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(Review)

The crucial role of long non-coding RNAs in the pathogenesis, therapeutic response, and clinical implications of esophageal cancer

Ahmed A. El-Husseiny [1,2*], Nada S. Ali [1], Morkoss M. Fakhry [1]

[1] *Department of Biochemistry, Faculty of Pharmacy, Egyptian Russian University, Badr City 11829, Cairo, Egypt.*

[2] *Biochemistry and Molecular Biology Department, Faculty of Pharmacy (Boys), Al-Azhar University, Nasr City 11231, Cairo, Egypt*

[*] **Corresponding author:** Assoc. Prof. Ahmed A. El-Husseiny

Department of Biochemistry, Faculty of Pharmacy, Egyptian Russian University, Badr City 11829, Cairo, Egypt, Email: ahmed-elhusseiny@eru.edu.eg ,

ORCID: https://orcid.org/0000-0003-0153-6555 Tel: +201020002796

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ABSTRACT

Esophageal cancer (EC) is the 2nd fatal gastrointestinal tract malignancy and the sixth most predominant driver of cancer-associated mortality worldwide. Interestingly, long non-coding RNAs (lncRNAs) have a sequence of more than 200 base pairs and are regarded as one of the epigenetic elements. LncRNAs have been demonstrated to influence EC features comprising initiation, development, angiogenesis, invasion, and metastasis. Notably, lncRNAs could modulate the expression of several genes and chromatin architectures which are implicated in EC pathogenesis. Besides, numerous lncRNAs have a crucial role in the chemotherapeutic response of EC cells. Furthermore, lncRNAs are thought to be a promising biomarker in EC whose expression patterns can distinguish between EC subtypes and stages as well as predict cancer aggressiveness. Thus, the

current review emphasizes the latest updates on the modulatory functions of lncRNAs in EC pathogenesis, their significance to the EC cells' therapeutic response, and their clinical efficacy as prognostic and diagnostic biomarkers.

Keywords: Esophageal cancer; LncRNAs; Chemotherapeutic resistance; Diagnosis; Prognosis

List of abbreviations:
5-FU: 5-fluorouracil, ABC: ATP-binding cassette, ABCG2: ATP-binding cassette G2, AKT: Protein kinase B, AUC: Area under the curve, Bcl2: B-cell lymphoma 2, BPTF: Bromodomain PHD finger transcription factor, BUBR1: Bub1-related kinase, CCAT2: Colon cancer-associated transcript 2, CDH3: Cadherin 3, CRT: Chemoradiotherapy, CSC: Cancer stem cell, CT: Computed tomography, DFS: Disease-free survival, DNMT: DNA methyltransferase, DPYD: Dihydropyrimidine dehydrogenase, EAC: Esophageal adenocarcinoma, EC: Esophageal cancer, EGFR: Epidermal growth factor receptor, EMT: Epithelial-mesenchymal transition, ERK1/2: Extracellular signal-regulated kinase 1/2, ESCC: Esophageal squamous cell carcinoma, EUS: Endoscopic ultrasonography, EZH2: Enhancer of zeste homolog 2, FAK: Focal adhesion kinase, FDG/PET: Fluoro-deoxy glucose positron emission tomography, GSTP1: Glutathione S-transferase P1, H3K27me3: Tri-methylation of lysine 27 on histone H3 protein, IGF2BP2: Insulin-like growth factor 2 mRNA-binding protein 2, IL-6: Interleukin-6, KLF2: Krüppel-like factor 2, KLK4: Kallikrein related peptidase 4, LASP1: LIM and SH3 domain protein 1, LncRNAs: Long non-coding RNAs, LRP6: LDL receptor-related protein-6, MALAT1: Metastasis-associated lung adenocarcinoma transcript 1, miR: microRNA, MMP3/10: Matrix metalloproteinase 3/10, MRPs: Multidrug resistance proteins, MTDH: Metadherin, MTHFR: Methylenetetrahydrofolate Reductase, mTOR: Mammalian target of rapamycin, ncRNAs: Noncoding RNAs, NEAT1: Nuclear paraspeckle assembly transcript 1, NF-κB: Nuclear factor kappa B, NONO: Non-POU domain-containing octamer-binding **protein,** NRF2: Nuclear factor erythroid 2-related factor 2, NSD 2: Nuclear receptor binding SET domain protein 2, OS: Overall survival, PI3K: Phosphoinositide-3 kinase PLK1: Polo-like kinase 1, SIRT1: Sirtuin 1, Sox-4: SRY-box 4, STAT: Signal transducer and activator of transcription, TAF1: TATA-box binding protein-associated factor 1, TNF-α: Tumor necrosis factor-α, TNM: Tumor-node- metastasis, TOP2A: Topoisomerase 2-alpha, TPX2: Targeting protein for Xklp2, WGCNA: Weighted Gene Co-expression Network Analysis, Wnt: Wingless/Integrated, WTAP: WT1 associated protein, ZEB 1: Zinc finger E-box binding homeobox 1.

1. Introduction

Worldwide, esophageal cancer (EC) is considered the 7th most prominent malignancy of the digestive system in terms of incidence, and it is considered one of the most fatal tumors. EC was classified into two pathological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) (1). The main risk factors for EC are tobacco use, alcohol drinking, gastroesophageal reflux, dietary carcinogens, inadequate consumption of vegetables and fruits, and inadequate vitamin intake. Besides, the genetic factors enhance the susceptibility of EC (2). Even though there is limited treatment for EAC patients, The combination of radiotherapy and chemotherapy serves as an irreplaceable anticancer agent during the whole therapy with neoadjuvant, palliative, and curative treatments. Chemotherapeutic agents are commonly used in the clinical fields of EAC and ESCC, comprising cisplatin, 5-fluorouracil (5FU), paclitaxel, Adriamycin, and gemcitabine. Additionally, radiotherapy is intended for the destruction of the DNA of cancer cells, especially for local advanced EC. Many reports have indicated that EC cells tend to be resistant to chemotherapy and radiotherapy, resulting in poor prognosis, cancer recurrence, and metastasis (3, 4).

Noncoding RNAs (ncRNAs) are RNA transcripts that encode noncoding sequences of the human genome and are divided into particular types related to their length and structure. It is now well documented that ncRNAs including long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) can influence many processes that contribute to multiple diseases, including cancers (5, 6), liver diseases (7, 8), bone diseases (9, 10), multiple myeloma (11, 12), cardiovascular diseases (13, 14), rheumatoid arthritis (15, 16), diabetes (17, 18), obesity and metabolic syndrome (19, 20) .

Notably, lncRNAs are comprised of a sequence of more than 200 base pairs and have been demonstrated to exist both in the cytoplasm and nucleus, functioning through a variety of signaling pathways (21). The lncRNAs expression is frequently modulated by several transcription factors. According to the biogenesis and functions of these lncRNAs, they were found to be extensively linked with different human cancer processes such as (apoptosis, epithelial-mesenchymal transition (EMT), autophagy, and metastasis) (22).

Recent studies have highlighted the abnormal expression of lncRNA in the EC and also shown the potential role of them as a therapeutic target in the carcinogenesis process (23, 24). In cancer types such as EAC and ESCC, dysregulated lncRNAs may act as potential biomarkers for the diagnosis and prognosis of these types of cancers, as they could participate in therapeutic resistance by regulating cell proliferation, apoptosis, DNA damage repair, and cancer stem cell (CSC) activation (25).

In the present review, we clarified the contemporary findings concerning the role of lncRNAs in EC pathogenesis and therapeutic resistance, with an emphasis on their promising role as diagnostic and prognostic biomarkers.

2. LncRNAs biogenesis and functions

Interestingly, lncRNAs are made up of molecules that are longer than 200 base pairs. RNA polymerase II is responsible for the transcription of these molecules. Like mRNA, lncRNAs undergo splicing, capping, and addition of poly A tail. It has been established that lncRNAs function through a variety of signaling pathways both in the cytoplasm and the nucleus (21). According to the latest research, lncRNAs control the main cancer-causing pathways at the epigenetic, transcriptional, and post-transcriptional mechanisms. The epigenetic control of target genes by lncRNAs, particularly through their repressive activities, is one of their most commonly recognized biological functions (26, 27). Besides, lncRNAs control the function of promoter enhancers to modulate gene expression directly. Moreover, lncRNAs may further modulate the gene expression and mRNA translation by interfering with the post-transcriptional processing of mRNAs and governing mRNA stability, respectively. Furthermore, lncRNAs serve like sponges by joining the targeted miRNAs (28).

