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Chapter

From Diagnosis to Prognosis: The Transformative Impact of Exosomal ncRNAs in Head and Neck Cancer

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Abstract

This chapter explores the potential of exosome-derived non-coding RNAs (ncRNAs) as minimally invasive biomarkers for the early diagnosis and prognosis of head and neck cancers (HNC). Late-stage diagnosis, lack of disease-specific biomarkers and disease heterogeneity contribute significantly to the poor survival rates of HNC patients, highlighting the urgent need for novel biomarkers. The chapter reviews the emerging role of exosome-derived ncRNAs in HNC in predicting early onset of HNC, with improved and accurate risk assessment and better prognosis. The chapter also offers insights into the future of ncRNA-based diagnostics and personalized patient management aimed at improving 5-year survival outcomes and reducing the burden of HNC.

Keywords: head and neck cancer, exosomes, non-coding RNAs, microRNA, lncRNA, circRNA, diagnosis, prognosis

1. Introduction

Head and neck cancer (HNC) is one of the most prevalent cancers worldwide, with 9,47,211 new cases and 4,82,428 deaths reported in 2022. The incidence of HNC continues to rise and is anticipated to increase globally by up to 30% by 2030 (Global Cancer Observatory (GLOBOCAN) [1–3]. The key etiological factors that contribute toward its high prevalence are consumption of smoking and smokeless tobacco, and/or excessive alcohol, betel-nut quid, infection with oncogenic strains of human papillomavirus (HPV-16 and HPV-18), Epstein-Barr virus (EBV) and herpes simplex virus type 1 (HSV1). Certain hereditary diseases that increase the risk of HNC include Fanconi's anemia (FA), ataxia, telangiectasia, Bloom's syndrome and Li-Fraumeni syndrome [4].

The histological progression to invasive HNC entails a systemic sequence of changes beginning with epithelial cell hyperplasia, advancing through various

degrees of dysplasia (mild, moderate and severe), carcinoma *in situ* and ultimately culminating in invasive carcinoma. HNC tumors are typically asymptomatic and are likely to be present as persistent ulceration, associated with leukoplakia (white patch), erythroplakia (red patch) or speckled leukoplakia (mixed red/white patch). HNC often has vague symptoms and few clear visible signs until late in the disease progression, resulting in delayed referral. HNC usually begins in the squamous cell lining of the mucosal surfaces inside the oral cavity, tongue, throat and voice box and is hence referred to as squamous cell carcinomas. While the rare type of squamous cell carcinomas also develops in the salivary glands, sinuses or muscles or nerves [5, 6]. Verrucous carcinoma is another low-grade variant of squamous cell carcinoma with specific clinical and morphological features which accounts for only 0.57–16.08% of HNC [7].

Despite the improvement in surgical and therapeutic approaches and ease of access to clinical examination, HNC patients often lose the opportunity for early diagnosis, leading to a poor overall survival rate (40–60%) [8]. At present, the conventional diagnostic approaches for HNC comprise physical examination, imaging techniques such as computed tomography (CT) scan, magnetic resonance imaging (MRI) and histopathological analysis of the tissue biopsies. Until now, tissue biopsy has been the gold standard method for diagnosis; however, it is invasive, painful, time-consuming, fairly challenging and possibly risky for the patient. Moreover, there is an un-accessibility of deeper sites, high false positive rates and intra-tumoral and metastatic heterogeneity remains undetected, affecting the specificity, sensitivity and accuracy of assessment [9]. Furthermore, the poor prognosis rate of HNC is also associated with lack of specific molecular biomarker(s) for early detection and real-time monitoring, locoregional aggressiveness, therapeutic refractoriness and high relapse rate [10]. Therefore, there is an urgent need to identify novel molecular biomarker(s) associated with the development, diagnosis and prognosis of HNC patients.

In recent years, liquid biopsy (LB) has emerged as a groundbreaking tool in cancer research, offering new avenues for diagnosis and prognosis of HNC. Unlike conventional tissue biopsies, which often require surgical procedures and can be uncomfortable for patients, LB allows for repeated sampling with minimal risk and discomfort. This makes it particularly useful in monitoring disease progression, treatment response and potential recurrence in HNC patients over time. The ability to conduct frequent tests without the need for invasive procedures holds great promise for improving patient care and outcomes [11].

