Molecular Biology Reports (2026) 53:783
https://doi.org/10.1007/s11033-026-11968-8

REVIEW

Circulating lncRNA as Biomarkers and Therapeutics in Oral Cancer: Silent Scripts with Loud Impact

Riddhiman Bhattacharyya[1] · Chandra Biswas[1] · Md Sadi Khan[2] · Sankhadeep Dutta[2] · Subhayan Sur[1]

Received: 17 January 2026 / Accepted: 11 May 2026
© The Author(s), under exclusive licence to Springer Nature B.V. 2026

Abstract

Oral squamous cell carcinoma (OSCC) remains a major global health challenge due to late diagnosis, high recurrence, and limited therapeutic success. This review focuses on circulating long non-coding RNAs (lncRNAs) as emerging biomarkers and therapeutic targets that can transform the clinical management of OSCC. Unlike earlier studies restricted to tissue-based analyses, this work emphasizes circulating lncRNAs detectable in saliva, plasma, and serum, highlighting their non-invasive diagnostic potential and mechanistic relevance in tumor progression, metastasis, and therapy resistance. Relevant studies published up to 2025 were systematically reviewed from PubMed and Google Scholar to synthesize current knowledge on their biogenesis, secretion through extracellular vesicles and RNA-binding proteins, detection technologies, and clinical applicability. Several circulating lncRNAs, including HOTAIR, MALAT1, MEG3, ANRIL, and LINC00657, show strong associations with tumor stage, prognosis, and therapeutic outcomes. The review also discusses emerging RNA-based therapeutic approaches such as antisense oligonucleotides, RNA interference, and CRISPR-based gene editing. Overall, the analysis underscores the diagnostic precision, prognostic power, and therapeutic promise of circulating lncRNAs, proposing them as key components in the future of liquid biopsy-driven, personalized oncology for OSCC.

Keywords Oral squamous cell carcinoma (OSCC) · Long non coding RNA (lncRNA) · Liquid biopsy · Diagnosis · Therapy · Clinical trial

Abbreviations

5-FU	5–fluorouracil
ABC	ATP–binding cassette
ACTB	Actin beta
ADAMTS9	AS2–ADAMTS9 antisense RNA 2
AFP	plasma alpha–fetoprotein
AHSG	Alpha–2–HS–glycoprotein
AKT	Protein kinase B
ANRIL	Antisense noncoding RNA in the INK4 locus
ANXA2	Annexin A2
ApoBDs	apoptotic bodies
ASOs	Antisense oligonucleotides
AUC	Area Under the Curve
AXL	AXL receptor tyrosine kinase
AZGP1	Zinc–alpha–2–glycoprotein
BANCR	BRAF–activated non–coding RNA
BLACAT1	Bladder cancer–associated transcript 1
CA125	cancer antigen 125
CA153	carbohydrate antigen 153
CAFs	cancer–associated fibroblasts
CAS9	CRISPR–associated protein 9
CCAT1	Colon cancer–associated transcript 1
CD59	CD59 glycoprotein
CEA	carcinoembryonic antigen
CLEC2B	C–type lectin domain family 2 member B

Riddhiman Bhattacharyya, Chandra Biswas and Md Sadi Khan are contributed equally.

✉ Sankhadeep Dutta
sankhadeepdutta@cnci.ac.in

✉ Subhayan Sur
subhayan.sur@dpu.edu.in

[1] Cancer and Translational Research Centre, Dr. D.Y. Patil Biotechnology and Bioinformatics Institute, Dr. D. Y. Patil Vidyapeeth (DPU), Tathawade, Pune 411033, India

[2] Department of Oncogene Regulation, Chittaranjan National Cancer Institution, Kolkata 700026, India

Published online: 16 May 2026

CRISPR	Clustered regularly interspaced short palindromic repeats
CSCs	cancer stem cells
CTCs	circulating tumour cells
ctDNA	circulating tumour DNA
DAZL	Deleted in azoospermia–like
ddPCR	Droplet digital PCR
EDNRB	Endothelin receptor type B
EGFR	Epidermal growth factor receptor
ELDR	EGFR Long Non–Coding Downstream RNA
EMA	European Medicines Agency
EMT	epithelial–to–mesenchymal transition
EVs	extracellular vesicles
F9	Coagulation factor IX
FDA	Food and Drug Administration
FUT4	Fucosyltransferase 4
GACAT2	Gastric cancer–associated transcript 2
GAPDH	Glyceraldehyde–3–phosphate dehydrogenase
GAS5	Growth arrest–specific 5
GAS6	Growth arrest–specific 6
H19	H19 imprinted maternally expressed transcript
HCC	hepatocellular carcinoma
HDL	High–density lipoprotein
HIV	Human immunodeficiency virus
HLEC	human lymphatic endothelial cell
hnRNPA1/A2/B1/ C	Heterogeneous nuclear ribonucleoprotein A1/ A2/ B1/ C
HNSCC	Head and neck squamous cell carcinoma
HOTAIR	HOX transcript antisense RNA
HOTTIP	HOXA distal transcript antisense RNA
HSPA5	Heat shock protein family A member 5
HULC	Highly upregulated in liver cancer
ICB	immune checkpoint blockade
ICGC	International Cancer Genome Consortium
IL	1β–Interleukin–1 beta
KIF1A	Kinesin family member 1 A
KNG1	Kininogen 1
KRT6C	Keratin 6 C
LNA	locked nucleic acids
lncRNAs	long non–coding RNAs
LSINCT	5–Long stress–induced non–coding transcript 5
LUNAR1	Leukemia–induced noncoding activator RNA 1
M2BP	Mac–2 binding protein
MALAT1	Metastasis–associated lung adenocarcinoma transcript 1
MEG3	Maternally expressed gene 3
MGMT	O6–methylguanine–DNA methyltransferase
miRNA	microRNA
MMP1	Matrix metalloproteinase 1
MRP14	Myeloid–related protein 14
mTOR	Mechanistic target of rapamycin
NCK1	AS1–NCK1 antisense RNA 1
ncRNAs	noncoding RNAs
NGS	next–generation sequencing
NNT	AS1–Nicotinamide nucleotide transhydrogenase antisense RNA 1
OPL	Oral premalignant lesion
OSCC	Oral squamous cell carcinoma
PAM50	Prediction Analysis of Microarray 50
PANDAR	Promoter of CDKN1A antisense DNA damage–activated RNA
PAPAS	Promoter and pre–rRNA antisense
PCAT1	Prostate cancer–associated transcript 1
PI3K	Phosphoinositide 3–kinase
PS	phosphatidylserine
PTENP1	Phosphatase and tensin homolog pseudogene 1
RBPs	RNA–binding proteins
RCC	renal cell carcinoma
RNAi	RNA Interference
ROC	Receiver Operating Characteristic
RT	qPCR–Reverse transcription quantitative polymerase chain reaction
SEPT9	Septin 9
SHOX2	Short stature homeobox 2
shRNA	short hairpin RNA
siRNA	small interfering RNA
SNHG3	Small nucleolar RNA host gene 3
STAT3	Signal transducer and activator of transcription 3
TAM	tumor–associated macrophage
TCGA	The Cancer Genome Atlas
TME	tumour microenvironment
UCA1	Urothelial cancer–associated 1
WHO	World Health Organization
Wnt2B	Wingless–type family member 2B
XIST	X–inactive specific transcript

Introduction

Oral cancer or Oral squamous cell carcinoma (OSCC), a major subtype of head and neck squamous cell carcinoma (HNSCC), remains a serious global health concern characterized by high morbidity and mortality, particularly in low- and middle-income countries [5, 6]. Tobacco and alcohol use, areca nut or betel quid chewing, viral infections, poor oral hygiene, and genetic predisposition are among the leading etiological factors [7]. According to GLOBOCAN 2025, oral cancer accounts for approximately 4,15,000 new cases and 2,01,000 deaths annually worldwide, highlighting the need for improved strategies for early detection and precision therapy (Cancer Tomorrow, WHO, 2025).The estimated number of new cases of cancers of the oral cavity and pharynx in the USA in 2025 is 59,660, with approximately 12,770 deaths reported across both genders [9]. Consequently, studies focusing on early detection strategies, genetic testing for disease aggressiveness, and more conservative treatment approaches have rapidly emerged.

Conventional treatment strategies, including surgery, chemotherapy, and radiotherapy, remain the mainstay for OSCC, while targeted agents such as cetuximab and immune checkpoint inhibitors (pembrolizumab, nivolumab) have shown clinical benefits in advanced cases [10]. Nevertheless, the five-year survival rate remains around 50%, dropping significantly in metastatic disease [11]. Delayed diagnosis and tumour heterogeneity are major contributors to poor outcomes, emphasizing the need for minimally invasive diagnostic modalities and molecularly informed treatment approaches [12].

Advances in omics technologies, genomics, transcriptomics, and proteomics have facilitated a shift from the traditional "one-size-fits-all" model toward personalized oncology [12, 13]. However, tissue biopsy and imaging, although standard for OSCC diagnosis, are invasive, spatially limited, and unable to capture tumour heterogeneity or detect micro-metastases [14]. These shortcomings have accelerated interest in liquid biopsy, a minimally invasive approach that enables real-time molecular profiling through the analysis of circulating tumour cells (CTCs), circulating tumour DNA (ctDNA), extracellular vesicles, and noncoding RNAs (ncRNAs) in body fluids such as blood and saliva.

Liquid biopsy has already demonstrated clinical value across cancers, with ctDNA and CTC-based assays incorporated into several international oncology guidelines [15]. Among circulating biomarkers, noncoding RNAs (ncRNAs), including microRNAs, circular RNAs, and long noncoding RNAs (lncRNAs), have shown high stability and specificity, making them promising candidates for early diagnosis, prognosis, and therapeutic monitoring [6, 16].

LncRNAs, a subclass of ncRNAs longer than 200 nucleotides, are transcribed by RNA polymerase II and exhibit diverse regulatory roles in gene expression, chromatin remodeling, and signal transduction [1, 2, 3, 4] **(Box 1)**. Their dysregulation has been linked to various malignancies, including head and neck, lung, ovarian, prostate, breast, and liver cancers [17]. The LncRNADisease database lists nearly 3,000 disease-associated lncRNAs, with emerging evidence supporting their potential as circulating biomarkers. For instance, elevated plasma levels of lncRNA H19 have been associated with lung cancer diagnosis, while HOTAIR and MALAT1 upregulation and MEG3 downregulation are observed across multiple tumour types [15].

BOX1 | Main Characteristics of Long Noncoding RNAs

Long noncoding RNAs (lncRNAs) are larger transcripts, exceeding 200 nucleotides in length, have a typical mRNA-type molecular structure transcribed by RNA polymerase II, having a 5'-methylcytosine cap and a 3'-poly A tail [1-3]. They are synthesized in a manner akin to messenger RNAs (mRNAs) but are not subject to translation into proteins. LncRNAs exhibit two primary functional elements: interactor elements, which facilitate direct physical interactions with other nucleic acids, proteins, or lipids, and structural elements, which enable the formation of secondary or tertiary three-dimensional RNA structures that guide functional interactions. This capacity for interaction with DNA, RNA, and proteins, whether through base pairing in their linear conformation or through chemical interactions in secondary structures, permits lncRNAs to function in a diverse array of manners, surpassing the capabilities associated with microRNAs (miRNAs) [4] Numerous lncRNAs have been identified as having significant gene regulatory roles, influencing factors such as transcription factor binding or epigenetic modifications. Furthermore, their interactions with mRNAs can modify mRNA stability or the efficiency of translation processes. Likewise, lncRNA-protein interactions may affect specific proteins' stability, activity, or localization [8].

