, and ZEB2	[87]
miR-222	TSCC	Downregulated	Upregulation of miR-222 represses migration of TSCC cells via modulating MMP1 and SOD2 expression levels	MMP1, SOD2, and p27	[97]
	TSCC	Downregulated	Therapeutically increased miRNA levels could reduce TSCC cell lines invasion and resistance to cisplatin treatment	ABCG2	[98]
miR-375	NPC	Downregulated	Induced overexpression or reduction of PDK1 expression level might lead to inhibition of tumor growth and promote apoptosis	PDK1, PI3K, AKT, and USP1	[93]
			Upregulation of miRNA or inhibiting USP1 expression through a selective PI3K inhibitor may result in attenuated cell migration and higher apoptosis rates		[94]
miR-617	OSCC	Downregulated	Promoting miR-617 expression could lead to a reduction of SERPINE1 and its oncogenic effect on proliferation, viability, and apoptosis	SERPINE1	[96]
miR-774-3p	LSCC	Upregulated	Repressing expression of miR-774-3p might suppress the malignant phenotype of LSCC through inactivating AKT/mTOR and NF-κB (p65) signaling cascade, and as a consequence, inhibiting MMP-9 level	PTEN and PDCD4	[90]

ESCC — esophageal squamous cell carcinoma; HNSCC — head and neck squamous cel carcinoma; LSCC — laryngeal squamous cell carcinoma; NPC — nasopharyngeal carcinoma; OSCC — oral squamous cell carcinoma; TSCC — tongue squamous cell carcinoma; Ki67 (MKI-67) — marker of proliferation Ki-67; TP53 — tumor protein P53; TAGLN2 — transgelin 2; SORBS2 — sorbin and SH3 domain containing 2; RB1 — RB transcriptional corepressor 1; TP53INP1 — tumor protein P53 inducible nuclear protein 1; PTEN — phosphatase and tensin homolog; AKT — protein kinase B; FGF-11 — gibroblast growth factor 11; EMT — epithelial-mesenchymal transition; ITGA5 — integrin subunit alpha 5; Nrf2 — nuclear factor erythroid 2-related factor 2 (NRF2); ARID1A — AT-Rich interaction domain 1A; Nanog — homeobox transcription factor Nanog; OCT4 (POU5F1) — POU domain, class 5, transcription Factor 1; Sox2 — SRY-Box transcription factor 2; EpCAM — epithelial cell adhesion molecule; ID1 — inhibitor of DNA binding 1; EGR2 — early growth response protein 2; MMP — metalloproteinase; FGFR3 — fibroblast growth factor receptor 3; KLF13 — KLF transcription factor 13; CXCL11 — C-X-C motif chemokine ligand 11; FOXA1 — forkhead box A1; VEGF — vascular endothelial growth factor; PAIP2 — Poly(A) binding protein interacting protein 2; BAG-2 — BAG cochaperone 2; H3F3B — H3.3 histone B; BMI-1 — B lymphoma Mo-MLV insertion region 1 homolog (BMI1 proto-oncogene); BAX — BCL2 associated X, apoptosis regulator; OTX1 — orthodenticle homeobox 1; GALNT7 — polypeptide N-acetylgalactosaminyltransferase 7; EZH2 — enhancer of zeste 2 polycomb repressive complex 2 subunit; CDH1 — cadherin 1; FN1 — fibronectin 1; ZEB2 — zinc finger e-box binding homeobox 2; SOD2 — superoxide dismutase 2; ABCG2 — ATP binding cassette subfamily G member 2 (Junior Blood Group); PDK1 — pyruvate dehydrogenase kinase 1; PI3K — phosphoinositide 3-kinase; USP1 — ubiquitin specific peptidase 1; SERPINE1 — serpin family E member 1; mTOR — mammalian target of rapamycin; NF-κB — nuclear factor kappa beta; PDCD4 — programmed cell death 4

of tomorrow - early administered personalized therapy with minimal side effects that will significantly improve the quality and extend the lives of HNSCC patients.

