

# Long non-coding RNA LOC541471: A novel prognostic biomarker for head and neck squamous cell carcinoma

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**Abstract.** Head and neck squamous cell carcinoma (HNSCC) is an aggressive cancer. Early detection and management of HNSCC may prevent progression of the disease. Long non-coding RNAs (lncRNAs) may serve as prognostic biomarkers for various cancer types. The current study downloaded an RNA-Seq dataset containing 43 tumor-normal pairs. An independent t-test identified that the expression level of lncRNA LOC541471 was significantly increased in tumor tissues compared with healthy tissues. Additionally, the current study demonstrated that high lncRNA LOC541471 expression was significantly associated with increasing lymph node metastasis classification and perineural invasion. A multivariate Cox regression analysis revealed that high lncRNA LOC541471 expression levels were an independent predictor for reduced overall survival (n=487) and relapse-free survival (n=355). According to the anatomic neoplasm subdivision, HNSCC samples were classified as oropharyngeal carcinoma (n=297), oral carcinoma (n=80), laryngeal carcinoma and hypopharyngeal carcinoma (n=123). A negative association was revealed between lncRNA LOC541471 expression and overall survival in all subtypes of HNSCC. Therefore, lncRNA LOC541471 is significantly negatively associated with overall survival and relapse-free survival of patients with HNSCC and may be considered a potential prognostic factor for HNSCC.

## Introduction

Long non-coding RNAs (lncRNAs) are a class of RNA molecules, longer than 200 nucleotides, with no protein-coding capacity (1,2). Previously, studies have identified that lncRNAs are aberrantly expressed in different cancer types and are closely associated with different disease processes (3,4). lncRNAs have been explored as a prognostic tumor biomarker as they can easily be detected in tissues and serum (5,6). Many lncRNAs have been identified to serve a role as prognostic biomarkers for various cancer types. Downregulation of lncRNA SDPR-AS is associated with poor prognosis in renal cell carcinoma (7). lncRNA CCAT1 promotes metastasis and is associated with poor prognosis in epithelial ovarian cancer (8). In addition, several molecular tools, including reverse transcription-quantitative polymerase chain reaction and RNA-fluorescent *in situ* hybridization, are used for examining the lncRNA expression levels in the saliva, plasma, urine, serum and tissues (5,9). Several lncRNAs, including PCA3, are routinely used in the clinic as a grade reclassification predictor in prostate cancer (10). Interest in therapeutic strategies against cancer based on lncRNAs continues to increase.

Head and neck squamous cell carcinoma (HNSCC), the sixth most common cancer worldwide, is an aggressive cancer type that has a high morbidity (11,12). Early detection and management of HNSCC may prevent progression of the disease. A previous study has demonstrated that a panel of three lncRNAs (KTN1-AS1, LINC00460 and RP5-894A10.6) may be a novel biomarker for the accurate prediction of the prognosis of patients with HNSCC (13).

In the present study, next-generation sequencing and clinical data of patients with HNSCC from The Cancer Genome Atlas (TCGA) were utilized. RNA-Sequencing (RNA-Seq) datasets for 43 paired tumor and adjacent normal tissues were downloaded from TCGA and significant differences in lncRNA expression between normal and cancer tissues were investigated. A novel lncRNA LOC541471 was revealed to be significantly upregulated in HNSCC. The lncRNA LOC541471 mRNA expression levels in various cases of HNSCC were also analyzed to evaluate its prognostic value. Overall, the potential of lncRNA LOC541471 as a biomarker and a therapeutic target in high-risk HNSCC was investigated in the current study.

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**Abbreviations:** HNSCC, head and neck squamous cell carcinoma; TCGA, The Cancer Genome Atlas; lncRNA, long non-coding RNA

**Key words:** head and neck squamous cell carcinoma, long non-coding RNA, prognostic biomarker, invasion, overall survival

Table I. The ID of 43 paired tumor and adjacent normal tissues from TCGA.