The sensitivity of LB is another factor that has propelled its growth as a valuable diagnostic tool. Over the past decade, LB has attracted considerable attention as a non-invasive diagnostic and monitoring method that uses biological fluids—such as blood, saliva, pleural effusions, urine and cerebrospinal fluid (CSF), to detect and analyze a wide range of biomolecular markers. Each of these fluids has unique advantages and disadvantages depending on the type and location of HNC. Pleural effusions and CSF are not always readily accessible in HNC patients and are typically associated with advanced or metastatic disease, making these fluids less useful for early detection and limiting their prognostic value for the overall management of HNC [11–13].

Saliva is particularly promising due to its simple, non-invasive collection, ease of repeated sampling, proximity to tumor sites and cost-effectiveness, providing a more direct readout of disease status in HNC patients. LB has been successful in diagnosing and monitoring other solid tumors, and studies on HNC have shown promise for its use as a less-invasive, more affordable alternative to conventional diagnostic methods [14, 15].

A third notable advantage of LB is its ability to detect biomarkers that remain in the bloodstream for extended periods of time [16].

The persistence of these biomarkers in the system makes it possible to track changes over time, offering a dynamic and real-time health status. This feature is particularly useful for assessing treatment response, detecting minimal residual disease and identifying potential relapse before it becomes clinically evident. By extracting and analyzing genetic material such as circulating tumor DNA (ctDNA), tumor-derived exosomes, tumor-educated platelets (TEPs) and circulating cell-free RNA (cfRNA) from blood or other fluids, LB can provide real-time insights into a patient's disease status [17]. Furthermore, LB has proven to be highly specific in identifying molecular changes associated with HNC, allowing clinicians to tailor treatments based on the unique genetic profile of the tumor.

2. Exosomes in liquid biopsy for head and neck cancer

As liquid biopsy continues to emerge as a powerful, non-invasive tool for diagnosis, prognosis and monitoring of HNC, one of the most promising components of this approach is the analysis of *exosomes*. Exosomes are small, membrane-bound vesicles with a diameter of 40–160 nm, secreted by almost all cell types and stably present in various body fluids [18, 19]. These vesicles carry a rich cargo of bioactive molecules, including nucleic acids (e.g., DNA and RNA), proteins and lipids, which are reflective of the physiological and pathological state of their parent cells, offering valuable insights into the molecular processes underpinning HNC [20–23]. This cargo allows exosomes to serve as a potential goldmine of biomarkers for the diagnosis, prognosis and monitoring of HNC [24–27]. Beyond their direct role in tumor growth, exosomes contribute to the formation of the pre-metastatic niche, promote tumor angiogenesis and support immune suppression in the tumor microenvironment.

Compared to other liquid biopsy markers, such as circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA), exosomes offer several advantages. First, exosomes are present in significantly higher quantities in biofluids—around 10^9 particles/mL—making them easier to isolate compared to CTCs, which are much less abundant in blood (only a few per mL) [23]. Second, exosomes are secreted by living cells and carry abundant biological information from their parental cells, making them more representative of the active tumor than ctDNA, which is primarily derived from apoptotic or necrotic tumor cells [18, 21]. Third, the lipid bilayer membrane of exosomes provides them with intrinsic stability, enabling them to circulate intact even in the harsh conditions of the tumor microenvironment. This high biological stability allows for long-term storage of exosome samples, facilitating both isolation and subsequent detection [28]. Despite their advantages, exosome-based LB faces challenges, particularly in isolating and purifying exosomes due to their nanoscale size and heterogeneity [29–31].

