Prognostic significance of the long noncoding RNAs in nasopharyngeal carcinoma: a systematic review and meta-analysis

Background and objective: Nasopharyngeal carcinoma (NPC) is a common head and neck malignancy. Despite recent advances in treatment, the prognosis, particularly for those at the advanced stages, remains poor. Moreover, the underlying genetic and molecular events have remained obscure so far. Recently, increasing evidence has demonstrated that long noncoding RNAs (lncRNAs) could act as either oncogenes or tumor suppressor genes in various cancers depending on their targets. And some lncRNAs have been shown to be aberrantly expressed in NPC. In this meta-analysis, we try to elucidate the possible role of lncRNAs and their expression on prognosis in NPC.

Methods: We searched the databases of PubMed, Embase, and Web of Science for relevant articles ranging from January 2000 to December 2017. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were used to evaluate the prognostic value of lncRNAs in NPC. Odds ratios (ORs) were used to assess the association between lncRNAs and clinicopathological characteristics.

Results: A total of 14 eligible publications including 14 on prognosis and eight on clinicopathological characteristics were identified. Our results demonstrated that the high expression of lncRNAs was related to poor overall survival (OS; HR = 1.55; 95% CI = 1.01, 2.40; \(P = 0.05\)) and disease-free survival (DFS; HR = 1.83; 95% CI = 1.07, 3.13; \(P = 0.03\)) of NPC. Moreover, the expression of lncRNAs was correlated with male gender (OR = 1.42; 95% CI = 1.05, 1.91; \(P = 0.02\)), lymph node status (OR = 2.20; 95% CI = 1.29, 3.73; \(P = 0.004\)), and tumor node metastasis (TNM) clinical stage (OR = 2.55; 95% CI = 1.12, 5.78; \(P = 0.03\)).

Conclusion: This meta-analysis shows that the level of expression of lncRNAs may be a potential prognostic indicator in NPC.

Keywords: long noncoding RNAs, nasopharyngeal carcinoma, prognosis, overall survival, meta-analysis

Introduction

Nasopharyngeal carcinoma (NPC) is a distinctive type of head and neck cancer and originates from nasopharyngeal epithelial cells. Although rarely occurring worldwide, the incidence and mortality rates of this tumor are remarkably high among Southeast Asia and Southern China. The distinct geographical distribution highlights the significance of several etiologic factors in NPC tumorigenesis, including Epstein–Barr virus (EBV) infection, genetic predisposition, and intake of preserved food. The World Health Organization (WHO) recognizes the following three histological patterns: type I, keratinizing squamous-cell carcinoma; type II, differentiated nonkeratinizing carcinoma; and type III, undifferentiated carcinoma; the nonkeratinizing subtypes constitute...
most cases.\(^3\) However, the understanding of the development of NPC is still unclear. Local recurrence and metastasis to cervical lymph nodes are the main cause of mortality in NPC. During the last decades, the outcome of the treatment has improved considerably. Concurrent chemoradiotherapy has become the choice of treatment for advanced NPC.\(^4\)

Patients with NPC often do not show specific symptoms in the early stage, and when first diagnosed, most of them have stepped into advanced stage. So far, the clinical tumor node metastasis (TNM) staging system is the most commonly used predictor of prognosis for NPC patients; what is troubling, the prognosis often varies even at the same stage. Therefore, more specific and sensitive prognostic indicators need to be discovered and applied for the early diagnosis and individualized treatment for NPC patients.

Previous studies have found that long noncoding RNAs (lncRNAs) are extensively transcribed from genomes. They have been shown to play a role in carcinogenesis and cancer progression by modulating the expression of many oncogenes or tumor suppressor genes.\(^5,7\) However, there are limited studies on lncRNAs in human NPC and the expression and function of lncRNAs in NPC remain uncovered. lncRNAs, >200 nucleotides (nts), with limited capacity of protein coding,\(^8,9\) were considered transcriptional “noisy” or “junk”. Now, increasing evidence has demonstrated that these lncRNAs are junk no more, and in contrast, these lncRNAs have important biological functions in transcriptional regulation, epigenetic gene regulation, and disease.\(^8-12\) Due to their essential role at every level of gene expression, lncRNAs have attracted major attention as molecules with structural and functional roles in various physiological processes, including development, differentiation, and metabolism.\(^13,14\) Nevertheless, functional roles of the majority of these molecules remain to be identified.

To date, several studies have shown that a number of lncRNAs are involved in the development and progression of NPC, including HOTAIR, MALAT1, NEAT1, HNF1A-AS, AFAP1-AS1, and LINC00312.\(^15-20\) He et al\(^21\) summarized the different types of associated lncRNAs and their functional mechanisms in the development of NPC, and lncRNA was considered as a novel biomarker for the clinical diagnosis and treatment of NPC. Many studies had already evaluated the role of lncRNAs in NPC for prognosis; however, the small number of studies, limited number of lncRNAs, and paucity of multivariate analyses are the limitations; hence, this meta-analysis aims to comprehensively assess the value of lncRNAs both in the prognosis and clinical outcomes for patients with NPC.