3. The role of lncRNAs in EC pathogenesis

In contrast to normal cells, EC tissues exhibit dysregulated lncRNAs, according to several studies. These lncRNAs have been demonstrated to control important EC growth and progression pathways, including cell proliferation, apoptosis, angiogenesis, and invasion (**Table 1**). For instance, it has been reported that one lncRNA, Nuclear paraspeckle assembly transcript 1 (NEAT1), is elevated in EC and modulates miR-377/ E2F3 signaling pathway to encourage EC cell growth and invasion. By controlling the expression of genes involved in cell motility and invasion, a different lncRNA known

as metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been related to the metastasis of EC (29, 30).

Awareness of the molecular processes that result in EC pathogenesis and the identification of new therapeutic targets for the creation of more potent treatments may be gained from an understanding of the role of lncRNAs in this illness. To completely understand the intricate relationships between lncRNAs and other genetic and environmental variables implicated in EC, more research is nonetheless required (31).

The tissue-specific nature of lncRNAs makes it difficult to research their impact on EC. LncRNA expression patterns can change depending on the stage and subtype of cancer, and they can be very specific to particular tissues or cell types. As a result, choosing the right lncRNA target for a particular patient can be difficult (32, 33).

The creation of efficient therapeutic approaches that can target dysregulated lncRNAs in EC is another difficulty. Large molecules like lncRNAs are unable to easily pass across biological barriers like the blood-brain barrier or the epithelial lining of the digestive system. Therefore, it is crucial to create efficient delivery tool that can get past these obstacles and transfer the medication to the intended area (34, 35).

Despite these obstacles, there is mounting proof that lncRNAs are essential in the development of EC. Additional study in this field may result in the creation of novel therapeutic and diagnostic approaches that can enhance the prognosis of disease patients. A number of additional lncRNAs, in addition to those already described, have been connected to the pathogenesis of esophageal cancer (36). By controlling the expression of genes associated with cell cycle progression and apoptosis, for instance, a study Sun et al. revealed that a lncRNA termed HOXA11-AS is elevated in tissues from patients with esophageal cancer and enhances cancer cell proliferation and invasion (37).

The expression of genes involved in the EMT process is controlled by a lncRNA known as colon cancer-associated transcript 2 (CCAT2), which was increased in EC. CCAT2 improves cancer cell proliferation and metastasis by modulating Wnt signaling axis (38).

These findings imply that, through controlling important physiological processes involved in cancer cell proliferation and invasion, dysregulated lncRNAs play a crucial function in the initiation and

spread of EC (24). As a result, focusing on these lncRNAs may be a useful therapeutic approach for the management of EC (39). However, there are a number of difficulties in creating efficient lncRNA-based treatments for esophageal cancer. These include the fact that lncRNAs are tissue-specific, the challenge of delivering lncRNAs to the target tissue, the possibility of off-target effects, and the requirement for properly planned clinical studies to guarantee the safety and effectiveness of the therapy (40).

Despite these difficulties, the potential advantages of lncRNA-based therapy for patients with EC make this a fascinating field of study that merits more investigation. Further investigation in this field may result in the discovery of novel diagnostic and prognostic biomarkers for esophageal cancer, which could improve patient outcomes by enabling earlier detection and more focused treatment (24). The potential benefits of these treatments for patients make this an attractive area of research that calls for additional inquiry, despite the difficulties in establishing effective lncRNA-based therapeutics for esophageal cancer (29).

Table 1. The role of lncRNAs in the pathogenesis of EC

LncRNAs	Alteration	Role in EC	Ref.
NEAT1	↑	Promote tumor growth, invasion, and metastasis by modulating miR-377/ E2F3 signaling pathway	(30)
HOTAIR	↑	Promotes the progression and EMT of EC by downregulating the Wnt inhibitory factor 1 expression	(41, 42)
MIR22HG	↑	Suppression of MIR22HG decreases proliferation and triggers apoptosis by targeting STAT3/c-Myc/FAK.	(43)
SNHG5	↑	Promotes the growth and migration of EC cells via modulation of the Wnt/β-catenin axis.	(44)
UCA1	↑	Promotes tumor growth and metastasis by modulating Sox-4.	(45, 46)
LINC00673	↑	Enhances ESCC cell growth by upregulating EZH2-induced H3K27me3.	(47)
FAM83H-AS1	↑	Improves tumor growth and metastasis of ESCC by modulating miR-10a-5p/Girdin.	(48, 49)

LUCAT1	↑	Enhances ESCC tumorigenesis by regulating DNA methyltransferase 1.	(50)
PANDAR	↑	Promotes ESCC cell proliferation by regulating SAFA.	(51)
LINC00857	↑	LINC00857 silencing represses EAC cell growth and increases apoptosis by modulating MET and STAT3.	(52)
SNHG7	↑	Promotes EC cell proliferation, migration and reduces apoptosis by modulating the production of p15 and p16.	(53)
GAS5	↑	Enhances tumor proliferation and invasion by targeting miR-301a/ Wnt/β-catenin signaling axis.	(54)
TTN-AS1	↑	Enhances ESCC cell growth and metastasis by modulating by miR-133b/ Snail1.	(55)
PVT1	↑	Promotes tumor growth and metastasis by modulating miR-203/LASP1 signaling axis.	(56, 57)
LINC00152	↑	Promotes cancer cell proliferation and EMT.	(58, 59)
DANCR	↑	Promotes ESCC cell growth, migration, and invasion.	(60)
RPL34-AS1	↓	Serves as a tumor suppressor by reducing EC cell proliferation and invasion.	(61)
CCAT1	↑	It has been associated with tumor progression and poor prognosis of EC.	(62, 63)
AFAP1-AS1	↓	Suppresses tumor growth and invasion.	(36)
LOC285194	↓	It has been associated with a poor prognosis of EC and its downregulation linked with advanced TNM stage.	(64)
MEG3	↑	Promotes tumor growth and metastasis.	(65)
ADAMTS9-AS2	↓	Suppresses tumor growth and metastasis through induction the methylation of the CDH3 promoter.	(66)
MALAT1	↑	Promotes tumor growth, invasion, and metastasis. It also associated with poor prognosis of EC.	(29)
ZFP36L1	↓	Inhibits tumor growth and invasion.	(36)
H19	↑	Enhances tumor growth and metastasis.	(67)
LIN28A	↑	Promotes tumor growth and metastasis	(68)

SNHG6	↑	Promotes tumor growth and metastasis.	(69)
RP11-465B22.8	↑	Promotes tumor growth and invasion by modulating miR-765/KLK4 signaling axis.	(70)
RP11-766N7.4	↓	Decreases tumor invasion and EMT.	(71)
FAM225A	↑	Enhances ESCC progression by targeting miR-197-5p and increasing NONO expression	(72)
LINC01296	↑	Enhances ESCC growth and invasion by downregulating KLF2	(73)
LINC02820	↑	Enhances ESCC invasion and metastasis by modulating TNFα and enhancing NF-κB cascade.	(74)
ESCCAL-1	↑	Increases ESCC progression by targeting miR-590/ LDL receptor-related protein-6 (LRP6)	(75)
HOXC-AS1	↑	Enhances ESCC progression by targeting IGF2BP2 /sirtuin 1 (SIRT1)	(76)

CDH3: Cadherin 3, EAC: Esophageal adenocarcinoma, EC: Esophageal cancer, EMT: Epithelial-mesenchymal transition, ESCC: Esophageal squamous cell carcinoma, FAK: Focal adhesion kinase, H3K27me3: Tri-methylation of lysine 27 on histone H3 protein, IGF2BP2: Insulin-like growth factor 2 mRNA-binding protein 2, KLF2: Krüppel-like factor 2, KLK4: Kallikrein related peptidase 4, LASP1: LIM and SH3 domain protein 1, LncRNAs: Long non-coding RNAs, miR: microRNA, NF-κB: Nuclear factor kappa B, NONO: Non-POU domain-containing octamer-binding protein, Sox-4: SRY-box 4,STAT: Signal transducer and activator of transcription, TNFα: Tumor necrosis factor α, TNM: Tumor-node- metastasis, Wnt: Wingless/Integrated.