Conflict of interest

Concerning the publication of an article titled: "miRNA in head and neck squamous cell carcinomas: promising but still distant future of personalized oncology" written by J.K.-M., K.G., T.K., K.L., and I.M., the authors declare:

1. The contents of this manuscript have not been copyrighted or published previously.
2. The contents of the manuscript are not now under consideration for publication elsewhere.
3. There is no conflict of interest including financial, personal, or other relationships with people or organizations regarding the publication of this paper.

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References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021 [Epub ahead of print], doi: 10.1002/ijc.33588, indexed in Pubmed: 33818764.
2. Joshi P, Dutta S, Chaturvedi P, et al. Head and neck cancers in developing countries. Rambam Maimonides Med J. 2014; 5(2): e0009, doi: 10.5041/RMMJ.10143, indexed in Pubmed: 24808947.
3. Fagan JJ. Semon Lecture: 'Laryngectomy Practice Based on Personal Research', Royal Society of Medicine, 5 November 2020, London, UK. J Laryngol Otol. 2021; 135(7): E3, doi: 10.1017/S0022215121001511, indexed in Pubmed: 34137368.
4. Patterson RH, Fischman VG, Wasserman I, et al. Global Burden of Head and Neck Cancer: Economic Consequences, Health, and the Role of Surgery. Otolaryngol Head Neck Surg. 2020; 162(3): 296–303, doi: 10.1177/0194599819897265, indexed in Pubmed: 31906785.
5. Sanderson RJ, Ironside JAD. Squamous cell carcinomas of the head and neck. BMJ. 2002; 325(7368): 822–827, doi: 10.1136/bmj.325.7368.822, indexed in Pubmed: 12376446.
6. Solomon B, Young RJ, Rischin D. Head and neck squamous cell carcinoma: Genomics and emerging biomarkers for immunomodulatory cancer treatments. Semin Cancer Biol. 2018; 52(Pt 2): 228–240, doi: 10.1016/j.semcancer.2018.01.008, indexed in Pubmed: 29355614.
7. Cohen N, Fedewa S, Chen AY. Epidemiology and Demographics of the Head and Neck Cancer Population. Oral Maxillofac Surg Clin North Am. 2018; 30(4): 381–395, doi: 10.1016/j.coms.2018.06.001, indexed in Pubmed: 30078696.
8. Johnson DE, Burtness B, Leemans CR, et al. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020; 6(1): 92, doi: 10.1038/s41572-020-00224-3, indexed in Pubmed: 33243986.
9. Karabajakian A, Toussaint P, Neidhardt EM, et al. Chemotherapy for recurrent/metastatic head and neck cancers. Anticancer Drugs. 2017; 28(4): 357–361, doi: 10.1097/CAD.0000000000000473, indexed in Pubmed: 28166090.
10. Friedman RC, Farh KKH, Burge CB, et al. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res. 2009; 19(1): 92–105, doi: 10.1101/gr.082701.108, indexed in Pubmed: 18955434.
11. Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol. 2014; 15(8): 509–524, doi: 10.1038/nrm3838, indexed in Pubmed: 25027649.
12. Lujambio A, Lowe SW. The microcosmos of cancer. Nature. 2012; 482(7385): 347–355, doi: 10.1038/nature10888, indexed in Pubmed: 22337054.
13. de Rie D, Abugessaisa I, Alam T, et al. FANTOM Consortium. An integrated expression atlas of miRNAs and their promoters in human and mouse. Nat Biotechnol. 2017; 35(9): 872–878, doi: 10.1038/nbt.3947, indexed in Pubmed: 28829439.
14. Kim YK, Kim VN. Processing of intronic microRNAs. EMBO J. 2007; 26(3): 775–783, doi: 10.1038/sj.emboj.7601512, indexed in Pubmed: 17255951.
15. Cai X, Hagedorn CH, Cullen BR. Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. RNA. 2004; 10(12): 1957–1966, doi: 10.1261/rna.7135204, indexed in Pubmed: 15525708.
16. Denli AM, Tops BBJ, Plasterk RHA, et al. Processing of primary microRNAs by the Microprocessor complex. Nature. 2004; 432(7014): 231–235, doi: 10.1038/nature03049, indexed in Pubmed: 15531879.
17. Han J, Lee Y, Yeom KH, et al. Molecular basis for the recognition of primary microRNAs by the Drosha-DGCR8 complex. Cell. 2006; 125(5): 887–901, doi: 10.1016/j.cell.2006.03.043, indexed in Pubmed: 16751099.