Cancer-derived exosomes represent only a small fraction of total exosomes, necessitating ultrasensitive and specific detection methods for accurate diagnostics. While progress has been made in exosome isolation and analysis of proteins and nucleic acids, issues with sensitivity, specificity, purity and throughput remain barriers to widespread clinical use [32–37]. As such, ongoing research is focused on developing more efficient, high-sensitivity and high-purity platforms for exosome separation and detection. Advancements in this area could significantly improve the use of exosomes in liquid biopsy, providing a powerful and non-invasive tool for the

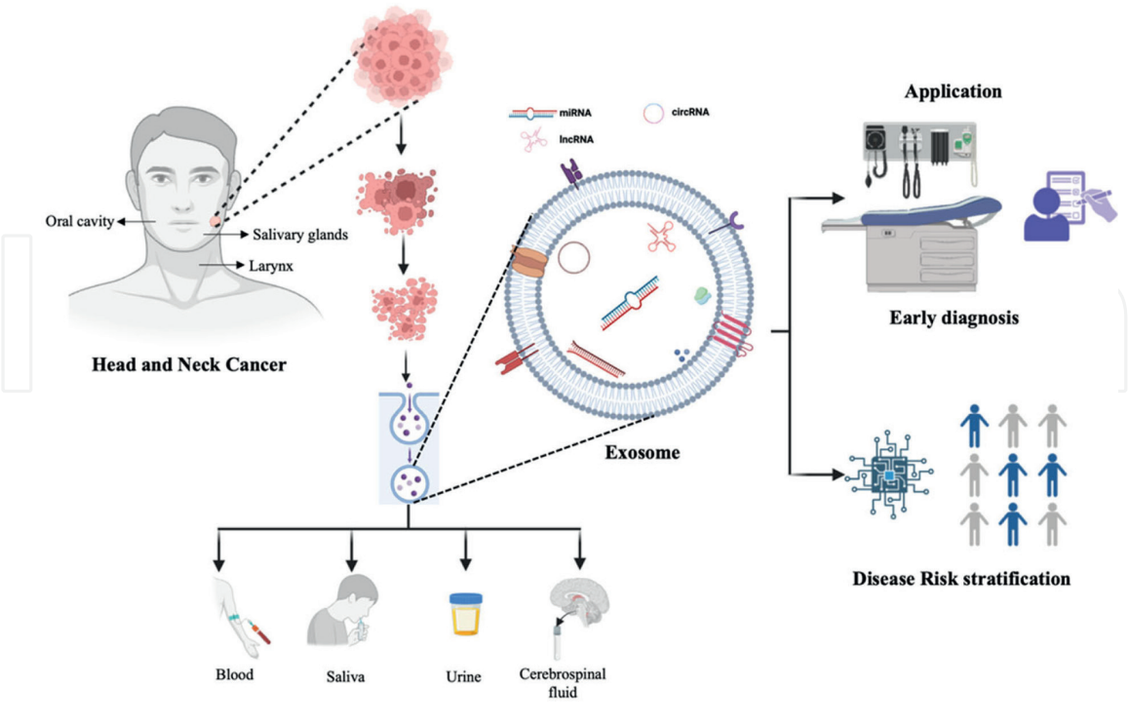


Figure 1.
A schematic representation of exosomal ncRNA involved in HNC diagnosis, prognosis and disease progression.

early detection, monitoring and prognosis of HNC [38]. Within the complex cargo of exosomes, ncRNAs have gained attention for their pivotal role in diagnosis and prognosis of HNC. ncRNAs enter exosomes *via* the double membrane invagination process associated with exosome formation. Studies have indicated that RNA-binding proteins (RBPs) are involved in the process by which exosomes selectively sort non-coding RNAs, including HnRNPA2B1, in addition to passively wrapping themselves around other substances within the cell. ncRNAs have been reported to play a role in cancer initiation, progression and metastasis, highlighting their potential as critical biomarkers in HNC management (**Figure 1**).

3. Exosomal non-coding RNAs: Classification, biogenesis and functions

Non-coding RNAs (ncRNAs) are functional RNA molecules that do not undergo protein translation. Approximately only 2% of RNAs are translated into proteins or are mRNAs, although 90% of the human genome is transcribed [39, 40].

The rest are called non-coding RNAs that were considered junk earlier but now are known to play a crucial role in regulating gene expression at the transcriptional, post-transcriptional and translational levels. The ncRNAs are divided into two main groups based on the length of the transcript. The short non-coding RNAs are less than 40 nt in length, and lncRNAs comprise more than 200 nt. The short non-coding RNAs include microRNAs (miRNAs), short interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs) and transfer RNA fragments (tRNAs) [41, 42].