Recent studies have developed lncRNA-based diagnostic and prognostic models, including m6A immune-associated risk models in bladder cancer and cuproptosis-related signatures predictive of immune checkpoint blockade (ICB) therapy response in hepatocellular carcinoma [15]. Large-scale initiatives such as The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC) have further validated RNA-based markers, as exemplified by the PAM50 gene panel used for breast cancer classification [18].

Collectively, these findings underscore the potential of circulating lncRNAs as noninvasive and dynamic biomarkers for OSCC detection, prognosis, and therapeutic decision-making. Their roles in OSCC and other cancers have been extensively reviewed in previously [2, 6, 19]. The present review offers an updated and comprehensive synthesis of current knowledge on circulating lncRNAs in OSCC, highlighting their novelty as stable, specific, and clinically meaningful biomarkers within liquid biopsy platforms. It further emphasizes their diagnostic precision, prognostic significance, and therapeutic potential, positioning circulating lncRNAs as pivotal elements in the advancement of liquid biopsy–based personalized oncology for OSCC.

Biogenesis and characteristics of circulating lncRNAs

The molecular mechanisms governing the secretion and transport of circulating lncRNA to the extracellular environment are unclear and have been investigated in only a few studies. Some researchers believe that the secretion of lncRNAs may be similar to miRNAs [8]. As per the recent studies, the secretion of lncRNA is via three routes (Fig. 1):

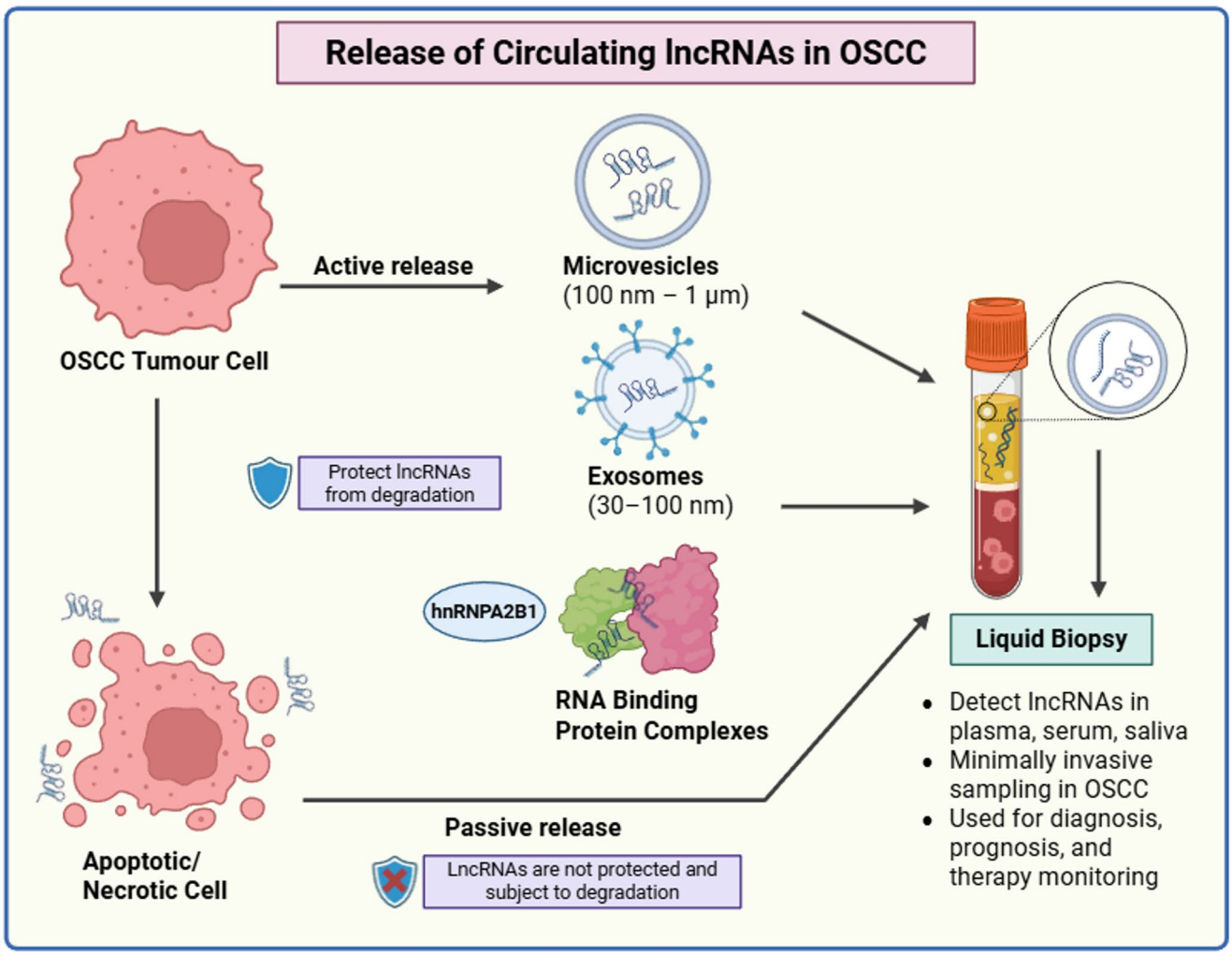

Fig. 1 Release of circulating lncRNAs in OSCC. LncRNAs are actively secreted via exosomes, microvesicles, or RNA-binding proteins, or passively released from dying cells. These circulating lncRNAs, detectable in plasma, serum, or saliva through liquid biopsy, serve as minimally invasive biomarkers for OSCC diagnosis and monitoring. (Created using BioRender.com)

Active release

Tumour cells actively release lncRNAs encapsulated within extracellular vesicles (EVs), including exosomes (30–100 nm) and microvesicles (100 nm–1 μm). This vesicular packaging safeguards lncRNAs from degradation in the bloodstream, allowing their stable transport to distant target cells. Exosomes derived from various tumour types are abundant in the tumour microenvironment (TME) and detectable in blood and body fluids of cancer patients.Exosomes play crucial roles in metastasis, angiogenesis, and epithelial-to-mesenchymal transition (EMT) during cancer progression [20]. However, the precise molecular mechanisms regulating their release remain complex, involving multiple signalling pathways such as ceramide synthesis and Ca^{2+} signalling [20].

Exosomes and other extracellular vesicles carry a diverse range of lncRNAs [20], which participate in key steps of tumour progression, including cell proliferation, angiogenesis, invasion, metastasis, drug resistance, and immune modulation [21]. For instance, exosomal APCDD1L-AS1 transfers 5-fluorouracil (5-FU) resistance to sensitive OSCC cells [22]. Similarly, exosomal ZFAS1 suppresses miR-124 expression, upregulates STAT3, and promotes proliferation and migration in esophageal squamous cell carcinoma [23]. In colorectal cancer, exosomal MALAT1 is upregulated in metastatic cells and enhances invasion and metastasis via the FUT4/PI3K/AKT/mTOR signalling pathway [24].Collectively, lncRNAs packaged within exosomes and microvesicles act as key mediators of intercellular communication, influencing both neighbouring and distant cells to remodel the tumour microenvironment and promote metastasis [25, 26].

Passive release: during cell death

LncRNAs can enter the circulation through passive release during cellular apoptosis or necrosis. When the plasma membrane integrity is compromised, intracellular components, including lncRNAs, leak into the extracellular environment. Dying cells generate membrane-bound apoptotic bodies (ApoBDs) ranging from 500 nm to 2 μm in diameter. During apoptosis, portions of the nucleus and cytoplasm are enclosed within these tightly membrane-bound vesicles, which are then released into the extracellular space.

Unlike microvesicles and exosomes, which are actively secreted and serve as regulated vehicles for intercellular communication, apoptotic bodies arise from the fragmentation of dying cells [27]. Although this release mechanism is non-specific and less controlled, it reflects cellular turnover and can provide valuable insights into disease progression and tissue injury [25].

Apoptotic bodies can encapsulate various biomolecules, including proteins, DNA, and noncoding RNAs, that may modulate intercellular communication and influence the tumour microenvironment [27]. Studies have shown that the number of ApoBDs correlates with tumour malignancy, as observed in prostate cancer, where higher ApoBD levels were detected in more advanced cases. Similarly, glioblastoma-derived ApoBDs have been reported to promote tumour growth, while phosphatidylserine (PS)-containing ApoBDs enhance tumour cell migration via the PS–GAS6–AXL signalling axis [28].

Collectively, these findings suggest that cancer cell, derived apoptotic bodies are not merely by-products of cell death but actively participate in cancer pathophysiology, contributing to tumour progression, metastasis, and intercellular signalling.

Through RNA-binding proteins

RNA-binding proteins (RBPs) play a crucial role in enhancing the stability, secretion, and selective packaging of lncRNAs into extracellular vesicles (EVs), including exosomes released during or after cell death. While the involvement of RBPs in RNA sorting has been more extensively studied for microRNAs (miRNAs), emerging evidence suggests similar mechanisms may regulate lncRNA loading into EVs.

Several RBPs, such as hnRNPA2B1, hnRNPA1, and hnRNPC, interact with specific EV-enriched miRNAs, influencing their selective incorporation into vesicles [29]. Although the mechanisms of long RNA loading are less defined, studies indicate that hnRNPA2B1 binds to conserved sequence motifs within long RNAs (both mRNAs and lncRNAs) to facilitate their sorting into EVs [29]. These recognition motifs, enriched in GGAG, UAG, or GC sequences, are characteristic binding sites for classical RBPs such as RBM5, LIN28A, RBM28, and hnRNPA2B1 [29].

RBPs may promote EV RNA loading through two possible mechanisms: Indirect loading, where RBPs localize RNA transcripts to EV biogenesis sites and facilitate their packaging. Direct loading, where RBPs bridge target RNAs with EV membrane-associated proteins, such as tetraspanins, to mediate their inclusion into vesicles [29, 30].

A notable example is the exosomal lncRNA LNMAT2, which promotes human lymphatic endothelial cell (HLEC) tube formation and migration in vitro, and enhances tumour lymphangiogenesis and lymph node metastasis in vivo. Mechanistically, LNMAT2 is selectively loaded into bladder cancer cell–derived exosomes through direct interaction with hnRNPA2B1 [31].

These findings highlight the pivotal role of RBPs in regulating the selective export of functional lncRNAs, thereby influencing intercellular communication and cancer progression through EV-mediated signalling.

Circulating lncRNAs as diagnostic and prognostic biomarkers in oral cancer

Early detection remains the cornerstone of improving survival outcomes in oral cancer, yet the lack of reliable and specific biomarkers continues to hinder timely diagnosis and disease monitoring. Traditional protein-based assays, though widely used, often fall short in distinguishing malignant from benign conditions with sufficient accuracy [32]. For instance, plasma alpha-fetoprotein (AFP), a classical biomarker for hepatocellular carcinoma (HCC), suffers from low sensitivity and specificity [32]. Similarly, conventional serological markers such as carbohydrate antigen 153 (CA153), cancer antigen 125 (CA125), CA27.29, and carcinoembryonic antigen (CEA) yield inconsistent diagnostic results due to poor reliability and non-specific elevation across multiple cancer types [32].