18. Zeng Y, Yi R, Cullen BR. Recognition and cleavage of primary microRNA precursors by the nuclear processing enzyme Drosha. EMBO J. 2005; 24(1): 138–148, doi: 10.1038/sj.emboj.7600491, indexed in Pubmed: 15565168.
19. Bohnsack MT, Czaplinski K, Gorlich D. Exportin 5 is a RanGTP-dependent dsRNA-binding protein that mediates nuclear export of pre-miRNAs. RNA. 2004; 10(2): 185–191, doi: 10.1261/rna.5167604, indexed in Pubmed: 14730017.
20. Okada C, Yamashita E, Lee SJ, et al. A high-resolution structure of the pre-microRNA nuclear export machinery. Science. 2009; 326(5957): 1275–1279, doi: 10.1126/science.1178705, indexed in Pubmed: 19965479.
21. Bernstein E, Caudy AA, Hammond SM, et al. Role for a bidentate ribonuclease in the initiation step of RNA interference. Nature. 2001; 409(6818): 363–366, doi: 10.1038/35053110, indexed in Pubmed: 11201747.
22. Zhang H, Kolb FA, Jaskiewicz L, et al. Single processing center models for human Dicer and bacterial RNase III.

Cell. 2004; 118(1): 57–68, doi: 10.1016/j.cell.2004.06.017, indexed in Pubmed: 15242644.
23. Macrae IJ, Zhou K, Li F, et al. Structural basis for double-stranded RNA processing by Dicer. Science. 2006; 311(5758): 195–198, doi: 10.1126/science.1121638, indexed in Pubmed: 16410517.
24. Park JE, Heo I, Tian Y, et al. Dicer recognizes the 5′ end of RNA for efficient and accurate processing. Nature. 2011; 475(7355): 201–205, doi: 10.1038/nature10198, indexed in Pubmed: 21753850.
25. Tian Y, Simanshu DK, Ma JB, et al. A phosphate-binding pocket within the platform-PAZ-connector helix cassette of human Dicer. Mol Cell. 2014; 53(4): 606–616, doi: 10.1016/j.molcel.2014.01.003, indexed in Pubmed: 24486018.
26. Huntzinger E, Izaurralde E. Gene silencing by microRNAs: contributions of translational repression and mRNA decay. Nat Rev Genet. 2011; 12(2): 99–110, doi: 10.1038/nrg2936, indexed in Pubmed: 21245828.
27. O'Brien J, Hayder H, Zayed Y, et al. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front Endocrinol (Lausanne). 2018; 9: 402, doi: 10.3389/fendo.2018.00402, indexed in Pubmed: 30123182.
28. Wu H, Ye C, Ramirez D, et al. Alternative processing of primary microRNA transcripts by Drosha generates 5′ end variation of mature microRNA. PLoS One. 2009; 4(10): e7566, doi: 10.1371/journal.pone.0007566, indexed in Pubmed: 19859542.
29. Mitra R, Adams CM, Jiang W, et al. Pan-cancer analysis reveals cooperativity of both strands of microRNA that regulate tumorigenesis and patient survival. Nat Commun. 2020; 11(1): 968, doi: 10.1038/s41467-020-14713-2, indexed in Pubmed: 32080184.
30. Elkayam E, Kuhn CD, Tocilj A, et al. The structure of human argonaute-2 in complex with miR-20a. Cell. 2012; 150(1): 100–110, doi: 10.1016/j.cell.2012.05.017, indexed in Pubmed: 22682761.
31. Babiarz JE, Ruby JG, Wang Y, et al. Mouse ES cells express endogenous shRNAs, siRNAs, and other Microprocessor-independent, Dicer-dependent small RNAs. Genes Dev. 2008; 22(20): 2773–2785, doi: 10.1101/gad.1705308, indexed in Pubmed: 18923076.
32. Huntzinger E, Izaurralde E. Gene silencing by microRNAs: contributions of translational repression and mRNA decay. Nat Rev Genet. 2011; 12(2): 99–110, doi: 10.1038/nrg2936, indexed in Pubmed: 21245828.
