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*Review article*

# Exosomes and Head and Neck Cancers: Can They Be Connected?

Ahmed Khaled Hanafy[1, *], Momen Mohammed Mahmoud[1], Abanoub Morkos[2], Dina Emad[3], Layla Hafed[4], Aliaa Shaban Soliman[3], Sherif AlBahrawey[1], Sally Ibrahim[5].

[1] *Oral Biology Department, Faculty of dentistry, Egyptian Russian University, Badr City, Cairo, Egypt.*
[2] *Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Beni-Suef University, Beni-Suef, Egypt.*
[3] *Master student of Oral and Maxillofacial surgery, Fayoum university.*
[4] *Assistant Professor of Oral and Maxillofacial Pathology, Faculty of Dentistry, Saba University, Sana'a, Yemen.*
[5] *Associate professor of oral and maxillofacial pathology, faculty of dentistry Fayoum University.*

*Corresponding author(s): Ahmed Khaled Hanafy, E-mail: ahmed-khaledhanafi@eru.edu.eg, Tel: (+20) 01008854656.

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## ABSTRACT

**Introduction:** Exosomes are extracellular microvesicles that are membranous, tiny, and have endocytic origins. Exosomes range in size from 30 to 150 nm and are rich in bioactive substances like metabolites, proteins, lipids, and nucleic acids. **Review of literature:** Exosomal miRNAs have the potential to serve as diagnostic biomarkers for a variety of malignancies, immunological responses, cell proliferation, tumor metastasis, tumor growth, and cell apoptosis. Exosomes have been connected to cancer progression, viral pathogenicity, immunological responses, and illnesses of the central nervous system. Exosome's properties are influenced by their lipid and protein content, and exosome's natural makeup may help them be more bioavailable and have fewer negative consequences. **Conclusion:** Exosomes are strongly associated to cancer diagnosis, tumor growth/metastasis and treatment of different head and neck cancers. **Recommendations:** multicomponent analysis of exosomes may be carried out for better understanding of their role in cancer progression and treatment response.

*Keywords:* Exosomes, head and neck cancers, biomarkers, miRNAs, cancer therapy, drug delivery.

## 1- Introduction

Exosomes are distinct from apoptotic bodies and microvesicles, which are produced directly from the cell membrane because they come from the endosome. Endocytosis is used to enclose internal proteins and nucleic acids, along with cell membrane proteins, to create the early endosome. Through a maturation process accompanied by a drop in pH, this early endosome evolves into a late endosome, and many intraluminal membrane vesicles (ILVs) form inside the endosome. ILVs are released into the extracellular space as multivesicular bodies (MVBs), which are vesicles containing several ILVs, re-fuse with the cell membrane. Exosomes are the ILVs that are secreted [1].

Exosomes are found in a variety of body fluids, including blood, cerebrospinal fluid (CSF), urine, saliva, and serous cavity effusion. As a result, exosomes are one of the three variables examined by liquid biopsy, along with circulating tumor DNA and circulating tumor cells. Exosomes are intriguing as possible indicators of several diseases since they are stable in the bloodstream and body fluids. In patients with head and neck squamous cell carcinoma, saliva, a body fluid made up of the secretions from the main salivary glands, is thought to be a valuable source of diagnostic and therapeutic indicators [2].

Salivary exosomes were also detected and analyzed, successfully confirming the existence of two distinct types of exosomes with varied protein compositions and mean diameters (I: 83.5 nm, II: 40.5 nm). Exosomes are formed from cells inside the individual salivary glands (such as the parotid, submandibular, and sublingual), and they may represent the protein- and regulatory-level physiology of the gland [3].

## 2- Review of literature

A key point in utilizing exosomes as potential alternative in regenerative approaches is the isolation and purification process, hence, different methods have been developed to isolate exosomes, in which the ultracentrifugation technique is the most commonly used isolation protocol. In addition to it, size-exclusion chromatography, and polymer precipitation were also developed.

Ultracentrifugation is the most widely accepted method for exosome separation. It is also, an earlier technique for the isolation of urine exosomes that served as the basis for the salivary exosome isolation process [4]. The ultracentrifugation technique's basic idea is based on the size

and density variations between the sample's contaminants and exosomes. It is considered to be the gold standard isolation technique as it is suitable for separating most samples, and having low operating costs [5].