The lncRNAs are found extensively in a large diversity of species, perform varied biological functions and are mostly categorized based on size, but current developments in transcriptome sequencing and analysis, have led to a further classification into different classes [43, 44].

Exosome-incorporated ncRNAs are released into the cytoplasm after being internalized by recipient cells, where they subsequently influence protein interactions, transcription activation, chromatin alteration and competitive splicing. By controlling cancer growth, metastasis, chemoresistance, immune evasion and angiogenesis, ncRNAs transported by exosomes have recently been discovered to play a crucial role in cancer development and progression [45]. Recent studies have investigated the biomarker potential of exosomal ncRNAs and a number of research teams have presented accumulating data supporting the use of ncRNA as biomarkers in HNC and its significance in oncogenic processes leading to growing evidence in diagnosis, risk assessment and monitoring of HNC.

3.1 Exosomal miRNA

MiRNAs are 20–25 nucleotides long single stranded RNAs encoded from introns that are involved in a number of biological functions. These coding regions are usually located in close proximity to one another referred to as poly-cistronic transcription unit. It is estimated that miRNAs regulate the expression of over 60% of all human genes and more than 1000 human miRNAs have been discovered to date. A growing body of evidence suggests that miRNAs are a crucial part of the intricate regulatory networks that govern a variety of cellular functions, such as the timing of developmental processes, immunological modulation, cell proliferation and differentiation, apoptosis and organ development [46].

miRNA dysregulation or their expression in tissues or biofluid samples, may represent an important diagnostic and prognostic factor for HNC. Extracellular miRNAs are found in different body fluids like saliva, serum plasma, breast milk and cerebrospinal fluid and they can be loaded into high-density lipoprotein (HDL) or bound by AGO2 protein. But exosomal miRNAs are packaged into exosomes or microvesicles that prevent miRNA from degradation and ensure their stability [47].

Due to the lack of endogenous RNase, a high concentration of multiple functional oncogenic miRNAs in HNC exosomes have been found [48, 49] miRNAs derived from exosomes have been extensively studied as potential biomarkers for HNC given their origin and representation of tumor cells [50, 51]. In a study by Li et al., they isolated miR-21 from serum exosomes of OSCC patients and found that significantly higher levels of circulating exosomal miR-21 was observed as compared to healthy individuals. Moreover, the level of circulating exosomal miR-21 was associated with late T stage ($p = 0.009$), positive HIFα expression ($p = 0.001$) and lymph node metastasis ($p = 0.021$). These results indicate that circulating serum exosomal miR-21 could be a potential biomarker for the diagnosis and predicting outcomes in OSCC patients [52].

Additionally, in another investigation miR-941 was significantly upregulated in Laryngeal Squamous Cell carcinoma (LSCC) serum exosomes compared to healthy controls with an area under the curve (AUC) of 0.797 (95% CI = 0.676–0.918) suggesting that serum exosomal miR-941 has the potential to be a therapeutic target and a promising oncogenic biomarker of LSCC [53]. In plasma exosomes the levels of miR-31 were found to be significantly higher in OSCC patients with an AUC of 0.82 compared to age and sex matched control individuals and a notable decrease in this marker expression was also observed following tumor resection indicating that miR-31 is associated with OSCC progression. Moreover, initial analysis for this study also highlighted the potential for detecting elevated miR-31 levels in the saliva of OSCC patients [54]. Consequently, these miRNAs may hold potential for use in the diagnostic, prognostic and therapeutic monitoring of HNC patients.

HPV has been considered to be an etiological factor for HNC and status of HPV infection can also be determined through specific miRNAs isolated from different body fluids. MiR-486-5p was elevated in salivary exosomes from patients with p16-positive oropharyngeal squamous cell carcinoma as compared to control subjects, while miR-10b-5p was linked to HPV-negative oropharyngeal SCC. Furthermore, higher expression levels of miR-486-5p were observed in later stages of the disease. Both miR-486-5p and miR-10b-5p dysregulations in salivary exosomes have been associated with oropharyngeal carcinoma and might serve as a potential prognostic marker [55]. However, the diagnostic significance of exosomal miRNAs in HNC is limited; thus, further research is essential to better define specific exosomal miRNAs and reassess their clinical relevance.