33. Xu W, San Lucas A, Wang Z, et al. Identifying microRNA targets in different gene regions. BMC Bioinformatics. 2014; 15 Suppl 7(Suppl 7): S4, doi: 10.1186/1471-2105-15-S7-S4, indexed in Pubmed: 25077573.
34. Kawamata T, Tomari Y. Making RISC. Trends Biochem Sci. 2010; 35(7): 368–376, doi: 10.1016/j.tibs.2010.03.009, indexed in Pubmed: 20395147.
35. Jo MH, Shin S, Jung SR, et al. Human Argonaute 2 Has Diverse Reaction Pathways on Target RNAs. Mol Cell. 2015; 59(1): 117–124, doi: 10.1016/j.molcel.2015.04.027, indexed in Pubmed: 26140367.
36. Ellwanger DC, Büttner FA, Mewes HW, et al. The sufficient minimal set of miRNA seed types. Bioinformatics. 2011; 27(10): 1346–1350, doi: 10.1093/bioinformatics/btr149, indexed in Pubmed: 21441577.
37. Nishi K, Nishi Ai, Nagasawa T, et al. Human TNRC6A is an Argonaute-navigator protein for microRNA-mediated gene silencing in the nucleus. RNA. 2013; 19(1): 17–35, doi: 10.1261/rna.034769.112, indexed in Pubmed: 23150874.
38. Chou CH, Shrestha S, Yang CD, et al. miRTarBase update 2018: a resource for experimentally validated microRNA-target interactions. Nucleic Acids Res. 2018; 46(D1): D296–D302, doi: 10.1093/nar/gkx1067, indexed in Pubmed: 29126174.
39. Denzler R, McGeary SE, Title AC, et al. Impact of MicroRNA Levels, Target-Site Complementarity, and Cooperativity on Competing Endogenous RNA-Regulated Gene Expression. Mol Cell. 2016; 64(3): 565–579, doi: 10.1016/j.molcel.2016.09.027, indexed in Pubmed: 27871486.
40. Tian S, Wang J, Zhang F, et al. Comparative Analysis of microRNA Binding Site Distribution and microRNA-Mediated Gene Expression Repression of Oncogenes and Tumor Suppressor Genes. Genes (Basel). 2022; 13(3), doi: 10.3390/genes13030481, indexed in Pubmed: 35328035.
41. Yoon JH, Abdelmohsen K, Gorospe M. Functional interactions among microRNAs and long noncoding RNAs. Semin Cell Dev Biol. 2014; 34: 9–14, doi: 10.1016/j.semcdb.2014.05.015, indexed in Pubmed: 24965208.
42. Fernandes JCR, Acuña SM, Aoki JI, et al. Long Non-Coding RNAs in the Regulation of Gene Expression: Physiology and Disease. Noncoding RNA. 2019; 5(1), doi: 10.3390/ncrna5010017, indexed in Pubmed: 30781588.
43. López-Urrutia E, Bustamante Montes LP, Ladrón de Guevara Cervantes D, et al. Crosstalk Between Long Non-coding RNAs, Micro-RNAs and mRNAs: Deciphering Molecular Mechanisms of Master Regulators in Cancer. Front Oncol. 2019; 9: 669, doi: 10.3389/fonc.2019.00669, indexed in Pubmed: 31404273.
44. Kozłowska J, Kolenda T, Poter P, et al. Long Intergenic Non-Coding RNAs in HNSCC: From "Junk DNA" to Important Prognostic Factor. Cancers (Basel). 2021; 13(12), doi: 10.3390/cancers13122949, indexed in Pubmed: 34204634.
45. Guglas K, Bogaczyńska M, Kolenda T, et al. lncRNA in HNSCC: challenges and potential. Contemp Oncol (Pozn). 2017; 21(4): 259–266, doi: 10.5114/wo.2017.72382, indexed in Pubmed: 29416430.
46. Victoria Martinez B, Dhahbi JM, Nunez Lopez YO, et al. Circulating small non-coding RNA signature in head and neck squamous cell carcinoma. Oncotarget. 2015; 6(22): 19246–19263, doi: 10.18632/oncotarget.4266, indexed in Pubmed: 26057471.
47. Kozłowska-Masłoń J, Guglas K, Paszkowska A, et al. Radio-lncRNAs: Biological Function and Potential Use as Biomarkers for Personalized Oncology. J Pers Med. 2022; 12(10), doi: 10.3390/jpm12101605, indexed in Pubmed: 36294743.