4. The signaling axis pathways modulated by lncRNAs in EC chemoresistance

Indeed, lncRNAs control the chemoresistance of EC by modulating numerous signaling networks (**Table 2**) that include:

4.1. Modulation of cellular apoptosis, proliferation, and cell cycle

LncRNAs play a vital action in modulating cellular apoptosis, proliferation, and their relationship to chemoresistance in EC cells (63, 77). For instance, lncRNAs FOXD2-AS1and NMR improves The EC's chemoresistance to cisplatin by modulating miR-195/ Protein kinase B (AKT)/ the mammalian target of rapamycin (mTOR) (78) and Bromodomain PHD finger transcription factor (BPTF)/ extracellular regulated kinase (ERK) 1/2/ the matrix metalloproteinase 3/10 (MMP3/10) signaling axis (79), respectively. Besides, *in vitro* experiment by Fu et al. revealed that Linc01014 increases

the EC chemoresistance to Gefitinib through targeting phosphoinositide-3 kinase (PI3K)/ AKT/ mTOR axis (80). Moreover, a study by Kang et al., found that lncRNA PART1 improves the EC chemoresistance to Gefitinib by miR-129/ B-cell lymphoma 2 (Bcl2) axis (81). Through targeting DNA methyltransferase (DNMT) and methylenetetrahydrofolate reductase (MTHFR), lncRNA HOTAIR was found to aggravate the EC chemoresistance to 5-FU (82). Remarkably, the Paclitaxel sensitivity of EC may by increased by repression of LncRNA DDX11-AS1 via downregulation of TATA-box binding *protein*-associated factor 1 (TAF1)/ topoisomerase 2-alpha (TOP2A) (83). On the other hand, Linc00261 inhibits the EC resistance to 5-FU by downregulation the expression of dihydro-pyrimidine dehydrogenase (DPYD) (84).

Interestingly, *in vivo* and *in vitro* experiments by Jia et al. revaeled that the NORAD/miR-224-3p/ metadherin (MTDH) axis can reduce the sensitization of ESCC cells to cisplatin by increasing the nucleus building up β-catenin. Besides, in ESCC cells the expression of MTDH was modulated by lncRNA NORAD and miR-224-3p, which shared a similar Argonaute-2 to create an RISC protein (85). Besides, It was reported that EMS and TUG-1 lncRNAs enhances the EC chemoresistance to cisplatin by modulating miR-758–3p/ a nuclear cell cycle regulator WT1 Associated *Protein* (WTAP) axis (86) and Nuclear factor erythroid 2-related factor 2 (NRF2) protein (87), respectively. The transcription mediator NRF-2 can modulate the production of antioxidant substances (88).

Through targeting DNMT/ glutathione S-transferase P1 (GSTP1), Both Linc01419 (89) and Linc01270 (90) can increase the EC chemoresistance to 5-FU. Indeed, GSTP1 has a vital role in the cellular protection towards oxidative damage (91). On the other hand, Chang et al. demonstrated that lncRNA TUSC7 represses the EC chemoresistance to 5-FU by modulating miR-224/ epidermal growth factor receptor (EGFR)/AKT axis (77).

According to Hu et al. research, the collaboration of the lncRNA CCAT1 and miR-143 axis activates the enzyme Polo-like Kinase 1 (PLK1), that controls the cell cycle and attenuatess apoptosis in ESCC. This results in upregulation of Bub1-related kinase (BUBR1) that regarded as a crucial part of the mitotic spindle formation checkpoint, increased cell growth, and resistance to cisplatin (63).

4.2. Modulating of multidrug resistance proteins

Multidrug resistance proteins (MRPs) have been established as ATP-binding cassette (ABC) pumps. As a result of their function as a medicine export pump, the intracellular amount of chemotherapy

medicines is declined, and their cytotoxicity is dropped (92). Adriamycin-resistant EC cells may increase the production of ATP-binding cassette G2 (ABCG2), which is thought to be an inducer of chemoresistance, by secreting linc-VLDLR through extracellular vesicles (93).

4.3. Modulating the repair of DNA damage

Notably, nuclear receptor-binding SET domain protein 2 (NSD2) has been implicated in the repair of DNA deterioration and thus it imparts resistance to chemotherapy**.** In order for ESCC cells to preserve their resistance to cisplatin, the upregulation of the lncRNA MACC1-AS1 generated by NSD2 is crucial (94).

4.4. Regulation of EMT

The key characteristics of EMT are the lack of cell connection, polarization, the acquisition of migratory and invasive features that result in the formation of mesenchymal stem cells. (95). Several studies have found a relationship between EMT and chemoresistance in a variety of tumor subtypes (96, 97). Through its association with enhancer of zeste homolog 2 (EZH2), linc00152 can stimulate the production of Zinc finger E-box binding homeobox 1 (ZEB1), which in turn increases E-cadherin expression, promoting EMT and EC resistance to oxaliplatin (59).

4.5. Modulation of cancer-associated fibroblasts (CAFs)

A vital component of the cancer stroma known as cancer-associated fibroblasts has been demonstrated to possess a significant role in chemoresistance. In ESCC cells, lncRNA POU3F3 may promote the transformation process of typical fibroblasts into activated CAFs, which in turn improves cellular growth and cisplatin resistance of ESCC cells by upregulating the production of interleukin-6 (IL-6) (98).

4.6. Modulating of autophagy

As a protective measure against detrimental stressful conditions like hypoxia and chemotherapy, the cancer cells adopt autophagy (99). It has been reported that autophagy contributes to lncRNA-mediated chemotherapeutic resistance. In order to improve autophagy while suppressing cellular apoptosis and cisplatin sensitization in EC, Linc00337 may activate E2F4 to improves the gene expression of the intended protein for Xenopus kinesin-like protein 2 (TPX2) and thereby increase a production of autophagy-associated factors (100).

Table 2. The impact of lncRNAs on the chemotherapeutic response of EC

LncRNAs	Alteration	Therapeutic impact	Target	System	Ref.
FOXD2-AS1	↑	Enhances the EC chemoresistance to cisplatin.	miR-195 - AKT/mTOR	*In vivo*, *In vitro*, Tissues	(78)
NMR	↑	Improves the EC chemoresistance to cisplatin.	BPTF/ ERK1/2/ MMP3/10	*In vitro*, Tissues	(79)
Linc01014	↑	Enhances the EC chemoresistance to Gefitinib.	PI3K/ AKT/ mTOR	*In vitro*	(80)
PART1	↑	Enhances the EC chemoresistance to Gefitinib.	miR-129 - Bcl2	*In vivo*, *In vitro*, Clinical	(81)
HOTAIR	↑	Increases the EC chemoresistance to 5-FU.	DNMT/ MTHFR	*In vivo*, *In vitro*, Tissues	(82)
DDX11-AS1	↑	Enhances the EC chemoresistance to Paclitaxel.	TAF1/ TOP2A	*In vivo*, *Invitro*, Tissues	(83)
Linc00261	↓	Decreases the EC chemoresistance to 5-FU.	DPYD	*In vivo*, *In vitro*, Tissues	(84)
NORAD	↑	Raises the EC chemoresistance to cisplatin	MiR-224–3p - MTDH	*In vivo*, *In vitro*, Tissues	(85)
EMS	↑	Represses the EC sensitivity to cisplatin	miR-758–3p - WTAP	*In vivo*, *In vitro*, Tissues	(86)
TUG1	↑	Represses the EC sensitivity to cisplatin	NRF2	*In vitro*, Tissues	(87)
Linc01419	↑	Increases the EC	DNMT/ GSTP1	*In vivo*,	(89)

		chemoresistance to 5-FU.		*In vitro*, Tissues	
Linc01270	↑	Represses the EC sensitivity to 5-FU.	DNMT/ GSTP1	*In vivo*, *In vitro*, Tissues	(90)
TUSC7	↓	Decreases the EC chemoresistance to 5-FU.	miR224/ EGFR/ AKT	*In vivo*, *In vitro*, Tissues	(77)
CCAT1	↑	Represses the EC sensitivity to cisplatin	miR-143 - PLK1/ BUBR1	*In vivo*, *In vitro*,	(63)
LincVLDLR	↑	Increases the EC chemoresistance to Adriamycin	ABCG2	*In vitro*, Tissues	(93)
MACC1-AS1	↑	Increases the EC chemoresistance to cisplatin	Mediated by NSD2	*In vivo*, *In vitro*, Tissues	(94)
Linc00152	↑	Raises the EC chemoresistance to Oxaliplatin	EZH2/ ZEB1	*In vivo*, *In vitro*, Tissues	(59)
POU3F3	↑	Represses the EC sensitivity to cisplatin	IL-6	*In vitro*, *Clinical*	(98)
Linc00337	↑	Increases the EC chemoresistance to cisplatin	E2F4/ TPX2	*In vivo*, *In vitro*, Tissues	(100)