In OSCC, molecular and epigenetic alterations are increasingly being explored as more precise diagnostic indicators. Promoter methylation of genes such as p16, MGMT, KIF1A, and EDNRB in saliva differentiates OSCC patients from healthy individuals, while methylation of SHOX2 and SEPT9 in serum-derived cell-free DNA from HNSCC patients demonstrates strong diagnostic potential [33].

Proteomic analyses have identified a variety of salivary biomarkers, including actin, myosin, resistin (RETN), angiogenic factors, matrix metalloproteinases (MMPs), and transferrin, associated with OSCC development [34]. Moreover, combinatorial panels such as MMP1–KNG1–ANXA2–HSPA5; interleukins IL-1β, IL-6, and IL-8; AHSG–KRT6C–AZGP1; and a five-protein set comprising M2BP, MRP14, CD59, catalase, and profilin have been evaluated to enhance diagnostic precision. Nonetheless, their limited sensitivity and specificity constrain their clinical applicability [34].

Amid these limitations, lncRNAs have emerged as promising non-invasive biomarkers with greater molecular specificity. For example, dysregulated lncRNAs such as BLACAT1, AC104041.1, ADAMTS9-AS2, ANRIL, and BANCR are implicated in OSCC progression through their regulatory roles in proliferation, migration, invasion, and metastasis [33]. Detectable in accessible biofluids like saliva, serum, and plasma, these molecules show expression patterns that correlate with tumor stage, metastasis, recurrence risk, and therapeutic outcomes [32, 35].

Circulating lncRNAs exhibit remarkable structural stability, protected from RNase-mediated degradation by encapsulation within exosomes, microvesicles, or ribonucleoprotein complexes, and by association with lipoproteins such as HDL [35]. Their persistence in circulation and tumor-specific dysregulation make them attractive candidates for liquid biopsy–based diagnostics and prognostics.

Several landmark studies in different cancer types have underscored the clinical utility of circulating lncRNAs. MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is elevated in both lung and prostate cancer patients, with levels correlating directly with tumor burden and decreasing post-surgery [32]. Similarly, elevated plasma levels of HULC, H19, HOTAIR, and GACAT2 have been reported in HCC and gastric cancers, while GIHCG and ARSR effectively differentiate renal cell carcinoma (RCC) patients from healthy controls with high specificity. Postoperative declines in circulating lncRNA levels further reinforce their tumor-derived origin [32].

Importantly, some circulating lncRNAs outperform conventional protein biomarkers. For example, H19 and RP11-445H22.4 exhibit superior diagnostic accuracy compared with CEA and CA153 in breast cancer, while a three-lncRNA serum signature (PTENP1, LSINCT-5, and UCA1) surpasses traditional markers such as CEA and CA19-9 for gastric cancer detection [32].

Although no circulating lncRNA has yet entered clinical use for OSCC, accumulating evidence supports their potential as sensitive and specific biomarkers. Their differential expression between normal and malignant tissues, coupled with high reproducibility through RT-qPCR and next-generation sequencing (NGS), underscores their promise for integration into future molecular diagnostic workflows [32]. The following section highlights the diagnostic and prognostic relevance of circulating lncRNAs identified in different body fluids. Table 1 provides a detailed summary of the lncRNAs dysregulated in OSCC, their biological roles, and corresponding molecular targets.

Salivary lncRNA biomarkers in OSCC

Saliva, being one of the most non-invasive, easily collectable, and cost-effective body fluids, offers a promising alternative to blood-based diagnostics. Despite its potential, it remains relatively underexplored in biomarker research. Only a few studies have profiled healthy saliva at the molecular level, encompassing proteins, RNAs, and DNA. The concept of "Salivaomics," introduced in 2008, has since emerged as a rapidly developing field that integrates genomics, transcriptomics, proteomics, metabolomics, and microbiomics of saliva [54].

Saliva is composed mainly of histatins, amylase, lactoferrin, peroxidases, mucins, statherins, and proline-rich proteins, which contribute to antibacterial activity and

Table 1 Overview of upregulated and downregulated circulating lncRNAs in Oral Squamous Cell Carcinoma (OSCC)

Name	Study Model	Target	Function	Reference
Upregulated				
HOTAIR	Plasma from OSCC patients	EZH2/H3K27me3	Correlates with tumor aggressiveness, and promotes invasion/metastasis	[36–38]
ANRIL	Serum and tissues from OSCC patients	TGF-β/Smad activation	Promotes proliferation	[39]
MALAT1	Saliva/ Salivary extracellular vesicles in OSCC cohorts	miR-124/STAT3	Promotes proliferation/ invasion	[34]
UCA1	Tissue and plasma from OSCC patients	miR-184	Promotes proliferation and chemoresistance	[40, 41]
LINC00657 (NORAD)	Saliva (unstimulated) from OSCC patients	Sequestration of PUMILIO, Inverse association with miR-106a	Good diagnostic marker; linked to OSCC progression	[42]
OIP5-AS1	Tissue and plasma from OSCC patients	miR-27b-3p	Promotes radiotherapy resistance, proliferation, stemness and drug resistance	[40]
AC007271.3	Tissue and Serum from OSCC patients	NF-κB/miR-125b-2-3p/Slug	Good diagnostic marker; promotes proliferation/ invasion	[43, 44]
NCK1-AS1	Plasma from OSCC patients	Inverse correlation with miR-100	Early-stage diagnostic discrimination	[45]
NEAT1	Plasma from OSCC patients	miR-365/RGS20, VEGF-A/Notch	Linked to OSCC progression, promotes proliferation, invasion, migration	[46, 47]
PAPAS	Plasma from OSCC patients	TGF-β1 pathway	Promotes invasion and migration	[48]
CCAT1	Tissue and plasma from OSCC patients	miR-181a, Wnt/β-catenin pathway	Promotes radiotherapy resistance, proliferation/ invasion, and OSCC progression	[40, 49]
Downregulated				
MEG3	Plasma from OSCC patients	Sponges oncogenic miR-21 and miR-548d-3p, influences JAK/STAT and Wnt/β-catenin pathways	Suppresses proliferation, migration and invasion	[36, 50]
CASC2	Plasma from OSCC patients	miR-21 / PDCD4 axis; cell-cycle control involving CDK1	Suppresses proliferation, migration, and invasion; lower levels predict local recurrence	[51]
ENST00000412740	Plasma from OSCC patients	-	Good diagnostic marker, linked to malignant progression.	• [46]
XIST	Saliva from OSCC patients	miR-455-3p/BTG2,miR-133a/VEGFB	Good diagnostic marker, associated with increased OSCC risk	[52, 53]

mineralization. Other constituents such as lysozyme, secretory IgA (sIgA), and lipase perform defense and digestive functions [54]. Several cancer-associated biomarkers, including EGFR, haptoglobin, calprotectin, HOXA9, valine, leucine, isoleucine, phenylalanine, porphyrin, miRNAs, lncRNAs, and circRNAs, have been identified in saliva [54]. Over time, many studies have standardized saliva collection, storage, and transport protocols, leading to the establishment of the Salivaomics Knowledge Base, which serves as an important platform for salivary diagnostic research.

Although the quantity and stability of coding and non-coding RNAs in saliva have been questioned due to their susceptibility to degradation, research has demonstrated that endogenous salivary RNAs degrade more slowly than exogenous RNA species [54]. This relative stability provides a basis for developing salivary RNA-based diagnostic assays. One study suggested that saliva may be a more suitable liquid biopsy medium than blood (plasma) for cfRNA analysis in detecting OSCC [55]. The expression of CLEC2B, DAZL, F9, and AC008735.2 in saliva could serve as potential diagnostic biomarkers for OSCC, warranting further investigation [55].

In a pioneering study, Tang et al. reported significant upregulation of HOTAIR and MALAT1 in the saliva of OSCC patients ($n=9$) [56]. Interestingly, while MALAT1 expression remained unaffected by lymph node metastasis, HOTAIR expression was elevated in metastatic samples compared to non-metastatic ones. Although this pilot study lacked comprehensive validation, sensitivity, and specificity analyses, both lncRNAs have been independently reported as oncogenic regulators in OSCC tissues and cell lines, where they promote cell proliferation, invasion, and metastasis through multiple signaling pathways [6].

Similarly, another study demonstrated that LINC00657 was highly expressed in saliva samples from OSCC patients ($n = 12$) as measured by qRT- PCR [42]. Receiver Operating Characteristic (ROC) curve analysis revealed a diagnostic accuracy (DA) of 83.3%, suggesting its potential use in distinguishing OSCC patients from healthy controls as well as in differentiating between OSCC grades II and III [42]. Furthermore, the loss of salivary XIST expression is associated with an increased risk of OSCC, particularly among female patients, indicating a possible role of XIST in sex-linked susceptibility to oral carcinogenesis [52].

In summary, salivary lncRNA profiling represents a promising yet still developing approach for non-invasive OSCC diagnostics. Preliminary findings on biomarkers such as HOTAIR, MALAT1, LINC00657, and XIST are encouraging. However, large-scale validation across diverse populations, standardized methodologies, and integration with multi-omics platforms are crucial to establish their clinical reliability and diagnostic potential.

Plasma and serum lncRNA biomarkers in OSCC

Blood serves as a major carrier of physiological and pathological information, containing immune cells, clotting factors, proteins, EVs, and circulating nucleic acids, including cfRNA [57]. In circulation, cfRNA exists either encapsulated within EVs or as ribonucleoprotein complexes. To minimize contamination from blood cells, plasma or serum is typically preferred over whole blood [57]. Both biofluids have shown diagnostic potential, although plasma generally yields higher cfRNA concentrations than serum [57]. Proper sample processing, avoiding cellular contamination, repeated freeze–thaw cycles, and long-term storage, is critical for ensuring RNA integrity and reproducibility [57].

Despite these advantages, cfRNA-based liquid biopsies face significant challenges, primarily due to a lack of standardized protocols, high interpersonal variability, and confounding factors such as age and sex [57]. The reliance on small retrospective cohorts further limits early diagnostic translation. Therefore, standardized workflows, rigorous validation, and integrative bioinformatics pipelines are essential to establish reproducible and clinically actionable cfRNA biomarkers [57].

Blood-based circulating lncRNAs have emerged as promising non-invasive biomarkers for OSCC. CASC2 was reported to be significantly downregulated in early-stage OSCC, with an AUC of 0.845 for early detection and a strong association with recurrence and proliferation inhibition via miR-21 suppression [51]. Microarray profiling in 67 OSCC patients identified 6,606 dysregulated lncRNAs, with ENST00000412740, NR_131012, ENST00000588803, and NR_038323 showing consistent stage-specific alterations; combined lncRNA panels demonstrated superior diagnostic accuracy compared to single markers [46].