Tumor tissue ID	Normal tissue ID
TCGA-CV-6933-01	TCGA-CV-6933-11
TCGA-CV-6934-01	TCGA-CV-6934-11
TCGA-CV-6935-01	TCGA-CV-6935-11
TCGA-CV-6936-01	TCGA-CV-6936-11
TCGA-CV-6938-01	TCGA-CV-6938-11
TCGA-CV-6939-01	TCGA-CV-6939-11
TCGA-CV-6943-01	TCGA-CV-6943-11
TCGA-CV-6955-01	TCGA-CV-6955-11
TCGA-CV-6956-01	TCGA-CV-6956-11
TCGA-CV-6959-01	TCGA-CV-6959-11
TCGA-CV-6960-01	TCGA-CV-6960-11
TCGA-CV-6961-01	TCGA-CV-6961-11
TCGA-CV-6962-01	TCGA-CV-6962-11
TCGA-CV-7091-01	TCGA-CV-7091-11
TCGA-CV-7097-01	TCGA-CV-7097-11
TCGA-CV-7101-01	TCGA-CV-7101-11
TCGA-CV-7103-01	TCGA-CV-7103-11
TCGA-CV-7177-01	TCGA-CV-7177-11
TCGA-CV-7178-01	TCGA-CV-7178-11
TCGA-CV-7183-01	TCGA-CV-7183-11
TCGA-CV-7235-01	TCGA-CV-7235-11
TCGA-CV-7238-01	TCGA-CV-7238-11
TCGA-CV-7242-01	TCGA-CV-7242-11
TCGA-CV-7245-01	TCGA-CV-7245-11
TCGA-CV-7250-01	TCGA-CV-7250-11
TCGA-CV-7252-01	TCGA-CV-7252-11
TCGA-CV-7255-01	TCGA-CV-7255-11
TCGA-CV-7261-01	TCGA-CV-7261-11
TCGA-CV-7406-01	TCGA-CV-7406-11
TCGA-CV-7416-01	TCGA-CV-7416-11
TCGA-CV-7423-01	TCGA-CV-7423-11
TCGA-CV-7424-01	TCGA-CV-7424-11
TCGA-CV-7425-01	TCGA-CV-7425-11
TCGA-CV-7432-01	TCGA-CV-7432-11
TCGA-CV-7434-01	TCGA-CV-7434-11
TCGA-CV-7437-01	TCGA-CV-7437-11
TCGA-CV-7438-01	TCGA-CV-7438-11
TCGA-CV-7440-01	TCGA-CV-7440-11
TCGA-H7-A6C4-01	TCGA-H7-A6C4-11
TCGA-HD-8635-01	TCGA-HD-8635-11
TCGA-HD-A6HZ-01	TCGA-HD-A6HZ-11
TCGA-HD-A6I0-01	TCGA-HD-A6I0-11
TCGA-WA-A7GZ-01	TCGA-WA-A7GZ-11

TCGA, The Cancer Genome Atlas.

## Materials and methods

**Patients and methods.** The clinical and RNA-Seq expression data for HNSCC were obtained from TCGA (<https://tcga-data>.

Table II. Demographics and clinical characteristics of the cohort of patients with head and neck squamous cell carcinoma downloaded from The Cancer Genome Atlas (n=487).

Characteristics	Sample no, n
Sex	
Male	356
Female	131
Age	
≤60	258
>61	229
T classification	
T1-2	180
T3-4	307
N classification	
N1-2	180
N3-4	307
Clinical stage	
I-II	115
III-IV	372

T, primary tumor stage; N, lymph node metastasis.