ABCG2: ATP-binding cassette G2, AKT: Protein kinase B, Bcl2: B-cell lymphoma 2, BPTF: Bromodomain PHD finger transcription factor, BUBR1: Bub1-related kinase, DNMT: DNA methyltransferase, DPYD: Dihydropyrimidine dehydrogenase, EAC: Esophageal adenocarcinoma, EC: Esophageal cancer, EGFR: Epidermal growth factor receptor, EMT: Epithelial-mesenchymal transition, ERK1/2: Extracellular signal-regulated kinase-1/2, ESCC: Esophageal squamous cell carcinoma, EZH2: Enhancer of Zeste homolog 2, FAK: Focal adhesion kinase, GSTP1: Glutathione S-transferase P1, IL-6: Interleukin-6, KLF2: Krüppel-Like Factor 2, LncRNAs: Long non-coding RNAs, miR: microRNA, MMP3/10: Matrix Metalloproteinase 3/10, MTDH: Metadherin, MTHFR: Methylenetetrahydrofolate reductase, mTOR: Mammalian target of rapamycin, NRF2: Nuclear factor erythroid 2-related factor 2, NSD: Nuclear receptor binding SET domain protein, PI3K: Phosphoinositide-3 kinase, PLK1: Polo-like Kinase 1, TAF1: TATA-box binding protein associated factor 1, TNF-α: Tumor necrosis factor-α, TOP2A: Topoisomerase 2-alpha, TPX2: Targeting protein for Xklp2, WTAP: WT1 associated protein, ZEB: Zinc Finger E-Box-Binding Homeobox.

5. The clinical implications of lncRNAs in EC

The histological examination of tumor tissue is very important before the diagnosis of EC. For small lesions, following histological analysis, endoscopic resection alone may represent suitable therapy if the tumor is small and superficial. Currently, endoscopic biopsy is the gold standard method for diagnosis of early EC; while (endoscopic visualization of a large mucosal mass is nearly pathognomonic of EC, and image-guided biopsy must be performed if metastases are present to confirm diagnosis. The early EC appears endoscopically as superficial plaques, nodules, or ulcerations**.** Advanced lesions appear as strictures, ulcerated masses**,** circumferential masses, or large ulcerations (101, 102).

The prognosis of EC is strongly associated with its clinical stage at diagnosis. Endoscopic ultrasonography (EUS) is the most accurate method for staging ESCC patients being regarded for surgery once distant metastases have been excluded by computed tomography (CT) or by integrated fluoro-deoxy glucose positron emission tomography (FDG/PET), while in the case of metastatic lymphadenopathy, the addition of EUS-guided fine-needle aspiration has further improved lymph node staging accuracy and should be performed routinely. Although EUS has a limited role in staging patients post-chemotherapy and/or radiotherapy, it is considered the most sensitive technique for detecting local tumor recurrence (103, 104)**.**

Nowadays, it is critical to develop non-invasive diagnostic methods to diagnose EC rather than invasive techniques. Besides, myriad published studies are addressing the circulating value of lncRNAs in ESCC as a potential non-invasive diagnostic biomarker for EC (105)**.** The results of different reports summarize the diagnostic/prognostic value of lncRNAs in EC in **Table 3**.

Ghafouri-Fard et al. study has shown the global coding and lncRNA signatures in the discrimination of adjacent noncancerous tissues from the EC cell samples (106). Indeed, lncRNAs are regarded as one of the crucial modulators of cancer and are transcribed prominently in the genome and several conditions. Many experimental and computational reports have described the role of lncRNAs as key protein-coding genes in the initiation and progression of ESCC. By utilizing microarray expression reports for mRNAs and lncRNAs from a large number of ESCC samples, the “Weighted Gene Co-expression Network Analysis” (WGCNA) method made a big coding/non-coding gene co-expression network and discovered an important functional module (107). A study by Hao et al. was the first to introduce ESCCAL-1 as one of the most prominent altered lncRNAs in ESCC specimens (108).

Functional enrichment analysis found that lncRNAs including (LINC00173, RP11-579D7.4, LA16c-325D7.2, RP1-251M9.2, RP5-1172N10.2, RP11-259O2.2, and RP11-89N17.4) might debate the cell cycle modulation, histone methylation, and cancer-associated signaling mechanisms including (PI3K/AKT and hypoxia-inducible factor-1) in the patient's survival with ESCC (23**).** Additional evaluation in recent in-silico enrichment analysis implied the possible participation of GK3P and RPL34-AS1 lncRNAs in the development of EC after RNA sequencing data analysis of ESCC samples provided by the Cancer Genome Atlas database (109).

The integrated bioinformatics analysis was utilized to recognize differentially expressed lncRNA genes (DELGs). They have recognized 259 lncRNAs between the early and advanced stages of ESCC samples. In addition to evaluations that identified another 5 lncRNAs, including (AC098973, RP11-51M24, RP11- 834C11, LINC00471, and RP1-124C) in which their expression could predict tumor behavior in ESCC patients and control cell cycle and DNA replication (110). Several reports have identified 6 lncRNAs whose expressions were correlated with the patient's outcome. RP11-1L12.3 and HERES lncRNAs were found to increase the survival of the disease, while CTD-2319I12.1, RP11- 114H23.1, and LINC00330 had a contrasting impact. Based on the expression of these lncRNAs, samples of ESCC could be classified into 4 classes correlated with smoking history and/or patient survival (106)**.** A comprehensive analysis of lncRNAs profile identified 7 up-regulated lncRNAs and 21 down-regulated lncRNAs whose signature was defined as poor survival (111)**.**

The study by Liu et al. applied the in-silico enrichment analysis method to recognize the altered lncRNA-miR-mRNA networks in EC samples. These dysregulated genes were enriched in extracellular matrix assembly, chromosome separation, cell cycle, and the cyclic GMP-protein kinase G signaling pathway (112)**,** while Wang et al. have revealed that the serum level of HOTAIR lncRNA has a powerful diagnostic value that could discriminate cases from healthy controls with 0.79 area under the curve (AUC) at a cut off-value of 0.094 with 90% specificity and 56% sensitivity, as it was found to be upregulated in the serum samples of the cases group compared to healthy controls, in addition to their expression levels being correlated with metastasis (113).

Table 3. The clinical relevance of lncRNAs in EC

LncRNAs	no. of (EC specimens +	Kaplan–Meier analysis	Univariate Cox regression	Multivariate Cox regression	Ref.

	controls)				
HOTAIR	93	↑ Expression with shorter survival	↑ Expression was correlated with clinical stage, TNM classification, vital status, and histological recognition.	It regarded as independent contributor for overall survival (OS)	(114)
	100		---	Correlated with lymph node metastasis, clinical stage, histological discrimination, TNM classification.	(115)
	137			Prognostic independent indicator for metastasis and death	(42)
MALAT 1	106		---	---	(116)
	132	↑ Expression with shorter survival		Independent predictor for EC patients' survival.	(117)
FOXCUT	82	↑ Expression with worse prognosis	---	---	(118)
NORAD	106	↑ Expression with poorer OS and disease-free survival (DFS)	Risk factor for OS in patients with ESCC	Independent prognostic factors in ESCC	(119)
NEAT1	96	increase Expression with shorter OS	Its expression correlate with TNM stage, tumor size, and lymph node metastasis.	Independent risk factor for OS	(120)
linc00460	65	↑ Expression with poorer OS	---	---	(121)
PCAT-1	130	↑ Expression with a poorer survival time	---	Independent predictor of poor survival	(122)
BANCR	142	↑ Expression with a poorer DFS and OS	---	Expression of BANCR among cases with ESCC following esophagectomy was independent indicator of a worse prognosis.	(123)
	90	↑ Expression with poorer prognosis	Expression was correlated with clinical stage,	Independent prognostic indicators for the OS	(124)

UCA1			tumor differentiation, lymph node metastasis, and OS rate.		
	66	↑ Expression with a poorer prognosis	---	---	(46)
ZEB1-AS1	87	↑ Expression with a poorer OS and DFS	---	Its expression increases after esophagectomy. Independent prognostic factors for OS	(125)
DUXAP8	78	Has a worse prognosis than those with diminished expression.	---	---	(126)
PVT1	104	↑ Expression with a lower OS	Identified as prognostic factors	Correlated with OS	(57)
SPRY4-IT1	92	↑ Expression with a lower OS time	---	Independent prognostic factors for the OS	(127)
TUG1	218	↑ Expression but with poor prognosis, particularly for cases with moderate/ well differentiation	↑ Expression corelated to poor prognosis	Independent predictors with poor survival	(128)
LOC285194	142	↓Expression with a poorer OS and DFS	↓ Expression was Correlated with CRT response	Reduced expression after esophagectomy Regarded as independent predictor with poor survival & independent prognostic factors that could affect the OS and DFS	(64)

CRT: Chemoradiotherapy, DFS: Disease-free survival, EC: Esophageal cancer, ESCC: Esophageal squamous cell carcinoma, LncRNAs: Long non-coding RNAs, OS: Overall survival, TNM: Tumor-node- metastasis.