A case-control study involving 80 OSCC patients revealed significant upregulation of HOTAIR (3.91-fold) and ANRIL (5.86-fold), alongside downregulation of MEG3 (0.12-fold), correlating with advanced stage, poor differentiation, and invasive features [36]. The three-lncRNA panel (HOTAIR + ANRIL + MEG3) achieved an AUC of 0.95, with 91.25% sensitivity and 92.50% specificity, while MEG3 alone exhibited superior performance in early-stage detection [36]. Similarly, PAPAS and NCK1-AS1 were significantly upregulated in OSCC, showing high diagnostic accuracy (AUCs 0.93 and 0.88) and associations with tumor aggressiveness [45, 48]. GAS5, a tumor-suppressive lncRNA, was linked to chemoradiation resistance, with higher plasma levels observed in poor responders [58]. Additionally, AC007271.3 and LOC284454 in serum showed high specificity in distinguishing OSCC from healthy controls, especially when combined with conventional tumor markers [35].

In a multi-cohort profiling study [46], identified four plasma lncRNAs whose expression progressively increased with OSCC advancement. Their combined ROC analysis achieved AUCs of 0.901–0.924, with 93.8% sensitivity and 91.0% specificity for OSCC/OPL discrimination, and effectively differentiated early- from late-stage tumors.

Thus, circulating lncRNAs in plasma and serum offer a novel, minimally invasive avenue for OSCC diagnosis, staging, and prognosis. Their ability to reflect tumor dynamics and treatment response underscores their potential as next-generation liquid biopsy biomarkers. However, large-scale prospective validation and methodological standardization are imperative for clinical translation. The integration of multi-lncRNA panels represents a novel and powerful strategy to enhance diagnostic precision and capture disease heterogeneity in OSCC.

In summary, both saliva and plasma/serum show strong potential for circulating lncRNA-based detection of OSCC, with some plasma panels achieving high diagnostic accuracy (AUC > 0.90). However, saliva offers a distinct translational advantage due to its non-invasive collection and suitability for large-scale screening. Supporting this, recent evidence suggests saliva may be a more suitable cfRNA medium than plasma. Validating key salivary lncRNAs, HOTAIR, MALAT1, LINC00657, and XIST, in large cohorts could therefore yield a practical and accurate diagnostic test. For blood-based assays, multi-lncRNA panels combining HOTAIR, ANRIL, MEG3, GAS5, and lncRNAs from Jia et al. (2021) could improve detection, staging, and treatment prediction [46]. Future work should focus on multi-center validation, standardized collection protocols, and integration of multi-omics and AI-driven analytics to enhance

reproducibility and precision. Such approaches will accelerate translation of lncRNA liquid biopsies into personalized diagnostic and prognostic tools for OSCC.

Detection Technologies for circulating lncRNAsand Methodological Challenges.

lncRNA in biofluids

The extraction of lncRNAs from different biofluids presents both advantages and limitations. Plasma and serum are the most commonly used sources of tumor-derived cell-free nucleic acids. Plasma, collected with anticoagulants, better preserves the integrity of circulating RNA, maintaining a more authentic molecular profile. In contrast, serum, obtained after coagulation, may contain additional RNAs released from platelet activation or hemolysis, potentially distorting tumor-specific lncRNA signatures [11]. Consequently, many protocols favor double-spun plasma to effectively remove residual blood cells and improve reproducibility of results.

Saliva represents another attractive biofluid because it can be collected non-invasively and directly interfaces with oral tumor tissues. Salivary lncRNAs may reflect both systemic circulation and local tumor shedding, making saliva particularly suitable for the early detection of oral cancer [59]. However, its diagnostic utility is limited by pre-analytical variability, including the time of collection, food intake, and oral hygiene, as well as enzymatic degradation of RNA within the oral cavity. Standardized saliva collection, handling, and stabilization protocols are therefore essential.

Technologies for detecting circulating lncRNAs

Multiple analytical platforms are available for detecting and quantifying circulating lncRNAs, each with specific advantages and constraints. qRT-PCR remains the gold standard due to its high sensitivity and specificity for target transcripts and is widely used for validation in patient-derived samples [60]. Despite its precision, qRT-PCR typically measures only a few targets per assay and requires careful normalization, limiting its scalability for large biomarker panels.

Droplet digital PCR (ddPCR) has recently gained prominence in liquid biopsy applications. By partitioning samples into thousands of nanodroplets, ddPCR enables absolute quantification of lncRNAs without the need for a standard curve, offering superior precision and tolerance to PCR inhibitors. This technology is particularly useful for detecting low-abundance transcripts and monitoring minimal residual disease (MRD) [11, 61]. However, ddPCR requires specialized instrumentation and is relatively cost-intensive per assay.

High-throughput approaches, including RNA sequencing (RNA-seq) and microarrays, are invaluable for discovering novel lncRNA biomarkers. Next-generation RNA-seq allows unbiased profiling of the circulating transcriptome, detecting hundreds of lncRNAs simultaneously [60]. Nonetheless, standard RNA-seq protocols typically require relatively large RNA inputs (>1 µg), which are challenging to obtain from plasma or serum. Optimized library preparation protocols and exosomal RNA extraction kits can now facilitate sequencing from smaller inputs, although low-abundance lncRNAs may still be overlooked due to background noise [60].

In practice, a tiered strategy, broad profiling with RNA-seq or microarrays followed by targeted validation with qPCR or ddPCR in larger cohorts, maximizes both discovery and quantitation accuracy.

Normalization, standardization, and reproducibility

Normalization is a critical challenge in circulating lncRNA studies. Unlike tissue-based assays, no universal housekeeping lncRNA maintains stable expression across extracellular fluids [62]. Reference genes such as ACTB, GAPDH, U6, or 18 S rRNA exhibit variable expression in cell-free RNA. Some studies employ the mean of multiple moderately abundant lncRNAs, while others use exogenous spike-ins from plants or *C. elegans* [35]. Despite these strategies, fold-change inconsistencies remain across studies. Quantitative methods like ddPCR, incorporating endogenous and exogenous controls alongside precise RNA input measurement (e.g., Qubit), currently represent best practices for improving reliability.

Reproducibility is further affected by both biological and technical variability. Individual baseline circulating RNA levels vary, and factors such as inflammation, infection, or comorbidities can alter lncRNA concentrations independently of cancer [35]. Pre-analytical issues, including delayed processing, hemolysis, and inconsistent RNA yields, also introduce bias. Plasma or serum should therefore be processed swiftly using standardized protocols, and saliva should be collected under controlled conditions. Technical variability in RNA extraction, enzymes, and qPCR reagents further underscores the need for harmonized workflows across laboratories.

Recommended approaches

Circulating lncRNAs hold significant promise as non-invasive diagnostic and prognostic biomarkers for oral cancer. For biofluid choice, plasma is preferred for robust systemic detection, whereas saliva is ideal for local tumor monitoring due to its non-invasive nature and proximity to oral lesions.

For detection, a tiered strategy combining high-throughput discovery (RNA-seq/microarrays) with targeted validation (qRT-PCR/ ddPCR) is recommended to ensure both sensitivity and reproducibility.

Standardization is critical: pre-analytical variables such as sample collection time, handling, storage, RNA extraction, and use of spike-in or endogenous controls must be rigorously controlled. ddPCR currently offers the most reliable quantitative readout for low-abundance lncRNAs, while RNA-seq remains indispensable for novel biomarker discovery. Integrating these approaches with multi-center validation studies will establish reproducible protocols, enabling circulating lncRNAs to serve as reliable tools for early detection, disease monitoring, and personalized therapeutic decision-making in oral cancer.

Therapeutic potential of lncRNAs

Beyond their diagnostic and prognostic value, lncRNAs have emerged as promising therapeutic targets and agents in oral squamous cell carcinoma (OSCC). Aberrant lncRNA expression contributes to tumor initiation, progression, metastasis, and therapy resistance, positioning these molecules as attractive candidates for targeted intervention. Therapeutic strategies may involve silencing oncogenic lncRNAs or restoring tumor-suppressive lncRNAs to modulate cancer cell behavior and improve treatment response.

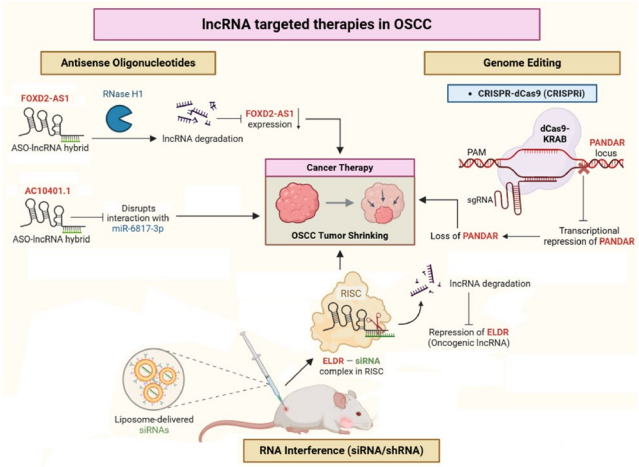

Fig. 2 LncRNA-targeted therapeutic strategies in OSCC. Schematic diagram summarizes emerging therapeutic approaches targeting oncogenic lncRNAs in OSCC. Antisense oligonucleotides (ASOs) induce RNase H1–mediated degradation of lncRNAs such as FOXD2-AS1 or disrupt functional interactions, as illustrated for AC10401.1. RNA interference–based strategies (siRNA/shRNA) delivered via liposomes lead to RISC-mediated degradation of target lncRNAs, exemplified by silencing of ELDR. Genome-editing approaches, such as CRISPR-Cas9 (CRISPRi), repress lncRNA transcription at specific genomic loci, as demonstrated by targeting the PANDAR locus. Collectively, these strategies contribute to inhibition of oncogenic lncRNA activity and potential shrinkage of OSCC tumors

Silencing oncogenic lncRNAs as a therapeutic strategy

Antisense oligonucleotides (ASOs) are short, synthetic DNA or RNA sequences (12–25 nucleotides) that hybridize with target RNA, promoting degradation or blocking its function [63] **(**Fig. 2**)**. Chemical modifications, such as locked nucleic acids (LNA), enhance ASO stability and affinity, improving RNase H-mediated cleavage. Although early applications were limited by poor stability and inefficient delivery, advances in nucleoside analog synthesis, chemical modifications, and nanocarrier systems have significantly improved their clinical potential. Currently, twelve ASO-based drugs have been approved by the FDA and/or EMA [63].

ASOs act through multiple mechanisms—blocking translation initiation, altering splicing, inhibiting miRNA binding, or inducing RNase H-mediated RNA degradation. Delivery methods, including intravenous injection and nanoparticle encapsulation, enhance bioavailability and tissue uptake [63]. Preclinical studies in HNSCC and OSCC have demonstrated that ASO-mediated knockdown of oncogenic lncRNAs, such as FOXD2-AS1, suppresses tumor growth [64]. Targeting AC104041.1 with LNA-modified ASOs disrupts its ceRNA interaction with miR-6817-3p, reactivating Wnt2B suppression and inhibiting tumor proliferation and metastasis [65]. Similarly, silencing lnc-POP1-1 via cholesterol-conjugated ASO reduced cisplatin-resistant tumor growth and Ki-67 expression in vivo [66]. Knockdown of PHACTR2-AS1 suppressed metastasis and prolonged survival in tongue squamous cell carcinoma [67]. Additionally, targeting ZEB1-AS1 using a nucleus-targeting nanoparticle–ASO/siRNA system effectively decreased tumor progression and cisplatin resistance in HNSCC [68]. Collectively, these findings underscore the therapeutic promise of ASO-mediated lncRNA silencing in OSCC.