Size-Exclusion Chromatography (SEC) is a methodology used for separation of exosomes based on the difference in their molecular sizes. The unique factor is that when the sample is introduced to the column containing porous beads, larger particles are not able to bypass through gel pores while smaller particles are able to enter the pores resembling a labyrinth, with a slow elution rate to achieve the purpose of separation. In this way, exosome separation can be accomplished only by gravity or low-speed centrifugation, consequently, maintaining the biological structure and function of the exosomes. Experimentally, separation results showed that more purified exosomes were isolated by SEC when compared to traditional ultracentrifugation technique [6,7].

Alternatively, the polymer precipitation technique originally has been used to isolate viruses or other biological macromolecules in the past [8], recently, this method has become an effective methodology to isolate exosomes.

Exosomal solubility is decreased through the action of polymers to enable exosome precipitation, Following which, low-speed centrifugation is utilized to obtain exosomes. This technique is straightforward to use, doesn't require complicated equipment or lengthy processes, works well with large-scale samples, and can be readily integrated with other separation techniques [9].

Saliva was immediately put on ice after collection, taken to the lab, and centrifuged at 15,000 g for 10 minutes at 4°C. In order to further eliminate undesirable organelles and cell fragments, the supernatant was then taken out, put in a different tube, and centrifuged at 17,000 g for 15 minutes at 4 °C. After ultracentrifugation, the pellet containing the exosomes was washed with phosphate buffered saline (PBS) and subjected to further ultracentrifugation at 16,000 g for an hour at 4 °C. The supernatant was taken out after the second ultracentrifugation and the particle was given a brief time to dry. After that, the materials could be used for protein or RNA isolation [10].

In order to properly prepare saliva samples for liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis, results suggested a standard approach for the extraction of salivary exosomes. They assessed that initial saliva processing had an impact on protein analysis,

with in-gel digestion and LC-MS/MS detection producing the most proteins. With the help of this method, they were able to determine that complement factor B and -1-B-glycoprotein were only found in the saliva of head and neck squamous cell carcinoma (HNSCC) patients as opposed to healthy people [11].

**Exosomes in Head and Neck Cancers (HNCs)**

Existence of exosomes is well established in the literature, nevertheless, by using Time-lapse imaging of individual human cells, it has been demonstrated that cancer cells, surprisingly, release more exosomes than healthy cells [12].

### 2.1. Molecular Composition of Exosomes in HNCs

#### 2.1.1. Proteins

Proteins are one of the main components of exosomes. Proteins found in exosomes are similar to those from the cell origin, and specific membrane proteins (e.g., CD9, CD63, and CD81) and intracellular proteins (e.g., HSP70 and tumor sensitivity gene 101) are often used as protein markers of exosomes. Exosomal programmed cell death ligand 1 (exoPD-L1) can inhibit antitumor immune response in various cancers, including nasopharyngeal carcinoma (NPC) [13].

#### 2.1.2. Noncoding RNAs (NcRNAs) and single-stranded DNA

Noncoding RNAs (ncRNAs) such as circular RNAs (CircRNAs), long ncRNAs (LncRNAs), and microRNAs (MiRNAs) are also abundant in exosomes. LncRNAs related to cancer function as tumor suppressor genes or oncogenes in various cell types and cancer stages; in fact, some LncRNAs linked to HNC are deregulated in cancer cells and have been demonstrated to influence the occurrence and progression of cancer, indicating that these LncRNAs may be useful as novel biomarkers and therapeutic targets in HNC. Compared to normal cells, exosomes derived from tumor cell-derived exosomes (TEXs) transport a greater species of DNA, primarily expressed as single-stranded DNA [14].

#### 2.1.3. Lipids

Large concentrations of lipids, such as sphingolipids, serine phospholipids, lecithin, phosphatidylinositol, and cholesterol, are found in the plasma membranes of exosomes. These lipids are present in the exosomal membrane at four times the concentrations found in the membrane of the parent cell, and their high concentration strengthens the exosome membrane. Lipids can serve as biomarkers due to the diversity of cells, exosomes, and other membrane

vesicles. Ceramide and cholesterol, for instance, are preferentially found in exosomes. Exosomes are distinctive in that they have surface-enriched α-2,6 sialic acid, mannose, polylactosamine, N-linked glycans, and saccharide chains [15].