nci.nih.gov) and the Gene Expression Omnibus (GEO) database (<http://www.ncbi.nlm.nih.gov/geo/>). To investigate differential lncRNA expression between normal and tumor tissues, the expression profile analysis was based on 43 paired tumor and adjacent normal tissues from TCGA (Table I). The RNA-Seq data were matched with clinical data and used to study expression profiles and search for lncRNAs associated with HNSCC. Prior to analysis, the HNSCC RNA expression data downloaded from TCGA were processed and normalized using the TCGA RNA-seq system (version 2,TCGA) and the Illumina HiSeq (v7) and Illumina GA microRNA (v7) sequencing platforms (Illumina, Inc., Hayward, CA, USA). A total of 511 HNSCC samples were included in the analysis of lncRNA LOC541471 and its association with clinicopathological features and patient survival. Clinical characteristics of the total HNSCC cohort used are provided in Table II. Patients were classified into two groups (high and low expression) according to the median lncRNA LOC541471 expression value. Known genes located close to LOC541471 were analyzed using the University of California, Santa Cruz (UCSC) genome browser (<http://genome.ucsc.edu>).

**Statistical analysis.** A paired Student's t-test was used to identify any significant differences in lncRNA LOC541471 expression between tumor and tumor-adjacent normal tissues according to data from TCGA and GEO, including 42 paired samples from TCGA and 24 paired samples from GEO (one sample lacked the corresponding clinical data). An independent sample t-test was used to identify significant differences in lncRNA LOC541471 expression according to data from patients with HNSCC with different lymph node metastasis (N) classification and perineural invasion. Significant differences in lncRNA LOC541471 expression between the groups

Table III. Dysregulated long non-coding RNAs identified in head and neck squamous cell carcinoma.

GeneID	Symbol	Fold-change	Style	P-value	FDR
112597	LINC00152	2.07	Up	0.0000036	0.000182
606	NBEAP1	2.06	Up	0.0002079	0.00649
440101	FLJ12825	2.06	Up	0.0000421	0.00165
29774	POM121L9P	2.05	Up	0.0000261	0.00108
400508	CRYM-AS1	2.05	Up	0.0000048	0.000236
100128191	TMPO-AS1	2.05	Up	0.0000005	0.0000307
440081	DDX12P	2.04	Up	0.0000001	0.00000747
3136	HLA-H	2.03	Up	0.0000001	0.00000747
344967	LOC344967	2.02	Up	0.0000053	0.000258
541471	LOC541471	2.02	Up	0.0000001	0.00000747
2679	GGT3P	2.00	Up	0.0009594	0.0227
10984	KCNQ1OT1	1.99	Up	0.0000067	0.000319
114043	TSPEAR-AS2	1.96	Up	0.0001926	0.00608
3139	HLA-L	1.95	Up	0.0000018	0.0000971
54718	BTN2A3P	1.94	Up	0.0000070	0.000332
145978	LINC00052	1.94	Up	0.0005988	0.0155
645166	LOC645166	1.94	Up	0.0000367	0.00146
692099	FAM86DP	0.66	Down	0.0000353	0.00113
729614	FLJ37453	0.66	Down	0.0000694	0.00204
84981	MIR22HG	0.65	Down	0.0011390	0.0251
284593	FAM41C	0.65	Down	0.0004447	0.0107
84852	ATP1A1-AS1	0.64	Down	0.0000839	0.00241
197187	SNAI3-AS1	0.64	Down	0.0005752	0.0135
400752	LINC01144	0.64	Down	0.0015342	0.0329
100093630	SNHG8	0.64	Down	0.0000012	0.000065
57061	HYMAI	0.63	Down	0.0000991	0.00279
282566	LINC00515	0.63	Down	0.0000965	0.00273
389741	GLIDR	0.63	Down	0.0000010	0.000056
653162	RPSAP9	0.63	Down	0.0000372	0.00118
114814	GNRHR2	0.62	Down	0.0000001	0.00000149
645683	RPL13AP3	0.62	Down	0.0006937	0.016
84837	ARHGAP5-AS1	0.61	Down	0.0003332	0.00826
284835	LINC00323	0.61	Down	0.0011373	0.0251
574036	SERTAD4-AS1	0.61	Down	0.0014364	0.031
100128782	LINC00476	0.61	Down	0.0000001	0.00000889
84983	FAM222A-AS1	0.6	Down	0.0002945	0.00739
387066	SNHG5	0.6	Down	0.0000029	0.000135