48. Ratti M, Lampis A, Ghidini M, et al. MicroRNAs (miRNAs) and Long Non-Coding RNAs (lncRNAs) as New Tools for Cancer Therapy: First Steps from Bench to Bedside. Target Oncol. 2020; 15(3): 261–278, doi: 10.1007/s11523-020-00717-x, indexed in Pubmed: 32451752.
49. Iftikhar H, Carney GE. Evidence and potential in vivo functions for biofluid miRNAs: From expression profiling to functional testing: Potential roles of extracellular miRNAs as indicators of physiological change and as agents of intercellular information exchange. Bioessays. 2016; 38(4): 367–378, doi: 10.1002/bies.201500130, indexed in Pubmed: 26934338.

50. Weber JA, Baxter DH, Zhang S, et al. The microRNA spectrum in 12 body fluids. Clin Chem. 2010; 56(11): 1733–1741, doi: 10.1373/clinchem.2010.147405, indexed in Pubmed: 20847327.
51. Kolenda T, Guglas K, Baranowski D, et al. cfRNAs as biomarkers in oncology - still experimental or applied tool for personalized medicine already? Rep Pract Oncol Radiother. 2020; 25(5): 783–792, doi: 10.1016/j.rpor.2020.07.007, indexed in Pubmed: 32904167.
52. Jain S, Lin SY, Song W, et al. Urine-Based Liquid Biopsy for Nonurological Cancers. Genet Test Mol Biomarkers. 2019; 23(4): 277–283, doi: 10.1089/gtmb.2018.0189, indexed in Pubmed: 30986103.
53. Rubio M, Bustamante M, Hernandez-Ferrer C, et al. Circulating miRNAs, isomiRs and small RNA clusters in human plasma and breast milk. PLoS One. 2018; 13(3): e0193527, doi: 10.1371/journal.pone.0193527, indexed in Pubmed: 29505615.
54. Umu SU, Langseth H, Bucher-Johannessen C, et al. A comprehensive profile of circulating RNAs in human serum. RNA Biol. 2018; 15(2): 242–250, doi: 10.1080/15476286.2017.1403003, indexed in Pubmed: 29219730.
55. McGranahan N, Swanton C. Clonal Heterogeneity and Tumor Evolution: Past, Present, and the Future. Cell. 2017; 168(4): 613–628, doi: 10.1016/j.cell.2017.01.018, indexed in Pubmed: 28187284.
56. Elazezy M, Joosse SA. Techniques of using circulating tumor DNA as a liquid biopsy component in cancer management. Comput Struct Biotechnol J. 2018; 16: 370–378, doi: 10.1016/j.csbj.2018.10.002, indexed in Pubmed: 30364656.
57. Fadhil RS, Wei MQ, Nikolarakos D, et al. Salivary microRNA miR-let-7a-5p and miR-3928 could be used as potential diagnostic bio-markers for head and neck squamous cell carcinoma. PLoS One. 2020; 15(3): e0221779, doi: 10.1371/journal.pone.0221779, indexed in Pubmed: 32208417.
58. Ganci F, Sacconi A, Manciocco V, et al. Altered peritumoral microRNA expression predicts head and neck cancer patients with a high risk of recurrence. Mod Pathol. 2017; 30(10): 1387–1401, doi: 10.1038/modpathol.2017.62, indexed in Pubmed: 28731048.
59. Vahabi M, Pulito C, Sacconi A, et al. miR-96-5p targets PTEN expression affecting radio-chemosensitivity of HNSCC cells. J Exp Clin Cancer Res. 2019; 38(1): 141, doi: 10.1186/s13046-019-1119-x, indexed in Pubmed: 30925916.
60. Hudcova K, Raudenska M, Gumulec J, et al. Expression profiles of miR-29c, miR-200b and miR-375 in tumour and tumour-adjacent tissues of head and neck cancers. Tumour Biol. 2016; 37(9): 12627–12633, doi: 10.1007/s13277-016-5147-2, indexed in Pubmed: 27440205.