miRNAs have been thoroughly examined in saliva for their role in regulating various HNC-related processes through interactions with target mRNAs [56]. Moreover, saliva is a more accessible and non-invasive medium for collection, which significantly streamlines the identification process and serves as an effective method for monitoring OSCC, but it has a lot of background noise and microbial content, which contaminates the sample and hence isolating exosomes from saliva leads to a better way of monitoring miRNAs. Compared to other potential HNC biomarker-based detection methods, salivary exosomal miRNAs detection offers certain advantages. They can be found in trace amounts of saliva and identified by either whole saliva or just the supernatant [57, 58]. Salivary exosomal miR-134, miR-140-5p, miR-143-5p, miR-145-5p, miR-302b-3p, miR-517-3p, miR-512-3p, miR-24-3p, miR-184, miR-27-3p, miR-494-3p, miR-1307-5p and miR-412-3p exhibited varied expression levels in HNC when compared to normal [59]. Elevated expression of some of the above-mentioned miRNAs has been observed, among which miR-24-3p has been significantly elevated in salivary exosomes from preoperative patients compared to healthy individuals. Additionally, ROC analysis demonstrated that miR-24-3p exhibited excellent OSCC diagnostic accuracy (AUC = 0.738; P = 0.02), suggesting that salivary exosomal miR-24-3p could be a potential novel diagnostic biomarker for OSCC [60]. In a study by Patel et al., it was observed that miR-140-5p, miR-143-5p and miR-145-5p were found to be significantly downregulated in salivary exosomes from OSCC patients as compared to control. The identified 3-miRNA signature exhibited higher potency in predicting disease progression and was clinically associated with poor prognosis in OSCC ($p < 0.05$) [61]. Gai et al. also demonstrated that miR-302b-3p and miR-517b-3p were exclusively found in salivary exosomes derived from patients with OSCC. Additionally, there was a notable overexpression of miR-412-3p (AUC - 0.871) and miR-512-3p (AUC - 0.847) in the salivary exosomes of patients with oral cancer as compared to control subjects with the ROC curve indicating strong diagnostic capability of these miRs for OSCC [62].

In a study by Patel et al., salivary exosomal miRNA-1307-5p expression was upregulated as compared to controls and there was a significant clinical association with disease progression, local aggressiveness and chemotherapeutic refractoriness, making it an ideal prognosticator for OSCC [63]. In recent investigations, Langevin et al. evaluated the expression of 3 miRNAs that were differentially expressed in salivary exosomes collected from HNC patients and healthy controls. Importantly, a subset of HNC patients had significantly higher salivary levels of *miR-10b-5p, miR-486-5p* and *miR-486-3p*, as compared to controls with an accuracy of 85%, highlighting the potential clinical utility of exosomal miRNA as non-invasive salivary biomarkers [50]. Collectively, all these studies have demonstrated that these salivary exosomal miRNAs have the potential to be used as diagnostic or prognostic biomarkers for HNC.

Salivary exosomal miRNAs have also exhibited a correlation with both the disease stage and the histopathological classification and grade of HNC patients. Notably, the expression of miR-134 was elevated in high-grade OSCC, whereas miR-200a showed increased expression in low-grade tumors [64]. Moreover, salivary exosomal microRNAs also have the potential to serve as indicators for the progression of precancerous lesions to malignant stages. Significant example includes miR-4484 which signifies the transition from oral lichen planus (OLP) and oral dysplasia to OSCC [65].

miR-200a has been linked to epigenetic alterations induced by smoking, with its reduced expression correlating with an increased risk of developing oral cancer [64]. Furthermore, along with its malignant nature it was observed that miR-200a levels were found to be significantly elevated a year following radiotherapy [66].

3.2 Exosomal lncRNAs

Long non-coding RNAs (lncRNA) comprise more than 200 nucleotides and are primarily classified into five types according to their formation and activity—sense lncRNA, antisense lncRNA, bidirectional lncRNA, intronic lncRNA and intergenic lncRNA [67]. The extensive diversity of lncRNAs has recently been uncovered through full-length cDNA sequencing of the human genome and according to the GENCODE project, the human genome contains over 16,000 lncRNAs [40].