Methods
Publication search strategy
PubMed, Embase, and Web of Science were searched for relevant literature published from January 2000 to December 2017. We mainly focused on “lncRNA”, “nasopharyngeal”, and “carcinoma”, and the specific search strategy was as follows: “long non-coding RNA”, “lncRNA”, “lincRNA”, “long intergenic non-coding RNA”, “long untranslated RNA” and “NPC”, “nasopharyngeal carcinoma”, “nasopharyngeal neoplasm”, “nasopharyngeal cancer”. Studies explored the expression level of lncRNAs in different data set were considered to be different studies.

Inclusion and exclusion criteria
In this meta-analysis, the inclusion criteria for the eligible studies were as follows: 1) diagnosed with NPC; 2) analyzed the association between lncRNAs and NPC; 3) prognostic values such as overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) were investigated; 4) usable and sufficient published data were provided to calculate hazard ratios (HRs) and 95% confidence intervals (CIs); and 5) more complete and updated studies and data are preferred. Exclusion criteria were as follows: 1) no usable or insufficient data; 2) case reports, reviews, letters, and conference abstracts; and 3) animal experiments and Chinese literature.

Data extraction
Three of us (HuanHuan Guo, Shuo Huang, and Shuang Li) extracted the provided data including author, publication year, lncRNAs and their biotypes, methods, case number, outcomes, cut-off value, and follow-up months. The HRs and 95% CIs for survival analysis were obtained from the articles if available, and for studies that did not provide OS, DFS, or RFS directly, we also digitized and extracted the data from the given Kaplan–Meier survival curves using the Engauge Digitizer version 4.1.\(^22\)

Statistical analysis
The relation between lncRNAs and prognosis in NPC was evaluated by the calculated HRs and 95% CIs. \(HR > 1\) implied a worse survival for the group with increased lncRNAs expression. Conversely, \(HR < 1\) implied a better survival for the group with increased lncRNAs expression. Meanwhile, the association between lncRNAs and clinicopathological characteristics (including gender, histological classification, tumor classification, lymph node status, metastasis, and
TNM clinical stage) were assessed by odds ratios (ORs) and 95% CIs. RevMan 5.2 software (RevMan; Cochrane Collaboration, Copenhagen, Denmark) was used to perform this meta-analysis, and the heterogeneity within studies was evaluated by Cochrane's $Q$ and $I^2$ tests. When heterogeneity was observed ($I^2 \leq 50\%$ and $P > 0.1$), the fixed-effect model was applied, otherwise, only the random-effect model was applied to calculate the pooled HRs or ORs. We evaluated the sensitivity and publication bias of the included articles by the Stata12.0 Software (StataCorp LP, College Station, TX, USA), and publication bias was evaluated by Begg’s rank correlation method and Egger's weighted regression method. $P<0.05$ was considered statistically significant.

**Results**

**Study characteristics**

We searched 219 publications in the databases including 70 in PubMed, 61 in Embase, and 88 in Web of Science, and the flowchart of the literature review is shown in Figure 1. A total of 104 duplicated publications were removed, then 41 articles...
were excluded after screening the titles and abstracts, and 55 articles were removed for no usable data. After reviewing the studies, five articles were eliminated for their biotypes (Table S1). As a result, 14 articles were included in this systematic review and meta-analysis.16–19,24–33

The main characteristics of the included 14 studies are summarized in Table 1, and the biotypes of different lncRNAs according to the Ensembl are shown later. Eight studies analyzed the association between the expression of lncRNAs and gender.16–19,24,25,28,29 Two studies indicated that lncRNAs were related to histological classification.17,24 Eight studies were on tumor classification.16–19,24,25,28,29 Seven studies were about lymph node status.16–19,24,25,28,29 Eight studies referred to the metastasis,16–19,24,25,28,29 and eight studies reported that lncRNAs were significantly correlated with TNM clinical stage (Table 2).16–19,24,25,28,29

### Prognosis

Among the included studies, 14 studies performed the correlation between lncRNAs and OS.16–19,24–33 HRs and 95% CIs were extracted or calculated by the provided data in these studies. The expression of lncRNAs was related to OS in NPC (HR =1.55; 95% CI =1.01, 2.40; P=0.05, random-effect) (Figure 2A). From the forest plot, we found that the high level of AFAP1-AS1, HULC, MALAT1, LINC00460, PCAT7, HOTAIR, EWSAT1, XIST, CASC9, and ANRIL was correlated with poor prognosis, whereas the low level of NEAT1 and LET was correlated with poor prognosis in NPC.