6. Conclusion

In summary, mounting evidence indicates that lncRNAs play a significant modulatory role in the etiology of esophageal cancer by controlling important physiological processes involved in cancer

cell development and invasion. Besides, lncRNAs have a significant relevance in EC diagnosis, prognosis, and therapy response. As a result, targeting lncRNAs may be a potentially effective treatment to improve the outcomes of EC patients.

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Competing interests

The authors report they have no conflict of interests.

References

1. Yang Z, Ma R, Li J, Zhao L. Noncoding RNAs in esophageal cancer: A glimpse into implications for therapy resistance. Pharmacological Research. 2023:106678.
2. Yang CS, Chen X, Tu S. Etiology and prevention of esophageal cancer. Gastrointestinal tumors. 2016;3(1):3-16.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021;71(3):209-49.
4. Doghish AS, El-Husseiny AA, Abdelmaksoud NM, El-Mahdy HA, Elsakka EG, Mageed SSA, et al. The interplay of signaling pathways and miRNAs in the pathogenesis and targeted therapy of esophageal cancer. Pathology-Research and Practice. 2023:154529.
5. Al-Noshokaty TM, Mansour A, Abdelhamid R, Abdellatif N, Alaaeldien A, Reda T, et al. Role of long non-coding RNAs in pancreatic cancer pathogenesis and treatment resistance-A review. Pathology-Research and Practice. 2023:154438.
6. El-Mahdy HA, Mohamadin AM, Abulsoud AI, Khidr EG, El-Husseiny AA, Ismail A, et al. miRNAs as potential game-changers in head and neck cancer: Future clinical and medicinal uses. Pathology-Research and Practice. 2023:154457.
7. Rowe MM, Kaestner KH. The Role of Non-Coding RNAs in Liver Disease, Injury, and Regeneration. Cells. 2023;12(3):359.
8. Doghish AS, Elballal MS, Elazazy O, Elesawy AE, Elrebehy MA, Shahin RK, et al. The role of miRNAs in liver diseases: Potential therapeutic and clinical applications. Pathology-Research and Practice. 2023:154375.
9. Song W, Xie J, Li J, Bao C, Xiao Y. The emerging roles of long noncoding RNAs in bone homeostasis and their potential application in bone-related diseases. DNA and cell biology. 2020;39(6):926-37.
10. Doghish AS, Elballal MS, Elazazy O, Elesawy AE, Shahin RK, Midan HM, et al. miRNAs as potential game-changers in bone diseases: Future medicinal and clinical Uses. Pathology-Research and Practice. 2023:154440.
11. Cui YS, Song YP, Fang BJ. The role of long non-coding RNAs in multiple myeloma. European Journal of Haematology. 2019;103(1):3-9.

12. Yehia AM, Elsakka EG, Abulsoud AI, Abdelmaksoud NM, Elshafei A, Elkhawaga SY, et al. Decoding the role of miRNAs in multiple myeloma pathogenesis: A focus on signaling pathways. Pathology-Research and Practice. 2023:154715.
13. Fang Y, Xu Y, Wang R, Hu L, Guo D, Xue F, et al. Recent advances on the roles of LncRNAs in cardiovascular disease. Journal of Cellular and Molecular Medicine. 2020;24(21):12246-57.
14. Khidr EG, Abulsoud AI, Doghish AA, El-Mahdy HA, Ismail A, Elballal MS, et al. The potential role of miRNAs in the pathogenesis of cardiovascular diseases-A focus on signaling pathways interplay. Pathology-Research and Practice. 2023:154624.
15. Li Z, Li X, Jiang C, Qian W, Tse G, Chan MT, et al. Long non-coding RNA s in rheumatoid arthritis. Cell proliferation. 2018;51(1):e12404.
16. Doghish AS, Ismail A, El-Mahdy HA, Elkhawaga SY, Elsakka EG, Mady EA, et al. miRNAs insights into rheumatoid arthritis: Favorable and detrimental aspects of key performers. Life Sciences. 2022:121321.
17. Tanwar VS, Reddy MA, Natarajan R. Emerging role of long non-coding RNAs in diabetic vascular complications. Frontiers in endocrinology. 2021;12:665811.
18. Mageed SSA, Doghish AS, Ismail A, El-Husseiny AA, Fawzi SF, Mahmoud AM, et al. The role of miRNAs in insulin resistance and diabetic macrovascular complications–A review. International Journal of Biological Macromolecules. 2023:123189.
19. Elkhawaga SY, Ismail A, Elsakka EG, Doghish AS, Elkady MA, El-Mahdy HA. miRNAs as cornerstones in adipogenesis and obesity. Life Sciences. 2023:121382.
20. Alipoor B, Nikouei S, Rezaeinejad F, Malakooti-Dehkordi S, Sabati Z, Ghasemi H. Long non-coding RNAs in metabolic disorders: pathogenetic relevance and potential biomarkers and therapeutic targets. Journal of Endocrinological Investigation. 2021;44:2015-41.
21. Sideris N, Dama P, Bayraktar S, Stiff T, Castellano L. LncRNAs in breast cancer: a link to future approaches. Cancer Gene Therapy. 2022;29(12):1866-77.
22. Qiao M, Li R, Zhao X, Yan J, Sun Q. Up-regulated lncRNA-MSX2P1 promotes the growth of IL-22-stimulated keratinocytes by inhibiting miR-6731-5p and activating S100A7. Experimental cell research. 2018;363(2):243-54.
23. Wang Y, Pang D, Zhang X. The Function of lncRNA LINC00997 as a Diagnostic Marker in the Progression of Esophageal Squamous Cell Carcinoma. Annals of Clinical & Laboratory Science. 2023;53(2):230-7.
24. Wang W, Dai Y, Yang X, Xiong X. Long non-coding RNA TRPM2 antisense RNA as a potential therapeutic target promotes tumorigenesis and metastasis in esophageal cancer. Bioengineered. 2022;13(2):4397-410.
25. Zhang L, Zong L, Li W, Ning L, Zhao Y, Wang S, et al. Construction of lncRNA prognostic model related to cuproptosis in esophageal carcinoma. Frontiers in Genetics. 2023;14:1120827.
26. Al-Imam MJ, Hussein UA-R, Sead FF, Faqri AMA, Mekkey SM, Almashhadani HA. The Interactions Between DNA Methylation Machinery and Long Non-Coding RNAs in Tumor Progression and Drug Resistance. DNA Repair. 2023:103526.
27. Fonseca-Montaño MA, Vázquez-Santillán KI, Hidalgo-Miranda A. The current advances of lncRNAs in breast cancer immunobiology research. Frontiers in Immunology. 2023;14:1194300.
28. Liu Y, Sharma S, Watabe K. Roles of lncRNA in breast cancer. Frontiers in bioscience (Scholar edition). 2015;7:94.