### 2.2. Role of Exosomes in HNCs

#### 2.2.1. Enlargement of Cancerous Tissue by Angiogenesis

Angiogenesis has been reported to be initiated during tumor growth when the tumor diameter is more than 2 to 3 mm. Whether it is a primary lesion or a metastatic lesion, angiogenesis is an essential process for the formation of solid tumors. It is important in supplying the cancer cells with nutrition and oxygen. It was discovered that surface molecules that change based on their function and the environment are included in the exosomes secreted by cancer cells. Furthermore, it was demonstrated that neutral sphingomyelinase 2 **(**n-SMase2) knockdown, which stops breast cancer cells from secreting exosomes, can prevent metastasis by decreasing angiogenesis. Also, miRNA-210 is a component of the exosomes secreted by breast cancer cells and promotes angiogenesis [16].

It was suggested that vascular endothelium cells take up exosomes from liver cancer cells, and the Lysyl Oxidase Like 4 (LOXL4) in the exosomes serves to encourage the proliferation of the vascular endothelial cells. Moreover, results showed that interferon regulatory factor 2 **(**IRF-2)-containing exosomes produced by colon cancer cells are ingested by macrophages and cause the synthesis of vascular endothelial growth factor cancer (VEGFC), which in turn encourages lymph node metastasis by causing lymphatic endothelial cell proliferation and lymphatic channel remodeling [17].

#### 2.2.2. Development of Metastatic Lesions

A characteristic feature of cancer is metastasis, which also serves as a key clinical prognostic indicator. Exosomes play a key role in the development of metastatic lesions, and under certain circumstances, they can encourage metastasis, for example, when cancer cells secrete exosomes with the intention of metastasizing them, or when exosomes from the primary lesion travel through the blood to a distant organ.

According to different studies, miRNA-105 is found in exosomes that are derived from metastatic breast cancer tissue. By acting on vascular endothelial cells, these miRNA-105-containing exosomes suppress the expression of the adhesion molecule ZO-1, ultimately

encouraging the migration of cancer cells outside of blood vessels. Additionally, a substantial association between the presence of miRNA-105 in blood exosomes and distant metastasis in breast cancer patients was found, supporting the significance of miRNA-105 [18].

Exosomes produced by salivary adenoid cystic carcinoma (SACC) cells are important in promoting angiogenesis and local vascular microleakage of SACC by transporting miRNA-23b-3p. This finding raises the possibility that miRNA-23b-3p in exosomes could serve as a biomarker for the distant metastasis of SACC. This demonstrates the treatment method's potential by delivering anti-miRNA-23b-3p, which affects exosomes [19].

### 2.3. Exosomes as a Potential Biomarker of HNCs

#### 2.3.1. In Saliva

Exosome-based liquid biopsies present a promising non-invasive approach for HNC patient screening, diagnosis, monitoring, prognosis, and prediction. Promising substitute liquid biopsies include circulating free DNA (cfDNA) and exosomes of the circulating tumor cells (CTC). According to a recent study, patients with oral malignancies' salivary CD63+/CD9+ exosomes display distinct and differentiable infrared fingerprints when compared to healthy controls [20].

Additionally, identification of human papillomavirus (HPV) DNA in entire saliva as a diagnostic tool for oropharyngeal cancer (OPC) is suggested to be linked to HPV (HPV-OPC). Salivary exosome-based liquid biopsy detection of HPV16 will benefit from the effective isolation of HPV16 from salivary exosomes using an acousto-fluidic platform. These benefits include early detection, risk assessment, and HPV-OPC screening [21].

#### 2.3.2. In Plasma

In addition to noting that baseline levels of plasma exosomes were higher in HNC patients than in healthy controls, it was also observed that only patients who experienced a recurrence exhibited an increase in plasma exosome protein during therapy, and that in patients who fully responded to treatment, plasma exosome levels fell in comparison to pre-therapy levels. While many reported that exosome biosynthesis and DNA packaging are incompatible and that the DNA cargo carried by exosomes is "non-specific," some have advanced the field of exosome DNA analysis, without requiring a direct tumor sample [22].

Many studies showed that combined detection of plasma erythropoietin (EP) associated miRNA-21 and HOTAIR (Lnc-RNA) could distinguish malignant laryngeal cancer from the

benign disease. A few recent studies have suggested that there are discrete miRNA signatures associated with plasma exosomes that can discriminate between patients with the potentially malignant disorder as oral lichen planus and healthy controls or patients with papillary thyroid carcinoma and healthy controls or benign thyroid nodules [23].