FDR, false discovery rate.

were presented by box plots (mean  $\pm$  standard deviation). Univariate Cox regression analysis was used to evaluate the overall survival (OS) and relapse-free survival of patients with clinical characteristics as categorical dependent variables. Furthermore, multivariate Cox analysis was employed to assess the association of lncRNA LOC541471 expression with the OS and relapse-free survival of patients together with other clinical factors, including age, sex, primary tumor stage (T), N and clinical TNM staging. Survival curves were constructed using Kaplan-Meier analysis and a log-rank test was performed to assess differences between the groups. All

data were analyzed with SPSS software (version 20.0; IBM Corp., Armonk, NY, USA)  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

*LncRNA LOC541471 upregulation in HNSCC and association with perineural invasion.* RNA-Seq datasets for 43 tumor-adjacent normal pairs were downloaded and significant differences in lncRNA expression were identified in HNSCC samples compared with healthy samples (Table III). It was revealed that

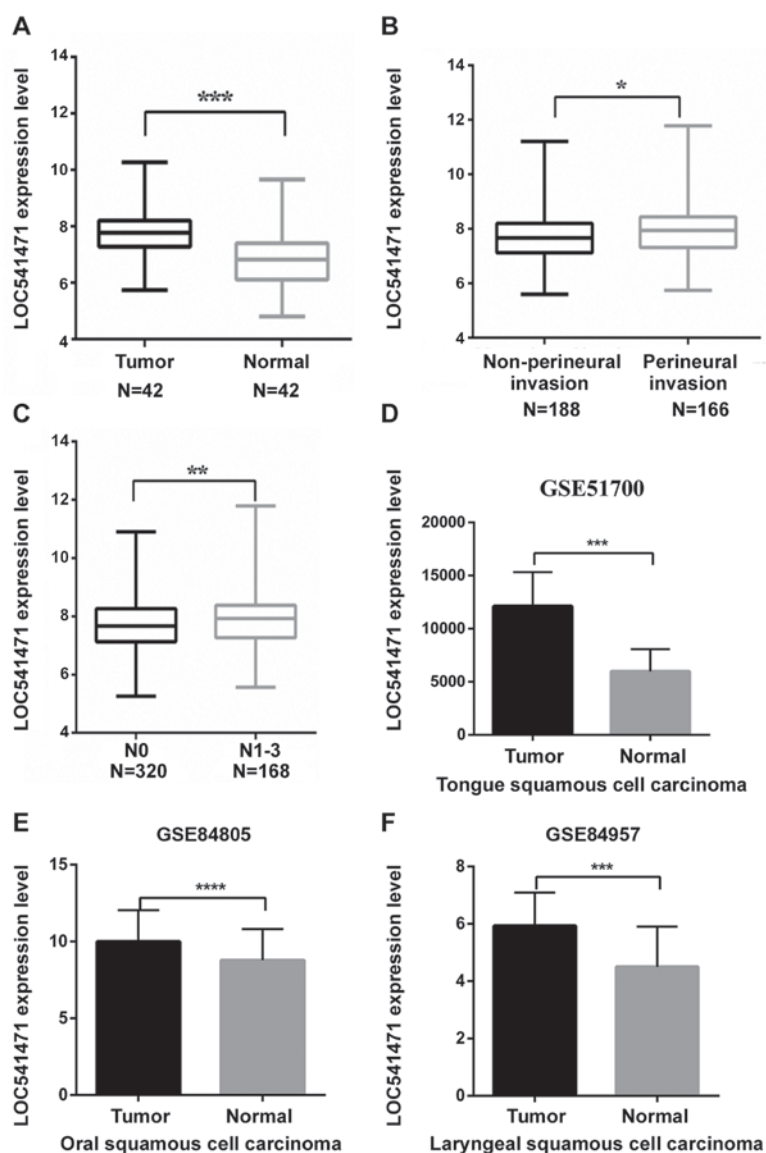


Figure 1. LncRNA LOC541471 expression in HNSCC and association with perineural invasion. (A) LncRNA LOC541471 expression was significantly higher in HNSCC tumor compared with normal tissue. (B) LncRNA LOC541471 expression was significantly higher in patients with HNSCC with perineural invasion compared with patients with no