61. Qi J, Fan W. miR-18a-5p and ATM Expression in Esophageal Squamous Cell Carcinoma and Their Correlations with Clinicopathological Features. Comput Math Methods Med. 2022; 2022: 5260608, doi: 10.1155/2022/5260608, indexed in Pubmed: 36267307.
62. Yu J, Chen S, Niu Yi, et al. Functional Significance and Therapeutic Potential of miRNA-20b-5p in Esophageal Squamous Cell Carcinoma. Mol Ther Nucleic Acids. 2020; 21: 315–331, doi: 10.1016/j.omtn.2020.05.015, indexed in Pubmed: 32622332.
63. Xue L, Zhao Z, Wang M, et al. A liquid biopsy signature predicts lymph node metastases in T1 oesophageal squamous cell carcinoma: implications for precision treatment strategy. Br J Cancer. 2022; 127(11): 2052–2059, doi: 10.1038/s41416-022-01997-y, indexed in Pubmed: 36207607.
64. Lucas Grzelczyk W, Szemraj J, Kwiatkowska S, et al. Serum expression of selected miRNAs in patients with laryngeal squamous cell carcinoma (LSCC). Diagn Pathol. 2019; 14(1): 49, doi: 10.1186/s13000-019-0823-3, indexed in Pubmed: 31138255.
65. Hu An, Huang JJ, Xu WH, et al. miR-21 and miR-375 microRNAs as candidate diagnostic biomarkers in squamous cell carcinoma of the larynx: association with patient survival. Am J Transl Res. 2014; 6(5): 604–613, indexed in Pubmed: 25360224.
66. Wang JL, Wang X, Yang D, et al. The Expression of MicroRNA-155 in Plasma and Tissue Is Matched in Human Laryngeal Squamous Cell Carcinoma. Yonsei Med J. 2016; 57(2): 298–305, doi: 10.3349/ymj.2016.57.2.298, indexed in Pubmed: 26847279.
67. Ye SB, Zhang H, Cai TT, et al. Exosomal miR-24-3p impedes T-cell function by targeting FGF11 and serves as a potential prognostic biomarker for nasopharyngeal carcinoma. J Pathol. 2016; 240(3): 329–340, doi: 10.1002/path.4781, indexed in Pubmed: 27538493.
68. Wen W, Mai SJ, Lin HX, et al. Identification of two microRNA signatures in whole blood as novel biomarkers for diagnosis of nasopharyngeal carcinoma. J Transl Med. 2019; 17(1): 186, doi: 10.1186/s12967-019-1923-2, indexed in Pubmed: 31159814.
69. Wei L, Shi C, Zhang Y. Expression of miR-34a and Ki67 in nasopharyngeal carcinoma and the relationship with clinicopathological features and prognosis. Oncol Lett. 2020; 19(2): 1273–1280, doi: 10.3892/ol.2019.11217, indexed in Pubmed: 31966057.
70. Scholtz B, Horváth J, Tar I, et al. Salivary miR-31-5p, miR-345-3p, and miR-424-3p Are Reliable Biomarkers in Patients with Oral Squamous Cell Carcinoma. Pathogens. 2022; 11(2), doi: 10.3390/pathogens11020229, indexed in Pubmed: 35215172.
71. Lee H, Chun SH, Moon SY, et al. MicroRNA-769-3p Acts as a Prognostic Factor in Oral Squamous Cell Cancer by Modulating Stromal Genes. Cancers (Basel). 2022; 14(18), doi: 10.3390/cancers14184373, indexed in Pubmed: 36139534.
72. Sasahira T, Kurihara M, Bhawal UK, et al. Downregulation of miR-126 induces angiogenesis and lymphangiogenesis by activation of VEGF-A in oral cancer. Br J Cancer. 2012; 107(4): 700–706, doi: 10.1038/bjc.2012.330, indexed in Pubmed: 22836510.
73. Chen L, Hu J, Pan L, et al. Diagnostic and prognostic value of serum miR-99a expression in oral squamous cell carcinoma. Cancer Biomark. 2018; 23(3): 333–339, doi: 10.3233/CBM-181265, indexed in Pubmed: 30223386.
74. Chen Z, Yu T, Cabay RJ, et al. miR-486-3p, miR-139-5p, and miR-21 as Biomarkers for the Detection of Oral Tongue Squamous Cell Carcinoma. Biomark Cancer. 2017; 9: 1–8, doi: 10.4137/BIC.S40981, indexed in Pubmed: 28096697.