CD63+/CD9+/CD81+/TSG101+ extracellular vesicles (EVs) enriched with CD44v3 from the plasma of patients with HNCs was associated with disease stage, lymph node metastasis, and immune dysfunction. When cyclophilin A levels in CD63+/TSG101+/HSP70+ EVs were combined with EBV viral capsid antigen (VCA-IgA) levels, they acted synergistically to provide a combinatorial biomarker with improved accuracy of nasopharyngeal carcinoma **(**NPC) diagnosis [24].

### 2.4. Exosomes as Diagnostic and Prognostic Indicator for HNSCC

Endoscopy, computed tomography (CT), positron emission tomography (PET) scan, magnetic resonance imaging (MRI), and invasive biopsy are examples of traditional cancer diagnosis techniques that are neither appropriate for usage in large populations nor repeated screening.

Since HNSCC produces exosomes in large quantities, exosome levels in HNSCC patients have been employed as diagnostic and prognostic indicators. Exosomes can be readily and safely extracted from body fluids, such as blood or urine, using minimally invasive or non-invasive techniques. Additionally, it was discovered that the protein levels in exosomes that were extracted from the plasma of HNSCC patients were adequate to separate stage I/II patients from stage III/IV patients [25].

According to this data, HNSCC exosomes may serve as "molecular markers" that offer pertinent data on the diagnosis and prognosis of HNSCC.

#### 2.4.1. Proteins

Many invasive compounds are present in the exosomes released by HNSCC, and certain proteins can be identified and used as biomarkers to track the development of the illness. High levels of HSP90 were indicated to a poor prognosis, notably in oral squamous cell carcinoma (OSCC) patients with metastasis, and were found to be present in exosomes from OSCC cells with lymph node metastasis [26].

Stage I/II HNSCC patients had considerably higher serum levels of lysyl oxidase-like 2 (LOXL2) than were healthy controls and stage III HNSCC patients. By modifying HNSCC

extracellular matrix and accelerating epithelial-mesenchymal transition (EMT), LOXL2 enhanced tumor growth. Additionally, earlier research had established that metastatic HNSCC cells expressed more LOXL2 mRNA than non-metastatic cells did [27].

Both the protein and mRNA levels of Annexin A1 (ANXA1) were down-regulated in HNSCC. ANXA1 knockdown of HNSCC cell lines resulted in decreased exosome synthesis and number of associated exosomes phosphorylated with epidermal growth factor receptor (EGFR).

Additionally, linked with the OSCC stage, the serum Alix level was significantly higher in those with lymph node metastases from OSCC than in healthy controls. The stage of OSCC has no bearing on the rise in Alix levels outside of saliva. Serum exosome Alix level has a high positive predictive value and high specificity, making it a useful prognostic indicator of therapeutic response [28].

**2.4.2. miRNAs**

miRNAs have been found to control cell differentiation, proliferation, and apoptosis and play a role in supporting tumor formation as tumor suppressors or oncogenes. Many researchers have discovered a significant concentration of numerous functional oncogenic miRNAs in HNSCC exosomes due to the absence of endogenous RNase. For example, in OSCC cells miRNA-365 levels were substantially greater than those necessary for routine cell maintenance. OSCC exosomes are transported by overexpressed miRNA-365, which may act as a biomarker for the disease in liquid biopsies such as salivary diagnostics [29].

Laryngeal squamous cell carcinoma (LSCC) serum exosomes contained miRNA-941, and quantitative reverse transcription polymerase chain reaction **(**PCR) and receiver operating characteristic **(**ROC) curve analysis revealed that miRNA-941 was up-regulated to increase cell proliferation and invasion [25]. In addition, MiRNA-382-5p may act as a mediator in the connection between cancer associated fibroblast (CAF) and OSCC cells, transferring miRNA-382-5p from exosomes produced from CAF to OSCC cells and encouraging OSCC invasion and metastasis [30].

HIF-1 and HIF-2 directly controlled the generation of miRNA-21-rich exosomes in OSCC cells, which may be stimulated by hypoxia. These miRNA-21-rich exosomes were used to generate pre-metastatic phenotypes in non-hypoxic cells and were crucial in the migration and invasion of OSCC. Notably, miRNA-21 from circulating exosomes was discovered to offer potential for OSCC diagnosis and prognosis [31].