perineural invasion. (C) LncRNA LOC541471 expression was significantly higher in patients with a greater N classification. LncRNA LOC541471 was significantly higher in (D) tongue squamous cell carcinoma, (E) oral squamous cell carcinoma and (F) laryngeal squamous cell carcinoma compared with normal tissue. LncRNA, long non-coding RNA; HNSCC, head and neck squamous cell carcinoma; N, lymph node metastasis. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

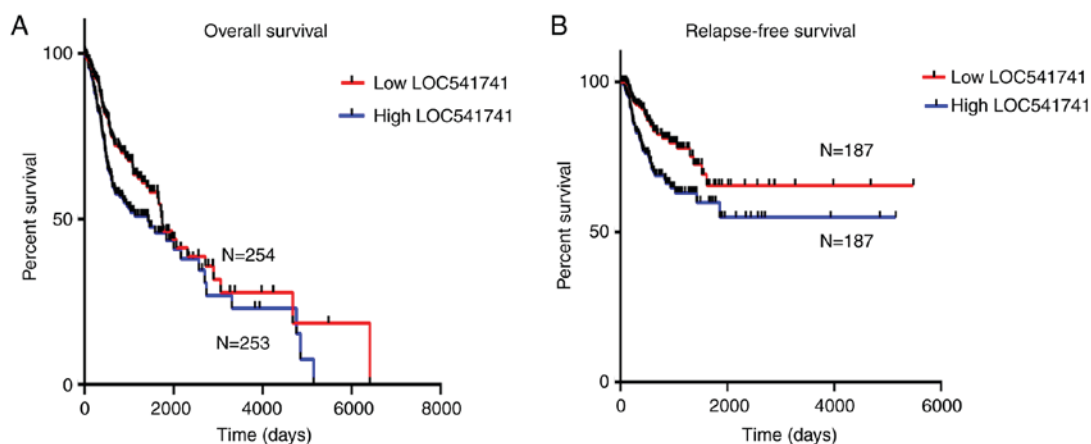


Figure 2. High lncRNA LOC541471 expression is negatively associated with the (A) overall and (B) relapse-free survival of patients with head and neck squamous cell carcinoma ( $P < 0.05$ ). LncRNA, long non-coding RNA; N, number of samples.

Table IV. Univariate and multivariate analysis of prognostic factors for overall survival using Cox proportional hazards regression model (n=487).

Variable	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI
Age				
≤60	0.722 <sup>a</sup>	0.541-0.963	0.772	0.571-1.043
>60	1		1	
Sex				
Male	0.753	0.555-1.023	0.801	0.583-1.102
Female	1		1	
Primary tumor stage				
T1-2	0.798	0.586-1.088	0.761	0.452-1.283
T3-4	1		1	
Lymph node metastasis				
N0-1	0.807	0.591-1.101	0.753	0.533-1.064
N2-3	1		1	
Clinical TNM staging				
I-II	0.835	0.590-1.180	1.159	0.624-2.152
III-IV	1		1	
LOC541471 expression level				
Low	0.677 <sup>a</sup>	0.507-0.904	0.722 <sup>a</sup>	0.539-0.968
High	1		1	

<sup>a</sup>P<0.05. HR, hazard ratio; CI, confidence interval.