Only two studies explored that the level of lncRNAs was associated with DFS in patients with NPC.17,28 The elevated level of HOATIR and ANRIL indicated a relatively poor prognosis. And the enrolled studies showed the correlation between the increased expression of lncRNAs and DFS in

| Author | Year | lncRNAs | Biotype (Ensembl)/length (bp) | Method | Case number (high/low) | Outcome | Cut-off | Follow-up months |
|--------|------|---------|-------------------------------|--------|-----------------------|---------|--------|-----------------|
| Nie et al17 | 2013 | HOTAIR | Antisense RNA/2421 | qRT-PCR and ISH | 91/69 | OS, DFS, and RFS | SI =6 | Median of 69 |
| Bo et al18 | 2015 | AFAP1-AS1 | Antisense RNA/6795 | qRT-PCR and ISH | 23/55 | OS and RFS | 1.5-Fold | 120 |
| Sun et al18 | 2015 | LET | Sense intronic/2283 | qRT-PCR | 34/34 | OS and RFS | Median | 100 |
| Jin et al19 | 2016 | MALAT1 | lincRNA/8708 | qRT-PCR and ISH | 66/66 | OS | SI =6 | 60 |
| Lu et al19 | 2016 | NEAT1 | lincRNA/22743 | qRT-PCR and ISH | 66/66 | OS | SI =6 | 60 |
| Song et al20 | 2016 | XIST | lincRNA/19275 | qRT-PCR | 76/32 | OS | 2.31-Fold | 140 |
| Song and Yin20 | 2016 | EWSAT1 | lincRNA/2498 | qRT-PCR | 76/32 | OS | 2.36-Fold | 140 |
| Zou et al21 | 2016 | ANRIL | Antisense RNA/3835 | qRT-PCR | 44/44 | OS and DFS | Median | 100 |
| Jiang and Liu21 | 2017 | HULC | lincRNA/556 | qRT-PCR | 78/42 | OS | 2.5-Fold | 50 |
| Liu22 | 2017 | PCAT7 | Retained intron/1164 | qRT-PCR | 38/12 | OS | NA | 140 |
| Su et al23 | 2017 | CASC9 | lincRNA/1164 | qRT-PCR | 45/45 | OS | 2.5-Fold | 60 |
| Tang et al23 | 2017 | AFAP1-AS1 | Antisense RNA/6795 | qRT-PCR and ISH | 68/28 | OS | NA | 120 |
| Wang et al23 | 2017 | NEAT1 | lincRNA/22743 | qRT-PCR and AM | 39/31 | OS | 2-Fold | 50 |
| Kong et al24 | 2018 | LINC00460 | lincRNA/739 | qRT-PCR | 25/25 | OS | Median | 140 |

**Table 1 Characteristics of studies included in this meta-analysis**

**Table 2 Correlation between high expression of lncRNAs and clinicopathological characteristics of patients with NPC**

**Characteristics** | **Studies** | **Case number** | **Pooled OR (95% CI)** | **P** | **Heterogeneity** | **P (%)** | **P** |
|-------------------|-------------|----------------|------------------------|-----|------------------|--------|-----|
| Gender (male/female) | 8 | 470 | 1.42 (1.05, 1.91) | 0.02 | 0 | 0.54 |
| Histological classification (WHO type II/III) | 2 | 106 | 0.91 (0.39, 2.13) | 0.82 | NA | NA |
| T classification (T1–T2/T3–T4) | 8 | 455 | 1.33 (0.69, 2.56) | 0.39 | 80 | <0.00001 |
| N classification (NO–NI/N2–N3) | 7 | 447 | 2.20 (1.29, 3.73) | 0.004 | 67 | 0.005 |
| Metastasis (no/yes) | 8 | 499 | 1.41 (0.69, 2.87) | 0.34 | 74 | 0.0004 |
| TNM clinical stage (I–II/III–IV) | 8 | 497 | 2.55 (1.12, 5.78) | 0.03 | 85 | <0.00001 |

**Abbreviations:** OR, odds ratio; CI, confidence interval; lncRNAs, long noncoding RNAs; NA, not applicable; NPC, nasopharyngeal carcinoma; OS, overall survival; qRT-PCR, quantitative real time polymerase chain reaction; RFS, recurrence-free survival; SI, staining index.

**Abbreviations:** CI, confidence interval; lncRNAs, long noncoding RNAs; NA, not applicable; NPC, nasopharyngeal carcinoma; OR, odds ratio; TNM, tumor node metastasis; WHO, World Health Organization.
NPC (HR = 1.83; 95% CI = 1.07, 3.13; P = 0.03, fixed-effect) (Figure 2B).

And three studies showed that lncRNAs’ expression was associated with the RFS in NPC (HR = 1.61; 95% CI = 0.67, 3.84; P = 0.28, random-effect) (Figure 2C). The high expression of AFAP1-AS1 and HOTAIR predicted a shorter RFS time, while the high expression of LET demonstrated a better outcome.

With only one or two studies included in this meta-analysis, with maybe the exception of NEAT1 (Figure 3), the analysis may be considered inadequate and this may be of limited practicability and should be elaborated prudently; furthermore, comprehensive and larger sample size studies are required to be validated.