### 2.4.3. Long noncoding RNA (LncRNA)

LncRNAs are also packaged in exosomes. The major functions of exosome LncRNA are as messengers in intercellular communication and as players in the control of the cell microenvironment. Exosomal LncRNA dysregulation will impact angiogenesis, metastasis, and treatment resistance, resulting in an increased risk of tumor incidence and growth [32].

Researchers discovered that the LncRNA ADAMTS9-AS2 was highly up-regulated in healthy oral mucosa tissues but down-regulated in OSCC and oral submucous fibrosis (OSF) tissues, and that low expression was linked to a poor prognosis. Further investigation into the mechanism showed that lncRNA ADAMTS9-AS2 decreased OSCC cell growth and metastasis, controlled epithelial-mesenchymal transition **(**EMT), and inhibited PI3K-Akt signaling pathway [33].

### 2.4.4. CircRNA

CircRNA can be utilized as a miRNA sponge, a competitive binding protein, or a protein scaffold to be employed as a tool for intracellular process modulation, response efficiency, and protein translation. These qualities make it a good treatment target or diagnostic biomarker for HNSCC [34].

Tumor size, lymph node involvement, and systemic metastasis were all strongly correlated with overexpressed circ 0000199 in circulating exosomes in OSCC patients. Additionally, survival rates and recurrency were greater in OSCC patients with reduced exosome circ 0000199. Gain and loss function studies revealed that overexpressing circ 0000199 could suppress apoptosis and boost cell proliferation, whereas circ 0000199 knockdown had the reverse effect. Transforming growth factor (TGF) signaling, the mitogen-activated protein kinase **(**MAPK) signaling pathway, and extra cellular matrix (ECM)-receptor interaction were the key downstream signaling pathways that controlled OSCC cell proliferation and death [35].

These findings point to the possibility that the highly expressed circulating exosome circ 0000199 can serve as a standalone predictor of survival and illness recurrence in OSCC patients, but further research into the precise regulatory mechanisms is still needed.

## 2.5. Exosomes in the Treatment of HNSCC

For patients who are radioresistant, employing interventional radiology **(**IR) in combination with exosomes that overexpress miRNA-34c may be an effective therapy. Exosomal miRNA-34c increases radiosensitivity primarily by inhibiting EMT and blocking B-

catenin to limit the formation of malignancy. Exosomal miRNA-197-3p suppressed nasopharyngeal carcinoma (NPC) cell proliferation, migration, tumor formation, and radiation resistance by regulating AKT/mTOR kinase activation and HSPA5-mediated autophagy [36].

Furthermore, exosomal-mediated miRNA-30a transfer in OSCC restored sensitivity of cisplatin-resistant cancer cells by inducing apoptosis and autophagy through Beclin1 and Bcl2 regulation. Exosomes derived from miR-101-3p-loaded human bone marrow mesenchymal stem cells regulated matrix metalloproteinase 2 **(**MMP2) levels and inhibited the migration and invasion of OSCC cells in vitro and in vivo [37].

OSCC serum exosomes had an increased level of the lncRNA zinc finger antisense 1 (ZFAS1). Overexpression caused OSCC cells to proliferate more quickly and become less sensitive to cisplatin. The expression of miRNA-421 was specifically downregulated by overexpressed ZFAS1, which in turn raised the expression of the myeloid ecotropic viral integration site 1 homolog 2 (MEIS2) and ultimately encouraged the development of chemical resistance to OSCC. The ZFAS1/miRNA-421/MEIS2 pathway regulates OSCC proliferation and chemoresistance to cisplatin, making it a possible therapeutic target for OSCC [38].

In addition, studies show that exosomes represent bioavailable vehicles that can deliver drugs, proteins, miRNAs, and other molecules to prevent tumor progression and improve therapeutic efficacy via crosstalk between tumor cells and stromal cells. In addition, making target-specific exosomes could improve the effectiveness of cancer therapy and they can bound to antibodies target cancer cells preferentially. Exosomes which have been magnetized or altered by pH-sensitive peptides also contribute to the buildup in cancer cells [39].

## 3- Conclusion

Direct association between exosomes and cancer diagnosis, tumor growth/metastasis and treatment of different head and neck cancers is strongly evident and well established in the literature. However, further investigations might be beneficial for better understanding of the underlying mechanisms governing this association.

## Recommendations

Further investigations are needed for better understanding of exosomes role in cancer progression and treatment response. This might be accomplished via a variety of techniques including exosomal multicomponent profiling and proteomics analysis.

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- **Conflict of Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this research paper.

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