RNA Interference (RNAi)-Based Silencing RNA interference (RNAi) utilizes small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) to degrade complementary RNA sequences through the RNA-induced silencing complex (RISC) **(**Fig. 2**)** [69]. siRNAs (20–25 bp) are powerful tools for silencing cytoplasmic lncRNAs, although their clinical translation faces challenges related to delivery, tissue specificity, and off-target toxicity. Delivery systems include lipid nanoparticles (LNPs), liposomes, micelles, polymer-based carriers, and exosomes [69]. Currently, rintatolimod (Ampligen) is the only FDA-approved RNAi drug, while multiple RNAi-based anticancer therapies are under clinical evaluation [69].

In OSCC, cholesterol-conjugated siRNA targeting LINC00460 significantly reduced tumor growth and Ki-67 expression in CAL-27 xenografts [70].

Liposome-conjugated siRNAs targeting the oncogenic lncRNAs ELDR and PCAT1, when administered via intratumoral injection, effectively suppressed OSCC xenograft tumor growth without inducing observable toxicity [71, 72]. Both lncRNAs function as oncogenic drivers that promote tumor cell proliferation and growth. Furthermore, shRNA-mediated KCNQ1OT1 knockdown enhanced cisplatin sensitivity and reduced tumor burden in OSCC models [37]. These results confirm that RNAi-based silencing of oncogenic lncRNAs can effectively inhibit tumor progression and overcome chemoresistance.

CRISPR-Based Gene Editing of lncRNAs The CRISPR/Cas system has revolutionized cancer research through its ability to precisely edit genetic and epigenetic elements **(**Fig. 2**)**. Cas9 nucleases, guided by short RNAs, enable targeted DNA cleavage, modification, or deletion, providing a means to permanently inactivate oncogenic lncRNAs or restore tumor-suppressor functions [73]. While over 800 CRISPR-based programs are under development, only a few have progressed beyond preclinical stages due to safety concerns, including off-target effects and immune activation.

In OSCC, CRISPR-dCas9-mediated silencing of PANDAR disrupted its interaction with the splicing factor SRSF7, reduced PIM1 expression, inhibited proliferation, and induced apoptosis, suggesting therapeutic potential [74]. Similarly, CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) platforms allow transcriptional modulation of lncRNA loci with high specificity [75].

Other genome-editing platforms, including TALENs and ZFNs, have shown clinical promise [73]. TALENs employ bacterial FokI nucleases to introduce double-strand breaks, as demonstrated in clinical trials for acute lymphoblastic leukemia using UCART19 (NCT02808442, NCT02746952). ZFNs, similarly fused with FokI, have been applied to introduce HIV-resistant mutations in $CD34^+$ hematopoietic stem cells (NCT02500849). These precision tools, while primarily targeting protein-coding genes, hold strong potential for future lncRNA-directed genome editing and personalized cancer therapy [73].

Exosomal lncRNAs as therapeutic targets and delivery vehicles

Circulating lncRNAs are frequently encapsulated within extracellular vesicles (EVs), particularly exosomes, which can be isolated from various biofluids such as blood, saliva, plasma, and serum [76]. While numerous studies have investigated blood-derived exosomes [32, 76, 77], there remains a significant gap in primary research characterizing lncRNAs contained within salivary exosomes from patients with OSCC.

Cancer cells actively release exosomes that mediate communication with surrounding cancer cells, stromal cells, immune cells, vascular endothelial cells, and cancer-associated fibroblasts (CAFs). This intercellular signaling promotes the formation of a tumor-supportive microenvironment that facilitates immune evasion, invasion, metastasis, and the establishment of pre-metastatic niches in distant organs [78–81]. Among the molecular cargo carried by these vesicles, lncRNAs have emerged as key regulators of tumor-microenvironment interactions, contributing to cancer initiation, progression, and therapeutic resistance.

Exosomal lncRNAs can be internalized by recipient cells through endocytosis, where they modulate gene expression and cellular function. Elevated levels of specific exosomal lncRNAs have been associated with poor chemotherapeutic response, implying their potential role as biomarkers and therapeutic targets in drug-resistant tumors. LncRNA-based therapeutic approaches may involve silencing oncogenic lncRNAs using antisense oligonucleotides or restoring tumor-suppressive lncRNAs via synthetic mimics [81]. Despite these advances, challenges remain regarding targeted delivery, off-target effects, and the safety of lncRNA-based therapeutics. Nonetheless, the ongoing development of small RNA therapeutics in preclinical and clinical settings supports the feasibility of using non-coding RNAs as potent anticancer agents [81].

In OSCC, tumor-derived exosomes enriched in pro-angiogenic lncRNAs promote angiogenesis, facilitating tumor growth and progression [82]. The exosomal lncRNA MALAT1 enhances cancer cell proliferation and metastasis in lung cancer through the transfer of oncogenic signals to recipient cells [79]. Similarly, exosomes carrying H19 from CAFs confer cisplatin resistance to oral cancer cells, whereas inhibition of H19 transfer restores chemosensitivity [37].

Li et al. demonstrated that exosomes derived from podoplanin-positive CAFs ($PDPN^+$ CAFs) are enriched in the lncRNA FTX [83]. In a cohort of 131 OSCC patients, elevated stromal PDPN and FTX expression independently predicted shorter overall and disease-free survival. Mechanistically, exosomal FTX interacts with FEN1, recruits TET2 to demethylate the FEN1 promoter, and activates the FEN1/ACSL4 axis, thereby suppressing ferroptosis and promoting migration and invasion. Similarly, RORA-AS1 is highly expressed in CAFs, CAF-derived exosomes, and OSCC tissues, where it enhances radioresistance by activating the IFITM1/STAT signaling pathway; knockdown of RORA-AS1 mitigates exosome-induced radioresistance in OSCC cells [84]. Moreover, tumor-associated macrophage (TAM)-derived exosomes have been shown to promote epithelial–mesenchymal transition (EMT) in head and neck squamous cell carcinoma (HNSCC), primarily via elevated

MIR4435-2HG expression, which is associated with EMT-promoting molecular pathways [85].

Beyond their pathogenic roles, exosomes also serve as promising natural delivery vehicles for therapeutic RNAs. Their nanoscale size, intrinsic biocompatibility, and capacity to encapsulate RNA molecules make them ideal for targeted gene therapy. Exosomes derived from non-tumorigenic donor cells, such as mesenchymal stem cells, can be engineered to carry small interfering RNAs (siRNAs) or antisense oligonucleotides (ASOs) targeting oncogenic lncRNAs, enabling site-specific gene silencing within tumors [86]. Preclinical models have demonstrated that exosomes loaded with tumor-suppressor microRNAs can effectively inhibit tumor growth, suggesting that exosome-mediated delivery of tumor-suppressor lncRNAs or siRNAs targeting oncogenic lncRNAs may represent a promising therapeutic approach for OSCC [87].

In conclusion, exosomal lncRNAs play multifaceted roles in OSCC progression, influencing angiogenesis, metastasis, therapeutic resistance, and intercellular signaling within the tumor microenvironment. While their diagnostic and prognostic value is increasingly recognized, their therapeutic potential remains largely untapped. Harnessing exosomes as delivery vehicles for RNA-based therapeutics offers an innovative and biologically compatible strategy for targeted cancer therapy.

Chemo- /Radio-sensitization of oral tumors by targeting lncRNA

Therapy resistance represents one of the most formidable challenges in the management of OSCC, often leading to therapeutic failure and poor clinical outcomes. Despite advances in surgery, chemotherapy, and radiotherapy, the recurrence and survival rates of OSCC patients remain unsatisfactory, largely due to intrinsic and acquired mechanisms of resistance. Understanding and overcoming these molecular barriers is therefore essential to improving treatment efficacy and patient prognosis.

Cancer drug resistance is a multifactorial process driven by several molecular and cellular mechanisms. These include enhanced drug efflux mediated by ATP-binding cassette (ABC) transporters such as P-gp, BCRP, and MRP1, which actively remove chemotherapeutic agents from tumor cells; and the suppression of apoptosis via anti-apoptotic proteins such as Survivin that activate the PI3K/AKT signaling pathway [88]. Additional resistance mechanisms involve increased DNA damage repair through upregulation of ERCC1, mutations or alternative activation of therapeutic targets like EGFR and RET, and phenotypic reprogramming through epithelial–mesenchymal transition (EMT) and enrichment of cancer stem cells (CSCs), both of which confer high adaptability and drug tolerance [88].

Since its approval by the U.S. Food and Drug Administration in 1978, cisplatin (CDDP) has remained a cornerstone of chemotherapy for various solid tumors, including head and neck cancers [88]. Cisplatin exerts its cytotoxic effect by forming DNA adducts that block replication and transcription, ultimately inducing cell-cycle arrest in the G phase and triggering apoptosis [88]. However, the development of cisplatin resistance severely limits its clinical utility in HNSCC and OSCC. In recent years, accumulating evidence has highlighted the pivotal role of lncRNAs in mediating cisplatin resistance in oral and head and neck cancers [88].

Several lncRNAs have been implicated in the modulation of chemoresistance in OSCC. HOXA11-AS is markedly upregulated in cisplatin-resistant OSCC cells, where it enhances DNA repair and promotes cell survival under drug stress; silencing HOXA11-AS restores cisplatin sensitivity and induces apoptosis [37]. Similarly, UCA1 contributes to cisplatin resistance by acting as a molecular sponge for miR-184, leading to upregulation of SF1 expression. Knockdown of UCA1 reverses this resistance and resensitizes tumor cells to cisplatin [37]. Another well-characterized oncogenic lncRNA, HOTAIR, promotes autophagy-mediated survival under chemotherapy; its inhibition not only suppresses tumor growth but also enhances cisplatin cytotoxicity [37]. Furthermore, ANRIL expression is induced by midkine secreted from cancer-associated fibroblasts (CAFs), contributing to cisplatin resistance; targeting ANRIL disrupts this tumor–stroma interaction and mitigates resistance [37].

In addition to chemotherapy, radioresistance remains a major obstacle in OSCC treatment. Several lncRNAs have been identified as critical regulators of radiation response. Knockdown of BLACAT1 enhances radiosensitivity by promoting DNA damage and apoptosis in irradiated OSCC cells, while LINC00473 mediates radioresistance through activation of the Wnt/β-catenin signaling pathway; silencing LINC00473 significantly improves radiation efficacy in preclinical models [37]. Similarly, LINC00662 is overexpressed in OSCC and its inhibition alleviates radioresistance by impairing survival signaling [89].