lncRNA LOC541471 expression was significantly higher in the HNSCC samples compared with the adjacent healthy samples, as presented in Fig. 1A. In addition, lncRNA LOC541471 was identified to be significantly upregulated in patients with HNSCC and perineural invasion compared with patients without perineural invasion from TCGA (Fig. 1B). Furthermore, high lncRNA LOC541471 expression was significantly associated with increased N classification (Fig. 1C). Previously, studies have revealed that perineural invasion and N classification are prognostic factors for HNSCC (14,15). Therefore, the current study analyzed whether lncRNA LOC541471 may be a biomarker and potential therapeutic target for high-risk HNSCC. Following clarification, HNSCC gene expression data and corresponding clinical data were obtained from the GEO database. The results revealed that lncRNA LOC541471 was significantly upregulated in tongue squamous cell carcinoma (GSE51700, n=18), oral squamous cell carcinoma (GSE84805, n=12) and laryngeal squamous cell carcinoma (GSE84957, n=18), as presented in Fig. 1D-F, respectively.

*lncRNA LOC541471 as an independent predictor of OS and relapse-free survival of patients.* The lncRNA LOC541471 mRNA expression level was analyzed in cases of HNSCC from TCGA and evaluated for its prognostic value and potential as a prognostic biomarker for HNSCC. Kaplan-Meier survival analysis was performed according to the expression

levels of lncRNA LOC541471. The results revealed that high expression of lncRNA LOC541471 was negatively associated with poor OS of patients compared with low expression of lncRNA LOC541471 (Fig. 2A). Univariate Cox regression analysis identified that lncRNA LOC541471 expression and age significantly affected OS of patients. Meanwhile, multivariate Cox regression analysis revealed that high lncRNA LOC541471 expression may be an independent predictor for reduced OS of patients with HNSCC (Table IV). Similarly, the results indicated that high lncRNA LOC541471 expression was negatively associated with relapse-free survival of patients compared with high lncRNA LOC541471 expression (Fig. 2B). A univariate analysis and multivariate Cox regression analysis also identified that high lncRNA LOC541471 expression may be an independent predictor for reduced relapse-free survival (Table V). These results indicate that lncRNA LOC541471 may be an independent predictor for OS and relapse-free survival of patients with HNSCC.

*Significant association of lncRNA LOC541471 with patient survival in subtypes of HNSCC.* According to the anatomic neoplasm subdivision, 500 HNSCC samples from TCGA were classified as oropharyngeal, oral, laryngeal and hypopharyngeal carcinomas. On the basis of lncRNA LOC541471 expression levels, Kaplan-Meier survival analysis was performed for each subtype. The results revealed that high

Table V. Univariate and multivariate analysis of prognostic factors for relapse-free survival using Cox proportional hazards regression model (n=355).

Variable	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI
Age				
≤60	0.937	0.604-1.454	0.974	0.617-1.536
>60	1		1	
Sex				
Male	1.026	0.619-1.703	1.075	0.637-1.814
Female	1		1	
Primary tumor stage				
T1-2	0.956	0.603-1.518	0.836	0.425-1.642
T3-4	1		1	
Lymph node metastasis				
N0-1	0.685	0.437-1.072	0.626	0.375-1.047
N2-3	1		1	
Clinical TNM staging				
I-II	1	0.585-1.712	1.462	0.620-3.447
III-IV	1		1	
LOC541471 expression level				
Low	0.563 <sup>a</sup>	0.360-0.881	0.574 <sup>a</sup>	0.365-0.904
High	1		1	

<sup>a</sup>P<0.05. HR, hazard ratio; CI, confidence interval.