Due to the expression of IncRNAs that varies in NPC and the disease-free survival in NPC, the high expression as shown earlier, some may be definitely be correlated with reduced survival; thus, we performed the subgroup analyses (Figure 4). The upregulated IncRNAs were divided into two groups according to helpful and the disease-free survival in NPC. On the other hand, some may be definitely be correlated with reduced survival; thus, we performed the subgroup analyses (Figure 4). The upregulated IncRNAs were divided into two groups according to helpful

### Table A

| Study or subgroup | log (Hazard ratio) | SE | Weight (%) | Hazard ratio IV, random, 95% CI | Hazard ratio IV, random, 95% CI |
|-------------------|--------------------|----|------------|---------------------------------|---------------------------------|
| Bo et al (2015)24 (AFAP1-AS1) | 1.7029 | 1.2541 | 2.6 | 5.49 (0.47, 64.13) | 5.49 (0.47, 64.13) |
| Jiang and Liu (2017)29 (HULC) | 0.9042 | 0.5443 | 7.8 | 2.47 (0.85, 7.18) | 2.47 (0.85, 7.18) |
| Jin et al (2016)16 (MALAT1) | 1.0818 | 0.4547 | 9.1 | 2.95 (1.21, 7.19) | 2.95 (1.21, 7.19) |
| Kong et al (2018)23 (LINC00460) | 0.4447 | 0.6231 | 6.8 | 1.56 (0.46, 5.29) | 1.56 (0.46, 5.29) |
| Liu et al (2017)21 (PCAT7) | 0.1222 | 0.8122 | 4.9 | 1.13 (0.23, 5.55) | 1.13 (0.23, 5.55) |
| Lu et al (2016)19 (NEAT1) | 0.9943 | 0.3968 | 10.0 | 0.37 (0.17, 0.81) | 0.37 (0.17, 0.81) |
| Nie et al (2013)17 (HOTAIR) | 0.5933 | 0.3565 | 10.6 | 1.81 (0.90, 3.64) | 1.81 (0.90, 3.64) |
| Song and Yin (2016)27 (EWSAT1) | 0.5653 | 0.4023 | 9.9 | 1.76 (0.80, 3.87) | 1.76 (0.80, 3.87) |
| Song et al (2016)26 (XIST) | 0.7514 | 0.415 | 9.7 | 2.12 (0.94, 4.78) | 2.12 (0.94, 4.78) |
| Sun et al (2017)30 (CASC9) | 1.5994 | 0.5133 | 8.2 | 4.59 (1.91, 13.54) | 4.59 (1.91, 13.54) |
| Sun et al (2015)25 (LET) | 0.5978 | 0.5991 | 7.1 | 0.55 (0.17, 1.78) | 0.55 (0.17, 1.78) |
| Tang et al (2017)10 (AFAP1-AS1) | 0.4824 | 0.9743 | 3.8 | 1.62 (0.24, 1.09) | 1.62 (0.24, 1.09) |
| Wang et al (2017)32 (NEAT1) | 0.5276 | 0.6658 | 6.3 | 0.59 (0.16, 2.18) | 0.59 (0.16, 2.18) |
| Zou et al (2016)28 (ANRIL) | 0.7747 | 1.0633 | 3.4 | 2.17 (0.27, 17.44) | 2.17 (0.27, 17.44) |

Total (95% CI) 100.0 1.55 (1.01, 2.40)

Heterogeneity: $\chi^2 = 0.34; \chi^2 = 28.10, df = 13 (P = 0.009); I^2 = 54$

Test for overall effect: $Z = 1.99 (P = 0.05)$

### Table B

| Study or subgroup | log (Hazard ratio) | SE | Weight (%) | Hazard ratio IV, random, 95% CI | Hazard ratio IV, random, 95% CI |
|-------------------|--------------------|----|------------|---------------------------------|---------------------------------|
| Nie et al (2013)17 (HOTAIR) | 0.5306 | 0.3078 | 79.4 | 1.70 (0.93, 3.11) | 1.70 (0.93, 3.11) |
| Zou et al (2016)28 (ANRIL) | 0.8838 | 0.6045 | 20.6 | 2.42 (0.74, 7.91) | 2.42 (0.74, 7.91) |

Total (95% CI) 100.0 1.83 (1.07, 3.13)

Heterogeneity: $\chi^2 = 0.27; \chi^2 = 1 (P = 0.60); I^2 = 0$

Test for overall effect: $Z = 2.20 (P = 0.03)$

### Table C

| Study or subgroup | log (Hazard ratio) | SE | Weight (%) | Hazard ratio IV, random, 95% CI | Hazard ratio IV, random, 95% CI |
|-------------------|--------------------|----|------------|---------------------------------|---------------------------------|
| Bo et al (2015)24 (AFAP1-AS1) | 1.3002 | 0.4332 | 33.4 | 3.67 (1.57, 8.58) | 3.67 (1.57, 8.58) |
| Nie et al (2013)17 (HOTAIR) | 0.4318 | 0.3216 | 39.0 | 1.54 (0.82, 2.89) | 1.54 (0.82, 2.89) |
| Sun et al (2015)25 (LET) | 0.462 | 0.5605 | 27.5 | 0.63 (0.21, 1.89) | 0.63 (0.21, 1.89) |

Total (95% CI) 100.0 1.61 (0.67, 3.84)

Heterogeneity: $\chi^2 = 0.40; \chi^2 = 6.39, df = 2 (P = 0.04); I^2 = 69$

Test for overall effect: $Z = 1.07 (P = 0.28)$

### Figure 2

- **A** Forest plot of studies evaluating HRs of lncRNAs’ expression and the overall survival in NPC.
- **B** Forest plot of studies evaluating HRs of lncRNAs’ expression and the recurrence-free survival in NPC.
- **C** Forest plot of studies evaluating HRs of lncRNAs’ expression and the disease-free survival in NPC.