The identification of these lncRNAs provides not only mechanistic insight into therapy resistance but also unveils novel therapeutic targets for sensitization strategies. Combining lncRNA-targeted interventions, such as ASOs or siRNAs with standard chemo- or radiotherapy offers a promising synergistic approach. For instance, co-administration of ASOs targeting HOTAIR or HOXA11-AS alongside cisplatin may prevent tumor cells from activating lncRNA-driven resistance mechanisms, thereby preserving drug efficacy. Similarly, inhibiting radioresistance-associated

Table 2 Overview of ClinicalTrials.gov–listed studies investigating lncRNAs in oral and various other cancers

Name of the lncRNA	Cancer model	Study type	Number of Subjects	Phase	Diagnostic/ Therapeutic	Status	Outcome	Ref ID
MALAT1	**Oral Cancer**	Observational (Case-control)	40	-	Diagnostic and prognostic	Completed	Not published	NCT05708209
EGFR-AS1		Interventional	24	Phase 2	Therapeutic	Ongoing (2027-05)	Not published	NCT04946968
DQ786243		Observational	45	-	Diagnostic	Completed	Not published	NCT05730855
H19	Acute Lymphoblastic Leukemia	Observational (Case-control)	96	-	Diagnostic and Prognosis	Ongoing	Not published	NCT05943093
	Hepatocellular carcinoma	Observational (Case-control)	101	-	Diagnostic and Prognosis	Completed	Not published	NCT04767750
HOTAIR	Thyroid cancer	Observational (Case-control)	90	-	Diagnostic and Prognosis	Completed	Not published	NCT03469544
CCAT1	Colorectal Cancer	Observational (Case-Crossover)	100	-	Diagnostic and Therapeutic	Completed	Not published	NCT04269746
SNHG3		Observational (Case-Control)	96	-	Diagnostic and Prognosis	Completed	Not published	NCT06432413
LUNAR1		Observational (Case-Control)	96	-	Diagnostic and Prognosis	Completed	Not published	NCT06432413
NNT-AS1		Observational (Case-Control)	88	-	Diagnostic and Prognosis	Completed	Not published	NCT06531902
HOTTIP		Observational (Case-Control)	60	-	Diagnostic and Prognosis	Completed	Not published	NCT04729855
GC1	Gastric cancer	Observational(Cohort)	700	-	Diagnostic and Therapeutic	Completed	Not published	**NCT05647941**
Exosomal lncRNA-GC1		Observational(Cohort)	700	-	Diagnostic and Therapeutic	Completed	Not published	NCT05397548
Exosomal lncRNA-GC1		Observational	80	-	Diagnostic and Therapeutic	Completed	Not published	NCT05334849
THRIL		Observational	50	-	Diagnostic and Therapeutic	Completed	Not published	NCT03057171
PACER		Observational	50	-	Diagnostic and Therapeutic	Completed	Not published	NCT03057172
MFI2-AS1	Kidney Cancer	Observational	260	-	Diagnostic	Completed	Not published	NCT04946266
ELNAT1	Bladder Cancer	Observational	74	-	Diagnostic and Prognosis	Completed	Not published	NCT05270174
Serum exosomal lncRNA	Lung Cancer	Observational	1000	-	Diagnostic	Completed	Not published	NCT03830619
miRNA and lncRNA	High grade serous ovarian cancer	Observational	160	-	Diagnostic	Completed	Not published	NCT03738319
lncRNA	Prostate Cancer	Interventional	80	Not Applicable	Prognosis and therapeutic	Completed	Not published	NCT05141383

lncRNAs prior to radiotherapy could prime tumor cells for enhanced DNA damage and apoptotic response.

In conclusion, targeting lncRNAs represents a novel and mechanistically grounded approach to overcome chemo- and radioresistance in OSCC. By disrupting the lncRNA-mediated signaling networks that enable tumor survival under therapeutic stress, such strategies hold great potential to restore drug sensitivity, enhance treatment response, and ultimately improve clinical outcomes in oral cancer patients.

Integration into clinical practice

As discussed above, circulating lncRNAs, due to their high stability, disease specificity, and non-invasive accessibility, hold strong potential as diagnostic, prognostic, and therapeutic biomarkers in OSCC. Standardized sample processing and analytical methods are essential for reproducibility and clinical translation. Plasma or salivary lncRNA panels enhance early detection compared to conventional markers,

while salivary assays enable non-invasive screening and monitoring. Profiling resistance-associated lncRNAs can predict cisplatin or chemoradiation response and guide personalized therapy. Moreover, ddPCR-based lncRNA quantification facilitates sensitive surveillance of treatment response and minimal residual disease. Clinical studies across various malignancies are now translating these molecular insights into potential clinical applications, ranging from non-invasive cancer diagnostics to companion biomarkers and targeted therapeutic strategies. An overview of the clinical trials investigating lncRNAs in oral and other cancers, as registered on ClinicalTrials.gov, is summarized in Table 2.

In OSCC, the lncRNA MALAT1 has been the subject of a completed observational clinical trial (ClinicalTrials.gov Identifier: NCT05708209) involving 40 participants aged 20–65 years. The study aimed to evaluate circulating MALAT1 as a diagnostic biomarker as well as assessment of the salivary expression level of miRNA 124 which is targeted by MALAT1 in OSCC. MALAT1 is known to influence cancer cell proliferation, migration, and therapy resistance, and its elevated expression has been correlated with poor prognosis and enhanced metastatic potential in oral cancers. Low EGFR-AS1 lncRNA expression has recently been identified as a potential companion diagnostic biomarker in oral cancer, and a Phase II clinical study (ClinicalTrials.gov Identifier: NCT04946968) is currently ongoing to evaluate the therapeutic efficacy of an EGFR-associated drug in patients with advanced oral cancer characterized by low EGFR-AS1 expression. The outcome of this study may establish EGFR-AS1 as both a diagnostic and therapeutic biomarker, underscoring its dual clinical significance in oral cancer management. Another observational study involving 45 enrolled participants was conducted to evaluate the salivary expression of lncRNA DQ786243 as a potential diagnostic marker for oral potentially malignant lesions compared to normal controls, and to assess its correlation with the salivary expression of miRNA-146a (NCT05730855). However, the results have not yet been posted.

Beyond OSCC, numerous clinical trials have explored the clinical applicability of lncRNAs in other cancer types, offering valuable translational insights for oral cancer research. For example, H19, one of the most studied oncogenic lncRNAs, is under clinical evaluation in leukemia (NCT05943093) and HCC (NCT04767750) for its diagnostic and prognostic value. Similarly, HOTAIR, a well-known metastasis-promoting lncRNA, has been clinically investigated as a diagnostic marker in thyroid cancer (NCT03469544), reflecting its consistent association with tumor aggressiveness and poor outcomes across cancer types. Studies on circulating lncRNAs in ovarian cancer (NCT03738319) and prostate cancer (NCT05141383) demonstrate their potential as non-invasive "liquid biopsy" biomarkers capable of monitoring disease progression and therapeutic response.

In colorectal cancer, several lncRNAs, including CCAT1 (NCT04269746), SNHG3 and LUNAR1 (NCT06432413), NNT-AS1 (NCT06531902), and HOTTIP (NCT04729855), are being explored for their diagnostic potential, highlighting the expanding role of lncRNAs in early detection and patient stratification. Similarly, GC1, THRIL, and PACER have been evaluated in gastric cancer (NCT05647941, NCT05397548, NCT05334849, NCT03057171) for diagnostic and therapeutic applications, while MFI2-AS1 in kidney cancer (NCT04946266) and ELNAT1 in bladder cancer (NCT05270174) are being assessed for their roles in tumor detection. In lung cancer, serum exosomal lncRNAs (NCT03830619) are being tested for diagnostic and therapeutic relevance, providing mechanistic insights applicable to oral cancer due to shared molecular pathways involving EGFR signaling. Drawing from extensive lncRNA research in other malignancies, it is anticipated that incorporating lncRNA profiling into clinical practice will revolutionize oral cancer management by enabling earlier diagnosis, more accurate risk assessment, and personalized therapeutic interventions.

Collectively, these studies emphasize the translational potential of lncRNAs as robust, stable, and disease-specific molecular indicators that can be detected in both tissue and biofluids. Their integration into clinical workflows could significantly improve early detection, patient stratification, and treatment personalization.

Future perspectives

Circulating lncRNAs hold substantial promise as transformative tools for the diagnosis, prognosis, and therapy of OSCC. Future research should focus on elucidating the mechanisms underlying lncRNA secretion, stabilization, and transport via extracellular vesicles, apoptotic bodies, and RNA-binding proteins, which will help distinguish tumor-derived circulating lncRNAs from background noise and enhance biomarker specificity.

Standardization of pre-analytical and analytical workflows, including biofluid selection (plasma vs. saliva), RNA extraction, normalization strategies, and sensitive quantification platforms such as ddPCR, is critical to achieve reproducibility and cross-study comparability. Integrating multi-omics approaches, including transcriptomics, proteomics, and metabolomics, with AI-based predictive modeling will facilitate robust identification of clinically actionable lncRNA signatures. Tools like IntaRNA, CopraRNA, catRAPID, RPI-seq, CentroidAlifold, RNAalifold, RNAfold,

and CentroidFold can enhance prediction of RNA-RNA and RNA-protein interactions, conserved motifs, and secondary structures, improving annotation of circulating lncRNAs [90, 91].

From a translational perspective, validated lncRNA-based liquid biopsy assays could revolutionize early OSCC detection and real-time treatment monitoring. Saliva-based diagnostics, being non-invasive and patient-friendly, are promising for large-scale screening, whereas plasma-derived multi-lncRNA panels may support tumor staging, recurrence prediction, and therapy response assessment. Combining circulating lncRNAs, miRNAs, ctDNA and/ or protein biomarkers with imaging characteristics could further enhance diagnostic and prognostic accuracy [92].

Therapeutically, advances in ASOs, RNA interference, and CRISPR-based technologies hold potential for targeting oncogenic lncRNAs or restoring tumor-suppressive ones. Exosome-mediated lncRNA delivery represents an innovative avenue for precision drug delivery and gene modulation. Ongoing or proposed clinical trials evaluating lncRNAs will provide crucial insights into the diagnostic and therapeutic viability of lncRNA-based interventions.

Developing robust bioinformatics tools and cost-effective platforms is essential to overcome challenges such as variability in lncRNA expression due to tumor stage or patient heterogeneity, and the lack of standardized protocols. Circulating lncRNA panels tailored for high-risk populations, particularly tobacco users, could enable early detection, risk stratification, and non-invasive monitoring of treatment responses, marking a significant step toward precision oncology in resource-limited settings.

Conclusion

Circulating lncRNAs have emerged as pivotal regulators and potential clinical tools in OSCC. By bridging diagnostics and therapeutics, they embody a new era of molecular oncology characterized by non-invasive precision and dynamic disease monitoring. Their stability in biofluids, tumor-specific expression, and functional involvement in tumorigenesis, metastasis, and therapy resistance highlight their multifaceted clinical potential.

This review successfully consolidates and critically analyzes the most recent advances in circulating lncRNA research in OSCC, offering an integrated perspective on their biological roles, detection technologies, and translational opportunities. By mapping out both the promise and the persisting challenges, it provides a valuable reference point for researchers and clinicians seeking to transform these molecular insights into tangible clinical applications. The comprehensive synthesis of diagnostic, prognostic, and therapeutic dimensions underscores the importance of circulating lncRNAs as next-generation biomarkers for personalized oral cancer management.

The success of circulating lncRNAs in clinical practice will depend on rigorous validation, methodological standardization, and multi-omics integration. Composite biomarker panels combining lncRNAs with miRNAs, ctDNA, or proteins may enhance diagnostic accuracy and enable individualized treatment monitoring. With concerted global efforts and translational research, circulating lncRNAs hold the potential to revolutionize OSCC management, enabling earlier detection, targeted therapy selection, and real-time disease surveillance.