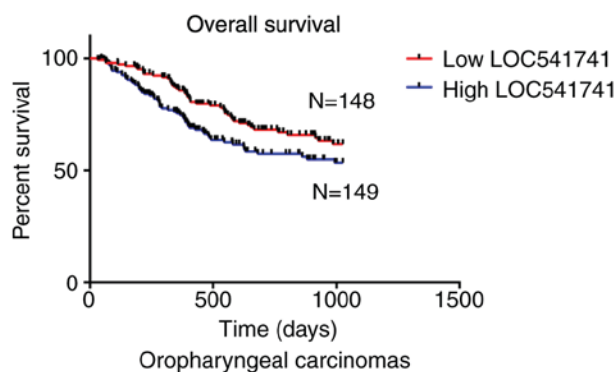


Figure 3. Negative association between high lncRNA LOC541471 expression and overall survival of patients with oropharyngeal carcinomas (P<0.05). LncRNA, long non-coding RNA; N, number of samples.

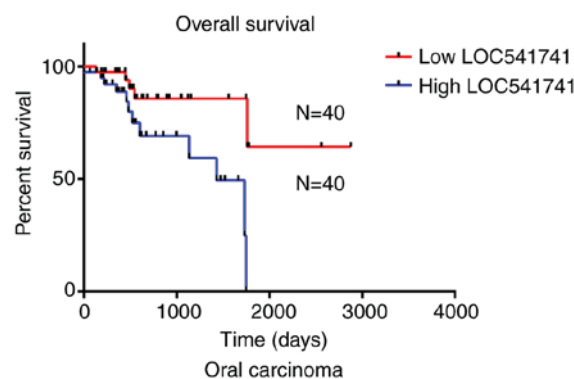


Figure 4. Negative association between high lncRNA LOC541471 expression and overall survival of patients with oral carcinoma (P<0.05). LncRNA, long non-coding RNA; N, number of samples.

lncRNA LOC541471 expression was associated with poor OS compared with low lncRNA LOC541471 expression for all classified subtypes of HNSCC (Figs. 3-5).

## Discussion

Recent studies have revealed that up to 70% of the mammalian transcriptome is transcribed into lncRNAs, while coding transcripts only account for 2% of the genome (16,17). Previously, lncRNAs have been regarded as nonfunctional transcripts

due to uncertainty of their function (17,18). However, recent studies have identified that lncRNAs serve an important role in tumor initiation and progression (19,20). In addition, previous studies have revealed that lncRNAs serve as vital participants in tumor cell proliferation, differentiation and apoptosis (9,21). Furthermore, lncRNAs exhibit structural stereospecificity and tissue selectivity (5,22). Therefore, dysregulated expression of lncRNAs has been identified as a biological marker in various cancer types. The lncRNAs, MALAT-1 and thymosin  $\beta$ -4, predict metastasis and survival in early-stage non-small cell

Table VI. A selection of known genes located close to LOC541741.

Ensembl_Gene_ID	Gene symbol	Gene_biotype
ENSG00000256671	LIMS4	protein_coding
ENSG00000183054	RGPD6	protein_coding
ENSG00000169679	BUB1	protein_coding
ENSG00000153093	ACOXL	protein_coding
ENSG00000153094	BCL2L11	protein_coding
ENSG00000153107	ANAPC1	protein_coding
ENSG00000153208	MERTK	protein_coding
ENSG00000153214	TMEM87B	protein_coding
ENSG00000144152	FBLN7	protein_coding
ENSG00000144161	ZC3H8	protein_coding
ENSG00000235881	AC114776.1	lincRNA
ENSG00000236330	RPL5P9	processed_pseudogene
ENSG00000204581	ACOXL-AS1	antisense_RNA
ENSG00000230499	AC108463.2	lincRNA
ENSG00000263881	MIR4436B2	miRNA
ENSG00000266139	MIR4435-2	miRNA
ENSG00000266063	MIR4771-2	miRNA