29. Zhang W, Zhang L, Cai XJ, Li D, Cao FJ, Zuo ZG, et al. Dexmedetomidine inhibits the growth and metastasis of esophageal cancer cells by down-regulation of lncRNA MALAT1. The Kaohsiung Journal of Medical Sciences. 2022;38(6):585-93.
30. Du W, Xu P, Yin H. LncRNA NEAT1 regulates the growth, migration, and invasion of the human esophageal cancer cells via the miR-377/E2F3 axis. Acta Biochimica Polonica. 2022;69(4):731-6.
31. Toden S, Zumwalt TJ, Goel A. Non-coding RNAs and potential therapeutic targeting in cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2021;1875(1):188491.
32. Huang T, Wu Z, Zhu S. The roles and mechanisms of the lncRNA-miRNA axis in the progression of esophageal cancer: a narrative review. Journal of Thoracic Disease. 2022;14(11):4545.
33. Chen X, Fan S, Song E. Noncoding RNAs: new players in cancers. The Long and Short Non-coding RNAs in Cancer Biology. 2016:1-47.
34. Liu J, Liu Z-X, Li J-J, Zeng Z-L, Wang J-H, Luo X-J, et al. The Macrophage-Associated LncRNA MALR Facilitates ILF3 Liquid–Liquid Phase Separation to Promote HIF1α Signaling in Esophageal Cancer. Cancer Research. 2023;83(9):1476-89.
35. Zeniya S, Kuwahara H, Daizo K, Watari A, Kondoh M, Yoshida-Tanaka K, et al. Angubindin-1 opens the blood–brain barrier in vivo for delivery of antisense oligonucleotide to the central nervous system. Journal of Controlled Release. 2018;283:126-34.
36. Yang C, Chen K. Long non-coding RNA in esophageal cancer: a review of research progress. Pathology and Oncology Research. 2022;28:1610140.
37. Sun X, Wang X, Cui Y, Cao X, Zhao R, Wei H, et al. Expression level and clinical significance of LncRNA HOXA11-AS in esophageal squamous cell carcinoma patients. Zhonghua Zhong liu za zhi [Chinese Journal of Oncology]. 2018;40(3):186-90.
38. Wang X, Wang X. Long non-coding RNA colon cancer-associated transcript 2 may promote esophageal cancer growth and metastasis by regulating the Wnt signaling pathway. Oncology Letters. 2019;18(2):1745-54.
39. Liu Y, Hao H, Kang L, Zheng G, Guo X, Li B, et al. Construction of a novel necroptosis-related lncRNA signature for prognosis prediction in esophageal cancer. BMC gastroenterology. 2022;22(1):1-18.
40. Du Q, Xiao R-D, Luo R-G, Xie J-B, Su Z-D, Wang Y. Construction of long non-coding RNA-and microRNA-mediated competing endogenous RNA networks in alcohol-related esophageal cancer. Plos one. 2022;17(6):e0269742.
41. Xu F, Zhang J. Long non-coding RNA HOTAIR functions as miRNA sponge to promote the epithelial to mesenchymal transition in esophageal cancer. Biomedicine & Pharmacotherapy. 2017;90:888-96.
42. Ge XS, Ma HJ, Zheng XH, Ruan HL, Liao XY, Xue WQ, et al. HOTAIR, a prognostic factor in esophageal squamous cell carcinoma, inhibits WIF-1 expression and activates W nt pathway. Cancer science. 2013;104(12):1675-82.
43. Su W, Guo C, Wang L, Wang Z, Yang X, Niu F, et al. LncRNA MIR22HG abrogation inhibits proliferation and induces apoptosis in esophageal adenocarcinoma cells via activation of the STAT3/c-Myc/FAK signaling. Aging (Albany NY). 2019;11(13):4587.
44. Han W, Shi J, Cao J, Dong B, Guan W. Latest advances of long non-coding RNA SNHG5 in human cancers. OncoTargets and therapy. 2020:6393-403.
45. Xue M, Chen W, Li X. Urothelial cancer associated 1: a long noncoding RNA with a crucial role in cancer. Journal of cancer research and clinical oncology. 2016;142:1407-19.

46. Jiao C, Song Z, Chen J, Zhong J, Cai W, Tian S, et al. lncRNA-UCA1 enhances cell proliferation through functioning as a ceRNA of Sox4 in esophageal cancer. Oncology reports. 2016;36(5):2960-6.
47. Zhou M, Mao Y, Yu S, Li Y, Yin R, Zhang Q, et al. LINC00673 represses CDKN2C and promotes the proliferation of esophageal squamous cell carcinoma cells by EZH2-mediated H3K27 trimethylation. Frontiers in oncology. 2020;10:1546.
48. Bu L, Wang R, Liu P, Da J. Aberrantly upregulated FAM83H-AS1 facilitates malignant progression of esophageal squamous cell carcinoma. Oncology Letters. 2020;20(6):1-.
49. Feng B, Wang G, Liang X, Wu Z, Wang X, Dong Z, et al. LncRNA FAM83H-AS1 promotes oesophageal squamous cell carcinoma progression via miR-10a-5p/Girdin axis. Journal of Cellular and Molecular Medicine. 2020;24(16):8962-76.
50. Yoon J-H, You B-H, Park CH, Kim YJ, Nam J-W, Lee SK. The long noncoding RNA LUCAT1 promotes tumorigenesis by controlling ubiquitination and stability of DNA methyltransferase 1 in esophageal squamous cell carcinoma. Cancer letters. 2018;417:47-57.
51. Shi W, Wang Q, Bian Y, Fan Y, Zhou Y, Feng T, et al. Long noncoding RNA PANDA promotes esophageal squamous carcinoma cell progress by dissociating from NF-YA but interact with SAFA. Pathology-Research and Practice. 2019;215(10):152604.
52. Su W, Wang L, Niu F, Zou L, Guo C, Wang Z, et al. LINC00857 knockdown inhibits cell proliferation and induces apoptosis via involving STAT3 and MET oncogenic proteins in esophageal adenocarcinoma. Aging (Albany NY). 2019;11(9):2812.
53. Xu L-J, Yu X-J, Wei B, Hui H-X, Sun Y, Dai J, et al. LncRNA SNHG7 promotes the proliferation of esophageal cancer cells and inhibits its apoptosis. European Review for Medical & Pharmacological Sciences. 2018;22(9).
54. Li W, Zhao W, Lu Z, Zhang W, Yang X. Long noncoding RNA GAS5 promotes proliferation, migration, and invasion by regulation of miR-301a in esophageal cancer. Oncology research. 2018;26(8):1285.
55. Lin C, Zhang S, Wang Y, Wang Y, Nice E, Guo C, et al. Functional role of a novel long noncoding RNA TTN-AS1 in esophageal squamous cell carcinoma progression and metastasis. Clinical Cancer Research. 2018;24(2):486-98.
56. Hu J, Gao W. Long noncoding RNA PVT1 promotes tumour progression via the miR-128/ZEB1 axis and predicts poor prognosis in esophageal cancer. Clinics and Research in Hepatology and Gastroenterology. 2021;45(4):101701.
57. Li P-D, Hu J-L, Ma C, Ma H, Yao J, Chen L-L, et al. Upregulation of the long non-coding RNA PVT1 promotes esophageal squamous cell carcinoma progression by acting as a molecular sponge of miR-203 and LASP1. Oncotarget. 2017;8(21):34164.
58. Ding Y, Guo H, Zhu L, Xu L, Pei Q, Cao Y. LINC00152 knock-down suppresses esophageal cancer by EGFR signaling pathway. Open Medicine. 2020;15(1):126-33.
59. Zhang S, Liao W, Wu Q, Huang X, Pan Z, Chen W, et al. LINC00152 upregulates ZEB1 expression and enhances epithelial-mesenchymal transition and oxaliplatin resistance in esophageal cancer by interacting with EZH2. Cancer cell international. 2020;20:1-14.
60. Shi H, Shi J, Zhang Y, Guan C, Zhu J, Wang F, et al. Long non-coding RNA DANCR promotes cell proliferation, migration, invasion and resistance to apoptosis in esophageal cancer. Journal of Thoracic Disease. 2018;10(5):2573.
61. Gong Z, Li J, Cang P, Jiang H, Liang J, Hou Y. RPL34-AS1 functions as tumor suppressive lncRNA in esophageal cancer. Biomedicine & Pharmacotherapy. 2019;120:109440.