Ultimately, this review underscores the significance of continued interdisciplinary collaboration in advancing lncRNA research, positioning these silent molecular players as central to the future of precision oncology in oral cancer.

Acknowledgements We express our gratitude to the Director, Dr. D. Y. Patil Biotechnology and Bioinformatics Institute, Dr. D. Y. Patil Vidyapeeth, Tathawade, Pune, India and to the Director, Chittaranjan National Cancer Institute, Kolkata, India for invaluable assistance and motivation.

Author contributions Study concept and design (S.D., and S.S), initial drafting (R.B., C.B., M.S.K., S.D., and S.S), critical revision and editing (R.B., C.B., M.S.K., S.D., and S.S). All authors read and approved the final manuscript.

Funding This work was supported by the Ramalingaswami Re-entry Fellowship from the Department of Biotechnology [BT/RLF/Re-entry/47/2021], Government of India, Prime Minister's Early Career Research Grant (PM-ECRG), Anusandhan National Research Foundation (ANRF) [ANRF/ECRG/2024/000735/LS], Department of Science & Technology, India, awarded to S. Sur. This work was also supported by Indian Council of Medical Research, Government of India (File No. 5/3/8/73/2020-ITR, dated April 1, 2024) and DSTBT-West Bengal (Memo No. 890(Sanc)/STBT-11012(12)/3/2024ST SEC dated 20/11/2024) Extramural Project fundings of S. Dutta.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

1. Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A et al (2011) Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev 25(18):1915–1927
2. Sur S, Ray RB (2022) Emerging role of lncRNA ELDR in development and cancer. FEBS J 289(11):3011–3023
3. Statello L, Guo CJ, Chen LL, Huarte M (2021) Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol 22(2):96–118

4. Fabbri M, Girnita L, Varani G, Calin GA (2019) Decrypting noncoding RNA interactions, structures, and functional networks. Genome Res 29(9):1377–1388
5. Jagadeesan D, Sathasivam KV, Fuloria NK, Balakrishnan V, Khor GH, Ravichandran M et al (2024) Comprehensive insights into oral squamous cell carcinoma: Diagnosis, pathogenesis, and therapeutic advances. Pathol Res Pract 261:155489
6. Sur S, Davray D, Basu S, Kheur S, Pal JK, Nagar S et al (2024) Novel insights on oral squamous cell carcinoma management using long non-coding RNAs. Oncol Res 32(10):1589–1612
7. Tranby EP, Heaton LJ, Tomar SL, Kelly AL, Fager GL, Backley M et al (2022) Oral Cancer Prevalence, Mortality, and Costs in Medicaid and Commercial Insurance Claims Data. Cancer Epidemiol Biomarkers Prev 31(9):1849–1857
8. Rinn JL, Chang HY (2012) Genome regulation by long noncoding RNAs. Annu Rev Biochem 81:145–166
9. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A, Cancer statistics (2025) CA: a cancer journal for clinicians. 2025 Jan-Feb 75(1):10–45
10. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR (2020) Head and neck squamous cell carcinoma. Nat reviews Disease primers 6(1):92
11. de Gonzalo-Calvo D, Sopic M, Devaux Y (2022) CA EU-CCA. Methodological considerations for circulating long noncoding RNA quantification. Trends Mol Med 28(8):616–618
12. Ribeiro IP, Barroso L, Marques F, Melo JB, Carreira IM (2016) Early detection and personalized treatment in oral cancer: the impact of omics approaches. Mol Cytogenet 9:85
13. Gupta S, Tomar A, Singh R (2025) Personalized medicine in oral cancer. Crit Rev Oncol/Hematol 209:104670
14. Prakash N, Pradeep GL (2022) Circulating biomarkers in oral cancer: Unravelling the mystery. J Oral Maxillofac Pathol 26(3):300–306
15. Ma L, Guo H, Zhao Y, Liu Z, Wang C, Bu J et al (2024) Liquid biopsy in cancer current: status, challenges and future prospects. Signal Transduct Target therapy 9(1):336
16. Kabzinski J, Kucharska-Lusina A, Majsterek I (2023) RNA-Based Liquid Biopsy in Head and Neck Cancer. Cells 12(14):1916
17. Le P, Romano G, Nana-Sinkam P, Acunzo M (2021) Non-Coding RNAs in Cancer Diagnosis and Therapy: Focus on Lung Cancer. Cancers 13(6):1372
18. Xi X, Li T, Huang Y, Sun J, Zhu Y, Yang Y et al (2017) RNA Biomarkers: Frontier of Precision Medicine for Cancer. Non-coding RNA 3(1):9
19. Dey S, Biswas B, Manoj Appadan A, Shah J, Pal JK, Basu S et al (2023) Non-Coding RNAs in Oral Cancer: Emerging Roles and Clinical Applications. Cancers 15(15):3752
20. Kolat D, Hammouz R, Bednarek AK, Pluciennik E (2019) Exosomes as carriers transporting long non–coding RNAs: Molecular characteristics and their function in cancer (Review). Mol Med Rep 20(2):851–862
21. Zhang W, Wang Q, Yang Y, Zhou S, Zhang P, Feng T (2021) The role of exosomal lncRNAs in cancer biology and clinical management. Exp Mol Med 53(11):1669–1673
22. Li S, Shi Z, Fu S, Li Q, Li B, Sang L et al (2021) Exosomal-mediated transfer of APCDD1L-AS1 induces 5-fluorouracil resistance in oral squamous cell carcinoma via miR-1224-5p/nuclear receptor binding SET domain protein 2 (NSD2) axis. Bioengineered 12(1):7188–7204
23. Li Z, Qin X, Bian W, Li Y, Shan B, Yao Z et al (2019) Exosomal lncRNA ZFAS1 regulates esophageal squamous cell carcinoma cell proliferation, invasion, migration and apoptosis via microRNA-124/STAT3 axis. J experimental Clin cancer research: CR 38(1):477
24. Xu J, Xiao Y, Liu B, Pan S, Liu Q, Shan Y et al (2020) Exosomal MALAT1 sponges miR-26a/26b to promote the invasion and metastasis of colorectal cancer via FUT4 enhanced fucosylation and PI3K/Akt pathway. J experimental Clin cancer research: CR 39(1):54
25. Wang JJ, Wang X, Song YX, Zhao JH, Sun JX, Shi JX et al (2019) Circulating Noncoding RNAs Have a Promising Future Acting as Novel Biomarkers for Colorectal Cancer. Dis Markers 2019:2587109
26. Trajkovic K, Hsu C, Chiantia S, Rajendran L, Wenzel D, Wieland F et al (2008) Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science 319(5867):1244–1247
27. Battistelli M, Falcieri E (2020) Apoptotic Bodies: Particular Extracellular Vesicles Involved in Intercellular Communication. Biology 9(1):21
28. Yu L, Zhu G, Zhang Z, Yu Y, Zeng L, Xu Z et al (2023) Apoptotic bodies: bioactive treasure left behind by the dying cells with robust diagnostic and therapeutic application potentials. J Nanobiotechnol 21(1):218
29. Papoutsoglou P, Morillon A (2024) Extracellular Vesicle lncRNAs as Key Biomolecules for Cell-to-Cell Communication and Circulating Cancer Biomarkers. Non-coding RNA 10(6):54
30. Gurunathan S, Kang MH, Qasim M, Khan K, Kim JH, Biogenesis (2021) Membrane Trafficking, Functions, and Next Generation Nanotherapeutics Medicine of Extracellular Vesicles. Int J Nanomed 16:3357–3383
31. Chen C, Luo Y, He W, Zhao Y, Kong Y, Liu H et al (2020) Exosomal long noncoding RNA LNMAT2 promotes lymphatic metastasis in bladder cancer. J Clin Investig 130(1):404–421
32. Badowski C, He B, Garmire LX (2022) Blood-derived lncRNAs as biomarkers for cancer diagnosis: the Good, the Bad and the Beauty. NPJ precision Oncol 6(1):40
33. Suri S, Boora GS, Kaur R, Chauhan A, Ghoshal S, Pal A (2024) Recent advances in minimally invasive biomarkers of OSCC: from generalized to personalized approach. Front oral health 5:1426507
34. Umapathy VR, Natarajan PM, Swamikannu B (2024) Molecular and Therapeutic Roles of Non-Coding RNAs in Oral Cancer-A Review. Molecules 29(10):2402
35. Dey Ghosh R, Guha Majumder S (2022) Circulating Long Non-Coding RNAs Could Be the Potential Prognostic Biomarker for Liquid Biopsy for the Clinical Management of Oral Squamous Cell Carcinoma. Cancers 14(22):5590
36. Ikram F, Mathur P, Dubey P, Verma S, Agarwal S, Tripathi S (2025) Diagnostic value of circulating lncRNAs HOTAIR, ANRIL, and MEG3 in oral squamous cell carcinoma and their correlation with clinicopathological features. J liquid biopsy 9:100315
37. Tang J, Fang X, Chen J, Zhang H, Tang Z (2021) Long Non-Coding RNA (lncRNA) in Oral Squamous Cell Carcinoma: Biological Function and Clinical Application. Cancers 13(23):5944
38. Wu Y, Zhang L, Zhang L, Wang Y, Li H, Ren X et al (2015) Long non-coding RNA HOTAIR promotes tumor cell invasion and metastasis by recruiting EZH2 and repressing E-cadherin in oral squamous cell carcinoma. Int J Oncol 46(6):2586–2594
39. Liu L, Ning SB, Fu S, Mao Y, Xiao M, Guo B (2019) Effects of lncRNA ANRIL on proliferation and apoptosis of oral squamous cell carcinoma cells by regulating TGF-beta/Smad pathway. Eur Rev Med Pharmacol Sci 23(14):6194–6201
40. An G, M R, Govindan R, Aravind A, Sa I, Pavshere R et al (2025) Expression of Long Non-coding RNA in Oral Squamous Cell Carcinoma and Its Implication in Response to Radiation Therapy. Cureus 17(5):e84839
41. Fang Z, Zhao J, Xie W, Sun Q, Wang H, Qiao B (2017) LncRNA UCA1 promotes proliferation and cisplatin resistance of oral squamous cell carcinoma by sunppressing miR-184 expression. Cancer Med 6(12):2897–2908