Exosomal lncRNAs as biomarkers offer several advantages: (I) lncRNAs within exosomes are protected from degradation by RNases, preserving their integrity and function [68]; (II) exosomes contain a higher quantity of lncRNAs compared to other types of extracellular vesicles [69] and (III) many lncRNAs exhibit tissue-specific expression patterns [70]. Moreover, it has been observed that dysregulation of exosomal lncRNA can adversely impact angiogenesis, metastasis and drug resistance, thereby facilitating the initiation and progression of HNC [71]. These factors make exosomal lncRNA profiling a promising approach for developing potential diagnostic markers. A growing number of studies suggests that various lncRNAs, including HOTAIR, UCA1, FOXC1, AFAP1-AS1, HNF1A-AS, ROR, LET, PlncRNA-1, GAS8-AS1, ADAMTS9-AS2, ESCCAL-1, PVT1, PTCSC2, PTCSC3, FIRRE, MEG3, MALAT1 and LOC541471, are involved in the initiation and progression of HNC [72].

These lncRNAs show potential as novel biomarkers and therapeutic targets, offering promise for improving diagnosis, prognosis and treatment strategies for HNC patients [73]. However, research on exosomal lncRNAs in the context of HNC remains limited, with one notable study by Li C et al. shedding light on this area. Serum exosomes are involved in rearranging the intercellular functional lncRNAs, which may also play a role in OSCC. Li C et al. investigated the efficacy of exosomal lncRNAs as a prognostic marker for recurrent OSCC (rOSCC) and OSCC with and without lymph node metastasis (OSCC-LNM and OSCC-NLNM, respectively). The expressions of the lncRNAs, namely MAGI2-AS3 and CCDC144NL-AS1, were significantly upregulated in rOSCC and OSCC-LNM, suggesting that these markers could be potential prognostic biomarkers, as well as therapeutic targets for OSCC [74]. lncRNAs hold potential as HNC biomarkers, however, most of the studies do not clarify whether these transcripts are contained within exosomes. Investigating how lncRNAs circulate in bodily fluids is crucial for understanding their roles and diagnostic and prognostic potential. Examining exosome membrane proteins can provide insights into the origin and uptake of lncRNAs, opening new research avenues. Exosomal lncRNAs may act as oncogenes or tumor suppressors, but further research is required to understand their mechanisms and functions.

3.3 Exosomal circRNAs

Circular RNA (circRNA), are a diverse class of closed-loop non-coding RNAs, lacking 5′capping or 3'poly(A) tail, with a more than 48 hours of average half-life. In 1976, these were first discovered in Sendai viruses and plant viroids [75]. Similar to lncRNAs, these are principally found in cytoplasm and nucleus. Numerous splicing-based models of circRNA biogenesis have been proposed: (1) circularization through canonical splicing-lariat or exon skipping, (2) circularization by splicing-intron pair or direct splicing. Majorly, circRNAs are of three different categories: (1) exonic circRNAs (EcRNAs): all introns are eliminated; (2) exon-intron circRNAs (EIcRNAs): few intronic sequences are conserved and (3) Circular intronic RNAs: derived from introns (ciRNAs) [24]. Moreover, it was first reported that c ircRNAs are enriched in exosomes with 2- to 6-fold higher expression than cells, indicating active incorporation of circRNAs into exosomes with high stability.

CircRNA has been stably present in exosomes derived from various cell lines including Oral Squamous cell carcinoma and Laryngeal carcinoma. Moreover, they have also been identified in exosomes from tumor tissues, patient saliva, serum and urine. Exosomal circRNAs may control tumor cell proliferation, invasion, metastasis, chemotherapeutic drug resistance and radiosensitivity, according to a number of studies that have linked them to the occurrence and progression of malignant tumors. These attributes position circRNA as a promising diagnostic biomarker or therapeutic target for HNC and many other cancers. Luo et al. demonstrated that elevated levels of circ_0000199 ($P < 0.001$) in circulating serum derived exosomes were significantly correlated with consumption of betel quid ($P < 0.01$), tumor size ($P < 0.01$), lymph node involvement ($P < 0.05$) and tumor staging ($P < 0.05$) in patients with OSCC. Furthermore, OSCC patients exhibiting high levels of exosomal circ_0000199 experienced higher rates of tumor recurrence and mortality. These findings indicate that high levels of circulating exosomal circ_0000199 may serve as an independent predictor of survival and disease recurrence in OSCC patients, although the specific regulatory mechanisms need to be further investigated [76].