62. Zhang E, Han L, Yin D, He X, Hong L, Si X, et al. H3K27 acetylation activated-long non-coding RNA CCAT1 affects cell proliferation and migration by regulating SPRY4 and HOXB13 expression in esophageal squamous cell carcinoma. Nucleic acids research. 2017;45(6):3086-101.
63. Hu M, Zhang Q, Tian XH, Wang JL, Niu YX, Li G. lncRNA CCAT1 is a biomarker for the proliferation and drug resistance of esophageal cancer via the miR-143/PLK1/BUBR1 axis. Molecular carcinogenesis. 2019;58(12):2207-17.
64. Tong Y-s, Zhou X-l, Wang X-w, Wu Q-q, Yang T-x, Lv J, et al. Association of decreased expression of long non-coding RNA LOC285194 with chemoradiotherapy resistance and poor prognosis in esophageal squamous cell carcinoma. Journal of Translational Medicine. 2014;12:1-9.
65. Dong Z, Zhang A, Liu S, Lu F, Guo Y, Zhang G, et al. Aberrant methylation-mediated silencing of lncRNA MEG3 functions as a ceRNA in esophageal cancer. Molecular Cancer Research. 2017;15(7):800-10.
66. Liu D, Wu K, Yang Y, Zhu D, Zhang C, Zhao S. Long noncoding RNA ADAMTS9-AS2 suppresses the progression of esophageal cancer by mediating CDH3 promoter methylation. Molecular carcinogenesis. 2020;59(1):32-44.
67. Tan D, Wu Y, Hu L, He P, Xiong G, Bai Y, et al. Long noncoding RNA H19 is up-regulated in esophageal squamous cell carcinoma and promotes cell proliferation and metastasis. Diseases of the Esophagus. 2017;30(1).
68. Yu Q, Dai J, Zhu Z, Shen H. Downregulation of RIKP by miR-200a promotes the invasive ability of esophageal cancer cells by upregulating the expression of LIN28 and MMP-14. International Journal of Clinical and Experimental Pathology. 2017;10(8):8452.
69. Tan R, Liu J, Wang J, Zhang W, He M, Zhang Y. Long noncoding RNA SNHG6 silencing sensitized esophageal cancer cells to 5-FU via EZH2/STAT pathway. Scientific Reports. 2023;13(1):5363.
70. Hu R, Bi R, Jiang L, Xiao H, Xie X, Liu H, et al. LncRNA RP11-465B22. 8 triggers esophageal cancer progression by targeting miR-765/KLK4 axis. Cell Death Discovery. 2021;7(1):262.
71. Yao G-L, Pan C-F, Xu H, Wei K, Liu B, Zhai R, et al. Long noncoding RNA RP11-766N7. 4 functions as a tumor suppressor by regulating epithelial-mesenchymal transition in esophageal squamous cell carcinoma. Biomedicine & Pharmacotherapy. 2017;88:778-85.
72. Zhu P, Huang H, Gu S, Liu Z, Zhang X, Wu K, et al. Long Noncoding RNA FAM225A promotes esophageal squamous cell carcinoma development and progression via sponging MicroRNA-197-5p and upregulating NONO. Journal of Cancer. 2021;12(4):1073.
73. Wang L, Meng D, Wang Y, Hu J. Long non-coding RNA LINC01296 promotes esophageal squamous cell carcinoma cell proliferation and invasion by epigenetic suppression of KLF2. American Journal of Cancer Research. 2018;8(10):2020.
74. Wang J, Huang T-J, Mei Y, Luo F-F, Xie D-H, Peng L-X, et al. Novel long noncoding RNA LINC02820 augments TNF signaling pathway to remodel cytoskeleton and potentiate metastasis in esophageal squamous cell carcinoma. Cancer Gene Therapy. 2023;30(2):375-87.
75. Guan H, Lv P, Han P, Zhou L, Liu J, Wu W, et al. Long non-coding RNA ESCCAL-1/miR-590/LRP6 signaling pathway participates in the progression of esophageal squamous cell carcinoma. Cancer medicine. 2023;12(1):445-58.
76. Yang Z, Wan J, Ma L, Li Z, Yang R, Yang H, et al. Long non-coding RNA HOXC-AS1 exerts its oncogenic effects in esophageal squamous cell carcinoma by interaction with IGF2BP2 to stabilize SIRT1 expression. Journal of Clinical Laboratory Analysis. 2023;37(1):e24801.

77. Chang Z-w, Jia Y-x, Zhang W-j, Song L-j, Gao M, Li M-j, et al. LncRNA-TUSC7/miR-224 affected chemotherapy resistance of esophageal squamous cell carcinoma by competitively regulating DESC1. Journal of Experimental & Clinical Cancer Research. 2018;37(1):1-12.
78. Liu H, Zhang J, Luo X, Zeng M, Xu L, Zhang Q, et al. Overexpression of the long noncoding RNA FOXD2-AS1 promotes cisplatin resistance in esophageal squamous cell carcinoma through the miR-195/Akt/mTOR axis. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics. 2020;28(1):65-73.
79. Li Y, Li J, Luo M, Zhou C, Shi X, Yang W, et al. Novel long noncoding RNA NMR promotes tumor progression via NSUN2 and BPTF in esophageal squamous cell carcinoma. Cancer Letters. 2018;430:57-66.
80. Fu X, Cui G, Liu S, Zhao S. Linc01014 regulates gefitinib resistance in oesophagus cancer via EGFR-PI3K-AKT-mTOR signalling pathway. Journal of cellular and molecular medicine. 2020;24(2):1670-5.
81. Kang M, Ren M, Li Y, Fu Y, Deng M, Li C. Exosome-mediated transfer of lncRNA PART1 induces gefitinib resistance in esophageal squamous cell carcinoma via functioning as a competing endogenous RNA. Journal of Experimental & Clinical Cancer Research. 2018;37(1):1-16.
82. Zhang S, Zheng F, Zhang L, Huang Z, Huang X, Pan Z, et al. LncRNA HOTAIR-mediated MTHFR methylation inhibits 5-fluorouracil sensitivity in esophageal cancer cells. Journal of Experimental & Clinical Cancer Research. 2020;39(1):1-13.
83. Zhang S, Jiang H, Xu Z, Jiang Y, She Y, Huang X, et al. The resistance of esophageal cancer cells to paclitaxel can be reduced by the knockdown of long noncoding RNA DDX11-AS1 through TAF1/TOP2A inhibition. American journal of cancer research. 2019;9(10):2233.
84. Lin K, Jiang H, Zhuang S-S, Qin Y-S, Qiu G-D, She Y-Q, et al. Long noncoding RNA LINC00261 induces chemosensitization to 5-fluorouracil by mediating methylation-dependent repression of DPYD in human esophageal cancer. The FASEB Journal. 2019;33(2):1972-88.
85. Jia Y, Tian C, Wang H, Yu F, Lv W, Duan Y, et al. Long non-coding RNA NORAD/miR-224-3p/MTDH axis contributes to CDDP resistance of esophageal squamous cell carcinoma by promoting nuclear accumulation of β-catenin. Molecular Cancer. 2021;20(1):162.
86. Zhu Z-J, Pang Y, Jin G, Zhang H-Y, Wang W-H, Liu J-W, et al. Hypoxia induces chemoresistance of esophageal cancer cells to cisplatin through regulating the lncRNA-EMS/miR-758-3p/WTAP axis. Aging (Albany NY). 2021;13(13):17155.
87. Zhang Z, Xiong R, Li C, Xu M, Guo M. LncRNA TUG1 promotes cisplatin resistance in esophageal squamous cell carcinoma cells by regulating Nrf2. Acta Biochimica et Biophysica Sinica. 2019;51(8):826-33.
88. Costilla M, Macri Delbono R, Klecha A, Cremaschi GA, Barreiro Arcos ML. Oxidative stress produced by hyperthyroidism status induces the antioxidant enzyme transcription through the activation of the Nrf-2 factor in lymphoid tissues of Balb/c mice. Oxidative medicine and cellular longevity. 2019;2019.
89. Chen J-L, Lin Z-X, Qin Y-S, She Y-Q, Chen Y, Chen C, et al. Overexpression of long noncoding RNA LINC01419 in esophageal squamous cell carcinoma and its relation to the sensitivity to 5-fluorouracil by mediating GSTP1 methylation. Therapeutic Advances in Medical Oncology. 2019;11:1758835919838958.
90. Li N, Zhao Z, Miao F, Cai S, Liu P, Yu Y, et al. Silencing of long non-coding RNA LINC01270 inhibits esophageal cancer progression and enhances chemosensitivity to 5-fluorouracil by mediating GSTP1methylation. Cancer Gene Therapy. 2021;28(5):471-85.