42. Tarrad NAF, Hassan S, Shaker OG, AbdelKawy M (2023) Salivary LINC00657 and miRNA-106a as diagnostic biomarkers for oral squamous cell carcinoma, an observational diagnostic study. BMC Oral Health 23(1):994
43. Shao T, Huang J, Zheng Z, Wu Q, Liu T, Lv X (2018) SCCA, TSGF, and the Long Non-Coding RNA AC007271.3 are Effective Biomarkers for Diagnosing Oral Squamous Cell Carcinoma. Cell Physiol Biochem 47(1):26–38
44. Zheng ZN, Huang GZ, Wu QQ, Ye HY, Zeng WS, Lv XZ (2020) NF-kappaB-mediated lncRNA AC007271.3 promotes carcinogenesis of oral squamous cell carcinoma by regulating miR-125b-2-3p/Slug. Cell Death Dis 11(12):1055
45. Le F, Ou Y, Luo P, Zhong X (2020) LncRNA NCK1-AS1 in plasma distinguishes oral ulcer from early-stage oral squamous cell carcinoma. J Biol Res 27:16
46. Jia H, Wang X, Sun Z (2021) Screening and validation of plasma long non-coding RNAs as biomarkers for the early diagnosis and staging of oral squamous cell carcinoma. Oncol Lett 21(2):172
47. He K, Zhu ZB, Shu R, Hong A (2020) LncRNA NEAT1 mediates progression of oral squamous cell carcinoma via VEGF-A and Notch signaling pathway. World J Surg Oncol 18(1):261
48. Zhang P, Liu Y, Li C, Zhang L, Liu Q, Jiang T (2019) LncRNA PAPAS promotes oral squamous cell carcinoma by upregulating transforming growth factor-beta1. J Cell Biochem 120(9):16120–16127
49. Li GH, Ma ZH, Wang X (2019) Long non-coding RNA CCAT1 is a prognostic biomarker for the progression of oral squamous cell carcinoma via miR-181a-mediated Wnt/beta-catenin signaling pathway. Cell Cycle 18(21):2902–2913
50. Xu Y, Jiang E, Shao Z, Shang Z (2020) Long Noncoding RNAs in the Metastasis of Oral Squamous Cell Carcinoma. Front Oncol 10:616717
51. Dong Y, Wu W (2019) Downregulation of lncRNA CASC2 promotes the postoperative local recurrence of early oral squamous cell carcinoma. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino. -Laryngological Soc 276(2):605–610
52. Shieh TM, Liu CJ, Hsia SM, Ningrum V, Liao CC, Lan WC et al (2021) Lack of Salivary Long Non-Coding RNA XIST Expression Is Associated with Increased Risk of Oral Squamous Cell Carcinoma: A Cross-Sectional Study. J Clin Med 10(19):4622
53. Wu K, Wu W, Wu M, Liu W (2023) Long non-coding RNA XIST promotes the malignant features of oral squamous cell carcinoma (OSCC) cells through regulating miR-133a-5p/VEGFB. Histol Histopathol 38(1):113–126
54. Rajendran P, Sekar R, Zahra HA, Jayaraman S, Rajagopal P, Abdallah BM et al (2023) Salivaomics to decode non-coding RNAs in oral cancer. A narrative review. Non-coding RNA Res 8(3):376–384
55. Hu Y, Xu M, Liu M, Peng H (2025) Comparison of saliva and blood derived cell free RNAs for detecting oral squamous cell carcinoma. Sci Rep 15(1):4645
56. Tang H, Wu Z, Zhang J, Su B (2013) Salivary lncRNA as a potential marker for oral squamous cell carcinoma diagnosis. Mol Med Rep 7(3):761–766
57. Cabus L, Lagarde J, Curado J, Lizano E, Perez-Boza J (2022) Current challenges and best practices for cell-free long RNA biomarker discovery. Biomark Res 10(1):62
58. Fayda M, Isin M, Tambas M, Guveli M, Meral R, Altun M et al (2016) Do circulating long non-coding RNAs (lncRNAs) (LincRNA-p21, GAS 5, HOTAIR) predict the treatment response in patients with head and neck cancer treated with chemoradiotherapy? Tumour biology: J Int Soc Oncodevelopmental Biology Med 37(3):3969–3978
59. Das S, Basak S, Sarkar S (2025) Decoding Salivary ncRNAomes as Novel Biomarkers for Oral Cancer Detection and Prognosis. Non-coding RNA 11(2):28
60. Qi P, Zhou XY, Du X (2016) Circulating long non-coding RNAs in cancer: current status and future perspectives. Mol Cancer 15(1):39
61. Ota Y, Yan IK, Patel T (2021) Quantitation of Long Noncoding RNA Using Digital PCR. Methods Mol Biol 2348:113–121
62. Iempridee T, Wiwithaphon S, Piboonprai K, Pratedrat P, Khumkhrong P, Japrung D et al (2018) Identification of reference genes for circulating long noncoding RNA analysis in serum of cervical cancer patients. FEBS open bio 8(11):1844–1854
63. Cakan E, Lara OD, Szymanowska A, Bayraktar E, Chavez-Reyes A, Lopez-Berestein G et al (2024) Therapeutic Antisense Oligonucleotides in Oncology: From Bench to Bedside. Cancers 16(17):2940
64. Liu Z, Zhou W, Lin C, Wang X, Zhang X, Zhang Y et al (2020) Dysregulation of FOXD2-AS1 promotes cell proliferation and migration and predicts poor prognosis in oral squamous cell carcinoma: a study based on TCGA data. Aging 13(2):2379–2396
65. Li M, Ding X, Zhang Y, Li X, Zhou H, Yang L et al (2020) Antisense oligonucleotides targeting lncRNA AC104041.1 induces antitumor activity through Wnt2B/beta-catenin pathway in head and neck squamous cell carcinomas. Cell Death Dis 11(8):672
66. Jiang Y, Guo H, Tong T, Xie F, Qin X, Wang X et al (2022) lncRNA lnc-POP1-1 upregulated by VN1R5 promotes cisplatin resistance in head and neck squamous cell carcinoma through interaction with MCM5. Mol therapy: J Am Soc Gene Therapy 30(1):448–467
67. Yuan F, Miao Z, Chen W, Wu F, Wei C, Yong J et al (2020) Long non-coding RNA PHACTR2-AS1 promotes tongue squamous cell carcinoma metastasis by regulating Snail. J BioChem 168(6):651–657
68. Yang H, Zhang Y, Tan Z, Liu Z, Yan Y, Li Q et al (2024) Nucleus-targeted Silencer nanoplatform regulating ZEB1-AS1 in head and neck squamous cell carcinoma therapy. Discover nano 19(1):192
69. Tian Z, Liang G, Cui K, Liang Y, Wang Q, Lv S et al (2021) Insight Into the Prospects for RNAi Therapy of Cancer. Front Pharmacol 12:644718
70. Jiang Y, Cao W, Wu K, Qin X, Wang X, Li Y et al (2019) LncRNA LINC00460 promotes EMT in head and neck squamous cell carcinoma by facilitating peroxiredoxin-1 into the nucleus. J experimental Clin cancer research: CR 38(1):365
71. Sur S, Nakanishi H, Steele R, Zhang D, Varvares MA, Ray RB (2020) Long non-coding RNA ELDR enhances oral cancer growth by promoting ILF3-cyclin E1 signaling. EMBO Rep 21(12):e51042
72. Sur S, Nakanishi H, Steele R, Ray RB (2019) Depletion of PCAT-1 in head and neck cancer cells inhibits tumor growth and induces apoptosis by modulating c-Myc-AKT1-p38 MAPK signalling pathways. BMC Cancer 19(1):354
73. Chehelgerdi M, Chehelgerdi M, Khorramian-Ghahfarokhi M, Shafieizadeh M, Mahmoudi E, Eskandari F et al (2024) Comprehensive review of CRISPR-based gene editing: mechanisms, challenges, and applications in cancer therapy. Mol Cancer 23(1):9
74. Jia T, Wang F, Qiao B, Ren Y, Xing L, Zhang H et al (2021) Knockdown of LncRNA PANDAR by CRISPR-dCas9 Decreases Proliferation and Increases Apoptosis in Oral Squamous Cell Carcinoma. Front Mol Biosci 8:653787
75. Morelli E, Gulla A, Amodio N, Taiana E, Neri A, Fulciniti M et al (2021) CRISPR Interference (CRISPRi) and CRISPR Activation (CRISPRa) to Explore the Oncogenic lncRNA Network. Methods Mol Biol 2348:189–204

76. Tellez-Gabriel M, Heymann D (2019) Exosomal lncRNAs: the newest promising liquid biopsy. Cancer drug Resist 2(4):1002–1017
77. Wang X, Tian L, Lu J, Ng IO (2022) Exosomes and cancer - Diagnostic and prognostic biomarkers and therapeutic vehicle. Oncogenesis 11(1):54
78. Pathania AS, Prathipati P, Pandey MK, Byrareddy SN, Coulter DW, Gupta SC et al (2022) The emerging role of non-coding RNAs in the epigenetic regulation of pediatric cancers. Sem Cancer Biol 83:227–241
79. Liu QW, He Y, Xu WW (2022) Molecular functions and therapeutic applications of exosomal noncoding RNAs in cancer. Exp Mol Med 54(3):216–225
80. Liu H, Huang Y, Huang M, Huang Z, Wang Q, Qing L et al (2022) Current Status, Opportunities, and Challenges of Exosomes in Oral Cancer Diagnosis and Treatment. Int J Nanomed 17:2679–2705
81. Pathania AS, Challagundla KB (2021) Exosomal Long Non-coding RNAs: Emerging Players in the Tumor Microenvironment. Mol therapy Nucleic acids 23:1371–1383
82. Sun Z, Yang S, Zhou Q, Wang G, Song J, Li Z et al (2018) Emerging role of exosome-derived long non-coding RNAs in tumor microenvironment. Mol Cancer 17(1):82
83. Li Y, Ma Z, Li W, Xu X, Shen P, Zhang SE et al (2023) PDPN(+) CAFs facilitate the motility of OSCC cells by inhibiting ferroptosis via transferring exosomal lncRNA FTX. Cell Death Dis 14(11):759
84. Li L, Ye P, Li G, Xie T, Zha C, Wang Z et al (2025) Carcinoma-associated fibroblast-derived exosomes lncRNA RORA-AS1 facilitates radiotherapy resistance of oral squamous cell carcinoma through the IFITM1/STAT axis. Biochim et Biophys acta Mol cell Res 1872(7):120015
85. Liu J, Mu J, Liang Z, Zhang Y, Hu T, Wu F et al (2025) TAM-Derived Exosomes Promote EMT by Upregulating lncRNA MIR4435-2HG in Head and Neck Cancer. Oral Dis 31(4):1154–1164
86. Chen H, Yao H, Chi J, Li C, Liu Y, Yang J et al (2023) Engineered exosomes as drug and RNA co-delivery system: new hope for enhanced therapeutics? Front Bioeng Biotechnol 11:1254356
87. Ubanako P, Mirza S, Ruff P, Penny C (2024) Exosome-mediated delivery of siRNA molecules in cancer therapy: triumphs and challenges. Front Mol Biosci 11:1447953
88. Dai F, Dai L, Zheng X, Guo Y, Zhang Y, Niu M et al (2020) Non-coding RNAs in drug resistance of head and neck cancers: A review, vol 127. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, p 110231
89. Chen Y, Bao C, Zhang X, Lin X, Fu Y (2020) Knockdown of LINC00662 represses AK4 and attenuates radioresistance of oral squamous cell carcinoma. Cancer Cell Int 20:244
90. Sato K, Hamada M, Asai K, Mituyama T (2009) CENTROIDFOLD: a web server for RNA secondary structure prediction. Nucleic Acids Res 37:W277–W280
91. Iwakiri J, Hamada M, Asai K (2016) Bioinformatics tools for lncRNA research. Biochim Biophys Acta 1859(1):23–30
92. Mallela VR, Rajtmajerova M, Trailin A, Liska V, Hemminki K, Ambrozkiewicz F (2024) miRNA and lncRNA as potential tissue biomarkers in hepatocellular carcinoma. Non-coding RNA Res 9(1):24–32

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.