**Abbreviations:** CI, confidence interval; HRs, hazard ratios; lncRNAs, long noncoding RNAs; NPC, nasopharyngeal carcinoma.
for prognosis and harmful to prognosis (Figure 4A). And we also divided the included studies into three subgroups based on the biotypes of lncRNAs in the Ensembl database (Figure 4B). As shown in the forest plots, the heterogeneity has been reduced to some extent in several subgroups, but the total heterogeneity still cannot be ignored. Due to the small sample sizes of the included studies, we did not perform meta-regression.

**Correlation between the expression of lncRNAs and clinicopathological characteristics in NPC**

Table 2 summarizes the association between the expression levels of lncRNAs and clinicopathological characteristics of NPC patients. ORs > 1 implied that elevated expression of lncRNAs might be more susceptible to the characteristic. And the analysis indicated that the increased expression of lncRNAs was correlated with gender (OR = 1.42; 95% CI = 1.05, 1.91; P = 0.02, fixed-effect), lymph node status (OR = 2.20; 95% CI = 1.29, 3.73; P = 0.004, random-effect), and TNM clinical stage (OR = 2.55; 95% CI = 1.12, 5.78; P = 0.03, random-effect) (Figure S1). Unfortunately, there was no correlation with histological classification (OR = 0.91; 95% CI = 0.39, 2.13; P = 0.82, fixed-effect), tumor classification (OR = 1.33; 95% CI = 0.69, 2.56; P = 0.39, random-effect), and metastasis (OR = 1.41; 95% CI = 0.69, 2.87; P = 0.34, random-effect) (Figure S2). As shown earlier, a significant heterogeneity was observed among tumor classification (I² = 80%), lymph node status (I² = 67%), metastasis (I² = 74%), and TNM clinical stage (I² = 85%). We suspected that the main causes of the significant heterogeneity in this analysis were the different cut-off definitions of the expression and the different roles of the lncRNAs in different studies. And we did not perform subgroup analysis due to the limited number of the enrolled studies, and further studies should be conducted to verify this conclusion.

**Publication bias and sensitivity analysis**

Begg’s funnel plot and Egger’s test were performed to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (Figure 5) and all the values of I² = 0%. Egger’s test also showed that there was no statistical significance for the evaluation of publication bias (Figure S3; OS: P = 0.732, RFS: P = 0.900; gender: P = 0.294, tumor classification: P = 0.679, lymph node status: P = 0.878, metastasis: P = 0.811, and TNM stage: P = 0.826).

Sensitivity analysis, after removing one study at a time, was performed to evaluate the stability of the result. We found little change in the estimated results (Figure 6), indicating that our results were statistically robust.

**Discussion**

In the patients with NPC, many factors including stage of disease, nodal involvement, distant metastasis, histopathologic type, tumor volume, age, and parapharyngeal extension have been evaluated as potential prognostic indicators. In recent years, the searches for novel prognostic factors that more
Test for subgroup differences:

Subtotal (95% CI)

Bad for OS

Bo et al (2015)24 (AFAP1-AS1) 1.7029 1.2541 2.6 5.49 (0.47, 64.13)
Jiang and Liu (2017)29 (HULC) 0.9042 0.5443 7.8 2.47 (0.85, 7.18)
Jin et al (2016)16 (MALAT1) 1.0818 0.4547 9.1 2.95 (1.21, 7.19)
Kong et al (2016)35 (LINC00460) 0.4447 0.6231 6.8 1.56 (0.46, 5.20)
Liu et al (2017)30 (PCAT7) 0.1222 0.8122 4.9 1.13 (0.23, 5.55)
Nie et al (2013)37 (HOTAIR) 0.5933 0.3565 10.6 1.81 (0.90, 3.64)
Song and Yin (2016)27 (EWSAT1) 0.5653 0.4023 9.9 1.76 (0.80, 3.87)
Song et al (2016)31 (XIST) 0.7514 0.415 9.7 2.12 (0.94, 4.78)
Su et al (2017)26 (CASC9) 1.5994 0.5133 8.2 4.95 (1.81, 13.54)
Tang et al (2017)35 (AFAP1-AS1) 0.4824 0.9743 3.8 1.62 (0.24, 10.94)
Zou et al (2016)30 (ANRIL) 0.7747 1.0633 3.4 2.17 (0.27, 17.44)

Subtotal (95% CI) 76.7 2.21 (1.61, 3.03)

Heterogeneity: $\chi^2 = 0.00; \phi^2 = 0.00; df = 10 (P = 0.88); I^2 = 0$

Test for overall effect: $Z = 4.91 (P < 0.00001)$

Good for OS

Song et al (2016)26 (XIST) 0.7514 0.415 9.7 2.12 (0.94, 4.78)
Su et al (2017)26 (CASC9) 1.5994 0.5133 8.2 4.95 (1.81, 13.54)
Zou et al (2016)30 (ANRIL) 0.7747 1.0633 3.4 2.17 (0.27, 17.44)

Subtotal (95% CI) 76.7 2.21 (1.61, 3.03)

Heterogeneity: $\chi^2 = 0.00; \phi^2 = 0.00; df = 10 (P = 0.88); I^2 = 0$

Test for overall effect: $Z = 4.91 (P < 0.00001)$

Figure 4 Forest plots of studies evaluating HRs of upregulated lncRNAs and the OS of NPC patients.