75. Duz MB, Karatas OF, Guzel E, et al. Identification of miR-139-5p as a saliva biomarker for tongue squamous cell carcinoma: a pilot study. Cell Oncol (Dordr). 2016; 39(2): 187–193, doi: 10.1007/s13402-015-0259-z, indexed in Pubmed: 26650483.
76. Maruyama T, Nishihara K, Umikawa M, et al. MicroRNA-196a-5p is a potential prognostic marker of delayed

lymph node metastasis in early-stage tongue squamous cell carcinoma. Oncol Lett. 2018; 15(2): 2349–2363, doi: 10.3892/ol.2017.7562, indexed in Pubmed: 29434944.
77. Blenkiron C, Goldstein LD, Thorne NP, et al. MicroRNA expression profiling of human breast cancer identifies new markers of tumor subtype. Genome Biol. 2007; 8(10): R214, doi: 10.1186/gb-2007-8-10-r214, indexed in Pubmed: 17922911.
78. Gilad S, Lithwick-Yanai G, Barshack I, et al. Classification of the four main types of lung cancer using a microRNA-based diagnostic assay. J Mol Diagn. 2012; 14(5): 510–517, doi: 10.1016/j.jmoldx.2012.03.004, indexed in Pubmed: 22749746.
79. Pentheroudakis G, Pavlidis N, Fountzilas G, et al. Novel microRNA-based assay demonstrates 92% agreement with diagnosis based on clinicopathologic and management data in a cohort of patients with carcinoma of unknown primary. Mol Cancer. 2013; 12: 57, doi: 10.1186/1476-4598-12-57, indexed in Pubmed: 23758919.
80. Hanna J, Hossain GS, Kocerha J. The Potential for microRNA Therapeutics and Clinical Research. Front Genet. 2019; 10: 478, doi: 10.3389/fgene.2019.00478, indexed in Pubmed: 31156715.
81. Zhang S, Cheng Z, Wang Y, et al. The Risks of miRNA Therapeutics: In a Drug Target Perspective. Drug Des Devel Ther. 2021; 15: 721–733, doi: 10.2147/DDDT.S288859, indexed in Pubmed: 33654378.
82. Lu WC, Liu CJ, Tu HF, et al. miR-31 targets ARID1A and enhances the oncogenicity and stemness of head and neck squamous cell carcinoma. Oncotarget. 2016; 7(35): 57254–57267, doi: 10.18632/oncotarget.11138, indexed in Pubmed: 27528032.
83. Chen Q, Xu J, Zhu M. miR-18a-5p Facilitates Malignant Progression of Head and Neck Squamous Cell Carcinoma Cells via Modulating SORBS2. Comput Math Methods Med. 2021; 2021: 5953881, doi: 10.1155/2021/5953881, indexed in Pubmed: 34707683.
84. Kolenda T, Guglas K, Kopczyńska M, et al. Quantification of long non-coding RNAs using qRT-PCR: comparison of different cDNA synthesis methods and RNA stability. Arch Med Sci. 2021; 17(4): 1006–1015, doi: 10.5114/aoms.2019.82639, indexed in Pubmed: 34336028.
85. Hauser B, Zhao Y, Pang X, et al. Functions of MiRNA-128 on the regulation of head and neck squamous cell carcinoma growth and apoptosis. PLoS One. 2015; 10(3): e0116321, doi: 10.1371/journal.pone.0116321, indexed in Pubmed: 25764126.
86. Nohata N, Sone Y, Hanazawa T, et al. miR-1 as a tumor suppressive microRNA targeting TAGLN2 in head and neck squamous cell carcinoma. Oncotarget. 2011; 2(1-2): 29–42, doi: 10.18632/oncotarget.213, indexed in Pubmed: 21378409.
87. Nourmohammadi F, Forghanifard MM, Abbaszadegan MR, et al. EZH2 regulates oncomiR-200c and EMT markers in esophageal squamous cell carcinomas. Sci Rep. 2022; 12(1): 18290, doi: 10.1038/s41598-022-23253-2, indexed in Pubmed: 36316365.