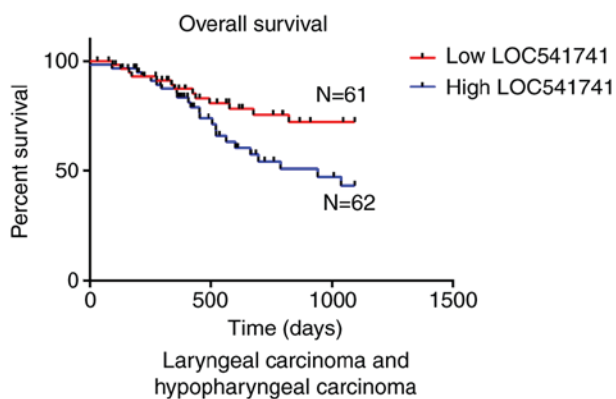


Figure 5. Negative association between high lncRNA LOC541741 expression and overall survival of patients with laryngeal carcinoma and hypopharyngeal carcinoma ( $P < 0.05$ ). lncRNA, long non-coding RNA; N, number of samples.

lung cancer (23). The current study demonstrated that lncRNA LOC541741 expression was upregulated in tumor tissues and positively associated with increasing N classification and perineural invasion in patients with HNSCC. Previously, studies have revealed that perineural invasion and N classification are prognostic factors for HNSCC (15,24). Therefore, the current study analyzed the potential of lncRNA LOC541741 as a prognostic biomarker for HNSCC.

To further validate the hypothesis that lncRNA LOC541741 is a prognostic biomarker for HNSCC, clinical characteristics were downloaded from TCGA and analyzed. It was revealed that upregulation of lncRNA LOC541741 was associated with poor OS and poor relapse-free survival of patients. In addition, a multivariate Cox regression analysis revealed that lncRNA LOC541741 expression levels may be an independent predictor for the OS and relapse-free survival of patients. To determine

whether lncRNA LOC541741 has similar prognostic potential in various subtypes of HNSCC, a total of 500 samples were classified as oropharyngeal, oral, laryngeal and hypopharyngeal. It was identified that upregulation of lncRNA LOC541741 was associated with poor survival outcomes in all subtypes of HNSCC studied. Therefore, it is proposed that lncRNA LOC541741 may have sufficient reliability and validity to serve as a prognostic biomarker for HNSCC.

The current study has indicated that LOC541741 may be considered an unfavorable prognostic factor for HNSCC. However, the specific mechanism by which LOC541741 participates in HNSCC development requires further investigation. Notably, lncRNAs can target RNA-binding proteins (RBPs) or competing endogenous RNA (ceRNA) (25). In future studies, the specific function of LOC541741, including targeting RBPs or ceRNA, may be investigated *in vitro* or *in vivo*. Identifying known genes located close to lncRNA could provide a basis for understanding its mechanism (26). Therefore, known genes located close to LOC541741 were analyzed using the University of California, Santa Cruz (UCSC) genome browser (<http://genome.ucsc.edu>). A selection of these analysis results is provided in Table VI. Several of these genes have previously been identified to be associated with tumors. Low budding uninhibited by benzimidazoles 1 (BUB1) expression is an adverse prognostic marker in gastric adenocarcinoma. Tumors with low BUB1 expression have been associated with larger tumor size (27). Bcl-2-like protein 11 belongs to the Bcl-2 family, and acts as a central regulator of the intrinsic apoptotic cascade and mediates cell apoptosis (28). Proto-oncogene tyrosine-protein kinase MER inhibition combined with radiation therapy has a therapeutic effect in a subset of glioblastoma (29).

The current study preliminarily concludes that lncRNA LOC541741 is significantly associated with OS and relapse-free survival of patients and may be considered a

potential unfavorable prognostic factor for HNSCC. However, information regarding the function of lncRNA LOC541471 is limited. Therefore, further studies are necessary to determine the involvement of lncRNA LOC541471 in mediating tumor biology.

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## Availability of data and materials

All the data and materials used in the present study are freely accessible in GEO (<https://www.ncbi.nlm.nih.gov/geo/>) and TCGA (<https://cancergenome.nih.gov/>).

## Authors' contributions

HW performed the statistical analysis and wrote the manuscript. DY performed the statistical analysis. MW and TH designed the research, collected the data, and submitted the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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