Notes: (A) Subgroup outcome and (B) subgroup biotype.

Abbreviations: CI, confidence interval; HRs, hazard ratios; lincRNA, long intergenic noncoding RNA; lncRNAs, long noncoding RNAs; OS, overall survival; NPC, nasopharyngeal carcinoma.
Figure 5 Begg's test for publication bias.

Notes: (A) Overall survival, (B) disease-free survival, (C) recurrence-free survival, (D) gender, (E) tumor classification, (F) lymph node status, (G) metastasis, and (H) TNM stage.

Abbreviations: HR, hazard ratio; TNM, tumor node metastasis; ES, effect size; SE, standard error.
## Prognostic significance of the lncRNAs in NPC

### Meta-analysis estimates, given named study is omitted

| Study       | Lower CI limit | Estimate | Upper CI limit |
|-------------|----------------|----------|----------------|
| Bo et al (2015)AFAP1-AS1 | -0.09 | 0.01 | 0.44 | 0.67 | 0.96 |
| Jiang and Liu (2017)HULC | -1.27 | 0.48 | 1.35 | 2.18 |
| Jin et al (2016)MALAT1 | -0.39 | 0.69 | 1.41 | 2.87 | 3.51 |
| Kong et al (2016)LINC00460 | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Liu et al (2017)PCAT7 | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Lu et al (2016)NEAT1 | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Nie et al (2013)HOTAIR | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Song and Yin (2016)EWSAT1 | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Song et al (2016)XIST | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Su et al (2017)CAST9 | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Sun et al (2015)LET | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Tang et al (2017)AFAP1-AS1 | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Wang et al (2017)NEAT1 | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |
| Zou et al (2016)ANRIL | 0.57 | 0.69 | 1.33 | 2.56 | 3.02 |

### Notes:

- (A) Overall survival, (B) disease-free survival, (C) recurrence-free survival, (D) gender, (E) tumor classification, (F) lymph node status, (G) metastasis, and (H) TNM stage.

### Abbreviations:

- CI: confidence interval
- TNM: tumor node metastasis
overexpressed in primary non-small-cell lung cancers, including breast, pancreatic, colorectal, and ovarian cancer and is a potential biomarker and therapeutic target. HULC, an oncogenic lncRNA, which was first identified in hepatocellular carcinoma (HCC), acts as a miRNA sponge and sequesters miR-372, and its knockdown inhibits cell proliferation and increases chemosensitivity. HULC promoter possesses a binding site for transcription factor CAMP response element binding (CREB), and its expression is potentially regulated by CREB phosphorylation. It is highly expressed in NPC patients and correlated with a poor prognosis in cancer patients. Overexpressed HULC promotes NPC cell growth, while downregulated HULC activated p53 and induced the increased expression of p21, which finally caused cell cycle arrest and cell apoptosis. Prostate cancer-associated transcript 7 (PCAT7), a novel lncRNA, was found to be overexpressed and associated with good prognosis in NPC, which might contribute to the tumor progression by functioning as a competitive endogenous RNA (ceRNA) to sponge miR-134-5p and regulating miR-134-5p/ELF2 signal pathway. FOXCUT, which is located upstream of forkhead box C1 (FOXC1), was upregulated in clinical NPC tissues and cultured NPC cell lines, and the high levels of FOXCUT expression were correlated with lymph node metastasis and distant metastasis.

There are also some reports suggesting that some lncRNAs may serve as antitumor factors in NPC and could predict a good prognosis, such as MEG3, LINC0086, LINC00312, LOC401317, LncRNA-LET, and NEAT1. LINC00312 was associated with good prognosis in NPC patients with no lymph node metastasis and was associated with poor prognosis in NPC patients with lymph node metastasis. Further studies indicated that LOC401317 is directly regulated by p53 through a p53-binding site adjacent to its potential promoter and that LOC401317’s overexpression inhibits HNE2 cell proliferation in vitro and in vivo by inducing cell cycle arrest and apoptosis. And positive expression of LINC00312 was associated with good prognosis in NPC patients with no lymph node metastasis and was associated with poor prognosis in NPC patients with lymph node metastasis.