88. Han M, Li Na, Li F, et al. MiR-27b-3p exerts tumor suppressor effects in esophageal squamous cell carcinoma by targeting Nrf2. Hum Cell. 2020; 33(3): 641–651, doi: 10.1007/s13577-020-00329-7, indexed in Pubmed: 32419118.
89. Niu JT, Zhang LJ, Huang YW, et al. MiR-154 inhibits the growth of laryngeal squamous cell carcinoma by targeting GALNT7. Biochem Cell Biol. 2018; 96(6): 752–760, doi: 10.1139/bcb-2018-0047, indexed in Pubmed: 29874469.
90. Li JZH, Gao W, Lei WB, et al. MicroRNA 744-3p promotes MMP-9-mediated metastasis by simultaneously suppressing PDCD4 and PTEN in laryngeal squamous cell carcinoma. Oncotarget. 2016; 7(36): 58218–58233, doi: 10.18632/oncotarget.11280, indexed in Pubmed: 27533461.
91. Tu XP, Li H, Chen LS, et al. OTX1 exerts an oncogenic role and is negatively regulated by miR129-5p in laryngeal squamous cell carcinoma. BMC Cancer. 2020; 20(1): 794, doi: 10.1186/s12885-020-07279-1, indexed in Pubmed: 32838760.
92. Ou H, Li Y, Kang M. Activation of miR-21 by STAT3 induces proliferation and suppresses apoptosis in nasopharyngeal carcinoma by targeting PTEN gene. PLoS One. 2014; 9(11): e109929, doi: 10.1371/journal.pone.0109929, indexed in Pubmed: 25365510.
93. Jia-Yuan Xu, Wei S, Fang-Fang Lu, et al. miR-375 Inhibits the Proliferation and Invasion of Nasopharyngeal Carcinoma Cells by Suppressing PDK1. Biomed Res Int. 2020; 2020: 9704245, doi: 10.1155/2020/9704245, indexed in Pubmed: 32280708.
94. Xu J, Li B, Song W, et al. Tumor suppressor functions of miRNA-375 in nasopharyngeal carcinoma through inhibition of ubiquitin-specific protease 1 expression. Int J Biochem Cell Biol. 2021; 141: 106092, doi: 10.1016/j.biocel.2021.106092, indexed in Pubmed: 34626803.
95. Henson BJ, Bhattacharjee S, O'Dee DM, et al. Decreased expression of miR-125b and miR-100 in oral cancer cells contributes to malignancy. Genes Chromosomes Cancer. 2009; 48(7): 569–582, doi: 10.1002/gcc.20666, indexed in Pubmed: 19396866.
96. Zhao C, Liu Z. MicroRNA 617 Targeting SERPINE1 Inhibited the Progression of Oral Squamous Cell Carcinoma. Mol Cell Biol. 2021; 41(6): e0056520, doi: 10.1128/MCB.00565-20, indexed in Pubmed: 33820852.
97. Liu X, Yu J, Jiang Lu, et al. MicroRNA-222 regulates cell invasion by targeting matrix metalloproteinase 1 (MMP1) and manganese superoxide dismutase 2 (SOD2) in tongue squamous cell carcinoma cell lines. Cancer Genomics Proteomics. 2009; 6(3): 131–139, indexed in Pubmed: 19487542.
98. Zhao L, Ren Y, Tang H, et al. Deregulation of the miR-222-ABCG2 regulatory module in tongue squamous cell carcinoma contributes to chemoresistance and enhanced migratory/invasive potential. Oncotarget. 2015; 6(42): 44538–44550, doi: 10.18632/oncotarget.6253, indexed in Pubmed: 26517090.
99. Li T, Wu Q, Liu D, et al. miR-27b Suppresses Tongue Squamous Cell Carcinoma Epithelial-Mesenchymal Transition by Targeting ITGA5. Onco Targets Ther. 2020; 13: 11855–11867, doi: 10.2147/OTT.S281211, indexed in Pubmed: 33239888.
100. Chakraborty C, Sharma AR, Sharma G, et al. Therapeutic advances of miRNAs: A preclinical and clinical update. J Adv Res. 2021; 28: 127–138, doi: 10.1016/j.jare.2020.08.012, indexed in Pubmed: 33364050.