91. Chen Y-L, Tseng H-S, Kuo W-H, Yang S-F, Chen D-R, Tsai H-T. Glutathione S-Transferase P1 (GSTP1) gene polymorphism increases age-related susceptibility to hepatocellular carcinoma. BMC medical genetics. 2010;11(1):1-8.
92. El-Mahdy HA, El-Husseiny AA, Kandil YI, El-Din AMG. Diltiazem potentiates the cytotoxicity of gemcitabine and 5-fluorouracil in PANC-1 human pancreatic cancer cells through inhibition of P-glycoprotein. Life sciences. 2020;262:118518.
93. Chen Y, Liu L, Li J, Du Y, Wang J, Liu J. Effects of long noncoding RNA (linc-VLDLR) existing in extracellular vesicles on the occurrence and multidrug resistance of esophageal cancer cells. Pathology-Research and Practice. 2019;215(3):470-7.
94. Xue W, Shen Z, Li L, Zheng Y, Yan D, Kan Q, et al. Long non-coding RNAs MACC1-AS1 and FOXD2-AS1 mediate NSD2-induced cisplatin resistance in esophageal squamous cell carcinoma. Molecular Therapy-Nucleic Acids. 2021;23:592-602.
95. Son M, Ryu B, Je J-G, Jeon Y-J, Kim DY. Ishophloroglucin A Ameliorates VEGF-Induced Epithelial-Mesenchymal Transition via VEGFR2 Pathway Inhibition in Microgravity-Stimulated Human Retinal Pigment Epithelial Cells. Antioxidants. 2022;11(11):2212.
96. Ashrafizadeh M, Zarrabi A, Hushmandi K, Kalantari M, Mohammadinejad R, Javaheri T, et al. Association of the epithelial–mesenchymal transition (EMT) with cisplatin resistance. International journal of molecular sciences. 2020;21(11):4002.
97. Dudás J, Ladányi A, Ingruber J, Steinbichler TB, Riechelmann H. Epithelial to mesenchymal transition: a mechanism that fuels cancer radio/chemoresistance. Cells. 2020;9(2):428.
98. Tong Y, Yang L, Yu C, Zhu W, Zhou X, Xiong Y, et al. Tumor-secreted exosomal lncRNA POU3F3 promotes cisplatin resistance in ESCC by inducing fibroblast differentiation into CAFs. Molecular Therapy-Oncolytics. 2020;18:1-13.
99. Lorin S, Hamaï A, Mehrpour M, Codogno P, editors. Autophagy regulation and its role in cancer. Seminars in cancer biology; 2013: Elsevier.
100. Yang C, Shen S, Zheng X, Ye K, Ge H, Sun Y, et al. Long non-coding RNA LINC00337 induces autophagy and chemoresistance to cisplatin in esophageal squamous cell carcinoma cells via upregulation of TPX2 by recruiting E2F4. The FASEB Journal. 2020;34(5):6055-69.
101. Obermannová R, Alsina M, Cervantes A, Leong T, Lordick F, Nilsson M, et al. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. Annals of Oncology. 2022;33(10):992-1004.
102. Cummings D, Wong J, Palm R, Hoffe S, Almhanna K, Vignesh S. Epidemiology, diagnosis, staging and multimodal therapy of esophageal and gastric tumors. Cancers. 2021;13(3):582.
103. Hipp J, Nagavci B, Schmoor C, Meerpohl J, Hoeppner J, Schmucker C. Post-neoadjuvant surveillance and surgery as needed compared with post-neoadjuvant surgery on principle in multimodal treatment for esophageal cancer: a scoping review. Cancers. 2021;13(3):429.
104. Xu X-L, Zheng W-H, Zhu S-M, Zhao A, Mao W-M. The prognostic impact of lymph node involvement in large scale operable node-positive esophageal Squamous cell carcinoma patients: a 10-year experience. PloS one. 2015;10(7):e0133076.
105. Sharma U, Barwal TS, Khandelwal A, Rana MK, Rana APS, Singh K, et al. Circulating Long Non-Coding RNAs LINC00324 and LOC100507053 as Potential Liquid Biopsy Markers for Esophageal Squamous Cell Carcinoma: A Pilot Study. Frontiers in Oncology. 2022;12:823953.
106. Ghafouri-Fard S, Shoorei H, Dashti S, Branicki W, Taheri M. Expression profile of lncRNAs and miRNAs in esophageal cancer: Implications in diagnosis, prognosis, and therapeutic response. Journal of Cellular Physiology. 2020;235(12):9269-90.

107. Alaei S, Sadeghi B, Najafi A, Masoudi-Nejad A. LncRNA and mRNA integration network reconstruction reveals novel key regulators in esophageal squamous-cell carcinoma. Genomics. 2019;111(1):76-89.
108. Hou H, Meng Z, Zhao X, Ding G, Sun M, Wang W, et al. Survival of esophageal cancer in China: a pooled analysis on hospital-based studies from 2000 to 2018. Frontiers in oncology. 2019;9:548.
109. Miao Y, Sui J, Zhang Y, Yin L. Development of a novel signature of long noncoding RNAs as a prognostic biomarker for esophageal cancer. BioRxiv. 2018:441568.
110. Tang L, Chen Y, Peng X, Zhou Y, Jiang H, Wang G, et al. Identification and validation of potential pathogenic genes and prognostic markers in ESCC by integrated bioinformatics analysis. Frontiers in Genetics. 2020;11:521004.
111. Liu W, Zhang Y, Chen M, Shi L, Xu L, Zou X. A genome-wide analysis of long noncoding RNA profile identifies differentially expressed lnc RNA s associated with Esophageal cancer. Cancer Medicine. 2018;7(8):4181-9.
112. Liu H, Zhang Q, Lou Q, Zhang X, Cui Y, Wang P, et al. Differential analysis of lncRNA, miRNA and mRNA expression profiles and the prognostic value of lncRNA in esophageal cancer. Pathology & Oncology Research. 2020;26:1029-39.
113. Wang W, He X, Zheng Z, Ma X, Hu X, Wu D, et al. Serum HOTAIR as a novel diagnostic biomarker for esophageal squamous cell carcinoma. Molecular Cancer. 2017;16(1):1-5.
114. Chen FJ, Sun M, Li SQ, Wu QQ, Ji L, Liu ZL, et al. Upregulation of the long non-coding rna hotair promotes esophageal squamous cell carcinoma metastasis and poor prognosis. Molecular carcinogenesis. 2013;52(11):908-15.
115. Li X, Wu Z, Mei Q, Guo M, Fu X, Han W. Long non-coding RNA HOTAIR, a driver of malignancy, predicts negative prognosis and exhibits oncogenic activity in oesophageal squamous cell carcinoma. British journal of cancer. 2013;109(8):2266-78.
116. Wang W, Zhu Y, Li S, Chen X, Jiang G, Shen Z, et al. Long noncoding RNA MALAT1 promotes malignant development of esophageal squamous cell carcinoma by targeting β-catenin via Ezh2. Oncotarget. 2016;7(18):25668.
117. Huang C, Yu Z, Yang H, Lin Y. Increased MALAT1 expression predicts poor prognosis in esophageal cancer patients. Biomedicine & Pharmacotherapy. 2016;83:8-13.
118. Pan F, Yao J, Chen Y, Zhou C, Geng P, Mao H, et al. A novel long non-coding RNA FOXCUT and mRNA FOXC1 pair promote progression and predict poor prognosis in esophageal squamous cell carcinoma. International journal of clinical and experimental pathology. 2014;7(6):2838.
119. Wu X, Lim Z-F, Li Z, Gu L, Ma W, Zhou Q, et al. NORAD expression is associated with adverse prognosis in esophageal squamous cell carcinoma. Oncology research and treatment. 2017;40(6):370-4.
120. Chen X, Kong J, Ma Z, Gao S, Feng X. Up regulation of the long non-coding RNA NEAT1 promotes esophageal squamous cell carcinoma cell progression and correlates with poor prognosis. American journal of cancer research. 2015;5(9):2808.
121. Liang Y, Wu Y, Chen X, Zhang S, Wang K, Guan X, et al. A novel long noncoding RNA linc00460 up-regulated by CBP/P300 promotes carcinogenesis in esophageal squamous cell carcinoma. Bioscience reports. 2017;37(5):BSR20171019.
122. Shi W-h, Wu Q-q, Li S-q, Yang T-x, Liu Z-h, Tong Y-s, et al. Upregulation of the long noncoding RNA PCAT-1 correlates with advanced clinical stage and poor prognosis in esophageal squamous carcinoma. Tumor Biology. 2015;36:2501-7.

123. Liu Z, Yang T, Xu Z, Cao X. Upregulation of the long non-coding RNA BANCR correlates with tumor progression and poor prognosis in esophageal squamous cell carcinoma. Biomedicine & Pharmacotherapy. 2016;82:406-12.
124. Li J-Y, Ma X, Zhang C-B. Overexpression of long non-coding RNA UCA1 predicts a poor prognosis in patients with esophageal squamous cell carcinoma. International journal of clinical and experimental pathology. 2014;7(11):7938.
125. Wang Y-L, Bai Y, Yao W-J, Guo L, Wang Z-M. Expression of long non-coding RNA ZEB1-AS1 in esophageal squamous cell carcinoma and its correlation with tumor progression and patient survival. International journal of clinical and experimental pathology. 2015;8(9):11871.
126. Xu L-J, Yu X-J, Wei B, Hui H-X, Sun Y, Dai J, et al. Long non-coding RNA DUXAP8 regulates proliferation and invasion of esophageal squamous cell cancer. European Review for Medical & Pharmacological Sciences. 2018;22(9).
127. Xie H-W, Wu Q-Q, Zhu B, Chen F-J, Ji L, Li S-Q, et al. Long noncoding RNA SPRY4-IT1 is upregulated in esophageal squamous cell carcinoma and associated with poor prognosis. Tumor Biology. 2014;35:7743-54.
128. Jiang L, Wang W, Li G, Sun C, Ren Z, Sheng H, et al. High TUG1 expression is associated with chemotherapy resistance and poor prognosis in esophageal squamous cell carcinoma. Cancer chemotherapy and pharmacology. 2016;78:333-9.