In another study Tian et al. discovered that serum exosomal circRASSF2 was significantly overexpressed in LSCC patients. Additionally, serum exosomes from LSCC patients showed a strong inverse association between the expression levels of miR-302b-3p and circRASSF2 ($P = 0.003$) and promotes LSCC progression through its sponge effect on miR-302b-3p. Thus, understanding the exosomal circRASSF2 in association with miR-302b-3p may aid in developing a new treatment approach for LSCC in the future [77]. However, both these studies focus on circRNAs as targeted therapy. The clinical studies of exosomal circRNAs and their mechanism of action have not been identified and hence additional research is required to explore their diagnostic role in HNC.

4. Conclusions

In recent years, significant advancements have been made in the studies of exosomal ncRNAs, suggesting their immense potential in the diagnosis and prognosis of HNC. These molecules, carried within exosomes, reflect the molecular landscape of tumors, making them promising candidates for non-invasive biomarker development. Their high concentration and stability in biological fluids such as saliva, serum and plasma, attributed to the lipid bilayer's protection from RNase degradation,

positions exosomal ncRNAs as superior candidates compared to non-exosomal counterparts for early detection and prognostic evaluation.

This book chapter has explored the roles of exosomal ncRNAs—including miRNAs, lncRNAs and circRNAs—in HNC, emphasizing their diagnostic and prognostic relevance (**Table 1**). Evidence suggests that exosomal miRNA profiles, in particular, offer reliable insights into HNC progression, recurrence and response to therapy. By enabling stratification of patients based on disease monitoring, therapeutic response prediction, recurrence propensity and metastatic potential, exosomal ncRNAs can contribute to more precise and personalized management of HNC.

Nevertheless, there are significant challenges that remain to be resolved. The clinical utility of these biomarkers requires further validation through extensive studies and by establishing standardized protocols for their detection and quantification in HNC patients. Addressing these gaps is essential to harness their full potential and translate these findings into routine clinical practice.

Exosomal cargo	Located gene	Outcome	Application	References
miRNA	miR-486–5p, miR-486–3p, miR-10b-5p	Possible biomarker for HNSCC	Diagnosis	[50]
	miR-21	Proliferation, metastasis and invasion Cisplatin resistance	Prognosis & Diagnosis	[52]
	miR-140-5p, miR-143-5p, miR-145-5p	Disease progression	Prognosis	[61]
	miR-31	Possible biomarker for HNSCC	Diagnosis	[54]
	miR-9	Radiosensitivity	Prognosis	[35]
	miR-941	Proliferation and Invasion	Diagnosis	[53]
	miR-134	Higher expression in high-grade OSCC	Prognosis	[64]
	miR-200a	Higher expression in low-grade OSCC	Prognosis	[64]
	miR-24-3p	Proliferation	Diagnosis	[60]
	miR-4484	Disease progression	Prognosis	[65]
	miR-412-3p, miR-512-3p	Upregulation in salivary exosomes	Diagnosis	[62]
	miR-1307-5p	Disease progression, local aggressiveness and resistance to chemotherapy	Prognosis	[63]
lncRNA	MAGI2-AS3 and CCDC144NL-AS1	Therapeutic targets	Prognosis	[74]
circRNA	circ_0000199	Tumor stage, size and metastasis	Targeted therapy	[76]
	circRASSF2	Proliferation, migration and invasion	Targeted therapy	[77]

Table 1.
Potential ncRNA biomarkers for head and neck squamous cell carcinoma.

In conclusion, exosomal ncRNAs are emerging as powerful diagnostic and prognostic tools for HNC. Their unique attributes such as stability, non-invasive accessibility and ability to reflect tumor-specific changes, highlight their transformative potential for improving early detection, monitoring and prognostic stratification. With continued research and technological advancements, exosomal ncRNAs hold immense potential to advance both diagnostic precision and personalized therapeutic approaches in HNC.

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Conflict of interest

The authors declare no conflict of interest.

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