Indeed, increasing evidence suggests that the dysregulation of lncRNAs was involved in cancer, and alterations in lncRNA expression and their mutations promote tumorigenesis and metastasis. Many cancer-associated lncRNAs have been identified and characterized, and these lncRNAs help further understand the molecular mechanism of cancer. In addition, most of these cancer-associated lncRNAs could be effective prognostic biomarkers and even therapeutic targets. HOTAIIR is transcribed from the antisense strand of homeobox C (HOXC) gene locus in chromosome 12, and it coordinates with chromatin-modifying enzymes and regulates gene silencing. It is a scaffolding lncRNA, silences genes via interaction with PRC2 and LSD1, and aids protein degradation via interaction with E3 ubiquitin ligases; the knockdown of HOTAIIR reduces tumor invasiveness and disrupts epithelial mesenchymal transition. And it is one of the well-studied lncRNAs that is overexpressed in various cancers including breast, pancreatic, colorectal, hepatocellular, gastrointestinal, and non-small-cell lung carcinomas. Furthermore, the aberrantly upregulated expression in NPC correlates with clinical stage progression and contributes to the malignant character of NPC cells through involvement in diverse cellular processes, including migration, invasion, and proliferation, and also indicates a poorer prognosis for DFS and OS. AFAP1-AS1 promoted cancer cell metastasis via regulation of actin filament integrity. And its knockdown significantly inhibited the NPC cell migration and invasive capability. The study indicated that the AFAP1-AS1 expression was upregulated in NPC and associated with NPC metastasis and poor prognosis. H19 affected the expression of enhancer of zeste homolog 2 (EZH2) to promote cell invasion by suppressing the activity of miR-630. Furthermore, H19 inhibited E-cadherin expression and promoted the cell invasion of NPC cells via the miR-630/EZH2 pathway. MALAT1 was originally found to be overexpressed in primary non-small-cell lung cancers, and it undergoes posttranscriptional processing to produce a short RNA (cytoplasmic MALAT1-associated small cytoplasmic RNA [mascRNA]) and a long MALAT1 transcript that are localized to nuclear speckles and influence the level of phosphorylated splicing-associated serine arginine (SR) proteins. And it is also overexpressed in other cancers including bladder carcinoma, breast cancer, prostate cancer, and ovarian cancer and is a potential biomarker and therapeutic target. HULC, an oncogenic lncRNA, which was first identified in hepatocellular carcinoma (HCC), acts as a miRNA sponge and sequesters miR-372, and its knockdown inhibits cell proliferation and increases chemosensitivity. HULC promoter possesses a binding site for transcription factor CAMP response element binding (CREB), and its expression is potentially regulated by CREB phosphorylation. It is highly expressed in NPC patients and correlated with a poor prognosis in cancer patients. Overexpressed HULC promotes NPC cell growth, while downregulated HULC activated p53 and induced the increased expression of p21, which finally caused cell cycle arrest and cell apoptosis. Prostate cancer-associated transcript 7 (PCAT7), a novel lncRNA, was found to be overexpressed and associated with good prognosis in NPC, which might contribute to the tumor progression by functioning as a competitive endogenous RNA (ceRNA) to sponge miR-134-5p and regulating miR-134-5p/ELF2 signal pathway. FOXCUT, which is located upstream of forkhead box C1 (FOXC1), was upregulated in clinical NPC tissues and cultured NPC cell lines, and the high levels of FOXCUT expression were correlated with lymph node metastasis and distant metastasis.
Resistance to radiotherapy and chemotherapy is the primary cause of NPC patients’ death. In the current studies, some lncRNAs played a critical functional role in chemoresistance or radioresistance. LincRNA-ROR was highly associated with the proliferation, metastasis, and apoptosis of NPC.\textsuperscript{52} And the enrichment of lincRNA-ROR was associated with chemoresistance.\textsuperscript{53} Further investigation found that NEAT1 upregulated ZEB1 expression by negatively regulating miR-204 expression and regulated radioresistance by modulating epithelial mesenchymal transition phenotype in NPC.\textsuperscript{39} Furthermore, MALAT1 regulated cancer stem cell activity and radioresistance by modulating miR-1/slug axis.\textsuperscript{18} Moreover, knockdown of ANRIL represses tumorigenicity and enhances cisplatin (DDP)-induced cytotoxicity via regulating microRNA let-7a in NPC cells.\textsuperscript{54} Upregulated CCAT1 results in significantly enhanced paclitaxel resistance in nasopharyngeal cancer cells. And lincRNA CCAT1 regulates the sensitivity of paclitaxel in NPC cells via miR-181a/CPEB2 axis.\textsuperscript{55} Together, the current study provides a molecular basis for a comprehensive understanding of, and exploring new therapies for, NPC.\textsuperscript{35}

At present, a number of studies have shown that the expression of lncRNAs was correlated with clinicopathological characteristics in NPC: histological type, tumor size, TNM clinical stage, and some others. In this meta-analysis, we also found that the lncRNAs were related to the male, lymph node status, and TNM clinical stage. There are some limitations in this meta-analysis. First, our results were based on unadjusted estimates, while the lack of information (such as age and family history) for the date analysis may cause serious confounding bias. Second, because of incomplete raw data or publication limitations (the enrolled studies are only English and all from China), some relevant studies could not be included in our analysis. Third, the number of published studies was not sufficiently large for a comprehensive analysis and some studies with small size may not have enough statistical power to explore the real association.

Taking these observations into consideration, the novel molecular mechanisms by which the lncRNAs regulate carcinogenesis and metastasis are expected to be elucidated. And they will develop to be new clinical prognostic biomarker as well as new therapeutic target for NPC. Nevertheless, discovering novel lncRNAs, identifying their function and association with various cancer subtypes, and developing novel lncRNA-based strategies for diagnosis and targeted therapies appear very promising, bring a new paradigm in cancer research, and may emerge as a major therapeutic strategy for the treatment of cancer in the near future.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All the authors approved the final paper.

Disclosure

The authors report no conflicts of interest in this work.

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Prognostic significance of the lncRNAs in NPC

Supplementary materials

Table A

| Study or subgroup | Male | Female | Odds ratio M-H, Fixed, 95% CI | Odds ratio M-H, Fixed, 95% CI |
|-------------------|------|--------|-----------------------------|-----------------------------|
|                   | Events | Total | Weight (%)                  |                             |
| Bo et al (2015)²⁴ (AFAP1-AS1) | 19 | 93 | 4 | 19 | 7.2 | 0.96 (0.29, 3.24) |
| Jiang and Liu (2017)²⁵ (HULC) | 56 | 80 | 22 | 40 | 12.0 | 1.91 (0.87, 4.19) |
| Jin et al (2016)¹⁸ (MALAT1) | 34 | 60 | 32 | 71 | 17.3 | 1.59 (0.80, 3.18) |
| Lu et al (2016)¹⁹ (NEAT1) | 34 | 60 | 32 | 71 | 17.3 | 1.59 (0.80, 3.18) |
| Nie et al (2013)¹⁷ (HOTAIR) | 65 | 100 | 26 | 51 | 19.5 | 1.42 (0.73, 2.77) |
| Sun et al (2015)²⁵ (LET) | 21 | 47 | 13 | 21 | 13.6 | 0.50 (0.17, 1.42) |
| Tang et al (2017)¹⁸ (AFAP1-AS1) | 57 | 80 | 11 | 16 | 7.2 | 1.13 (0.35, 3.60) |
| Zou et al (2016)²⁸ (ANRIL) | 38 | 70 | 6 | 18 | 5.9 | 2.38 (0.80, 7.04) |

Total (95% CI) | 599 | 307 | 100.0 | 1.42 (1.05, 1.91) |

Total events | 324 | 146 |

Heterogeneity: χ² = 5.99; df = 7 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)

Table B

| Study or subgroup | N2–N3 | N0–N1 | Odds ratio M-H, Fixed, 95% CI | Odds ratio M-H, Fixed, 95% CI |
|-------------------|-------|-------|-----------------------------|-----------------------------|
|                   | Events | Total | Weight (%)                  |                             |
| Bo et al (2015)²⁴ (AFAP1-AS1) | 13 | 61 | 7 | 44 | 12.0 | 1.43 (0.52, 3.95) |
| Jiang and Liu (2017)²⁵ (HULC) | 57 | 65 | 21 | 55 | 13.1 | 11.54 (4.60, 28.90) |
| Jin et al (2016)¹⁸ (MALAT1) | 49 | 70 | 29 | 61 | 15.5 | 2.57 (1.26, 5.27) |
| Lu et al (2016)¹⁹ (NEAT1) | 39 | 70 | 29 | 61 | 15.8 | 1.39 (0.70, 2.77) |
| Nie et al (2013)¹⁷ (HOTAIR) | 55 | 81 | 36 | 79 | 16.4 | 2.53 (1.33, 4.81) |
| Tang et al (2017)¹⁸ (AFAP1-AS1) | 40 | 56 | 28 | 40 | 13.4 | 1.07 (0.44, 2.61) |
| Zou et al (2016)²⁸ (ANRIL) | 28 | 51 | 16 | 37 | 13.8 | 1.60 (0.38, 3.75) |

Total (95% CI) | 454 | 377 | 100.0 | 2.20 (1.29, 3.73) |

Total events | 281 | 166 |

Heterogeneity: χ² = 0.34; χ² = 18.34, df = 6 (P = 0.005); I² = 67%
Test for overall effect: Z = 2.91 (P = 0.004)

Table C

| Study or subgroup | III–IV | I–II | Odds ratio M-H, Fixed, 95% CI | Odds ratio M-H, Fixed, 95% CI |
|-------------------|--------|------|-----------------------------|-----------------------------|
|                   | Events | Total | Weight (%)                  |                             |
| Bo et al (2015)²⁴ (AFAP1-AS1) | 18 | 83 | 4 | 24 | 11.4 | 1.38 (0.42, 4.57) |
| Jiang and Liu (2017)²⁵ (HULC) | 71 | 79 | 7 | 44 | 11.0 | 43.11 (14.44, 128.68) |
| Jin et al (2016)¹⁸ (MALAT1) | 44 | 61 | 36 | 70 | 13.4 | 2.44 (1.18, 5.07) |
| Lu et al (2016)¹⁹ (NEAT1) | 44 | 61 | 36 | 70 | 13.4 | 2.44 (1.18, 5.07) |
| Nie et al (2013)¹⁷ (HOTAIR) | 79 | 114 | 19 | 46 | 13.6 | 2.44 (1.21, 4.90) |
| Sun et al (2015)²⁵ (LET) | 16 | 41 | 18 | 27 | 12.2 | 0.32 (0.12, 0.88) |
| Tang et al (2017)¹⁸ (AFAP1-AS1) | 53 | 73 | 15 | 23 | 12.8 | 1.41 (0.52, 3.84) |
| Zou et al (2016)²⁸ (ANRIL) | 39 | 66 | 5 | 22 | 11.8 | 4.91 (1.62, 14.92) |

Total (95% CI) | 578 | 323 | 100.0 | 2.55 (1.12, 5.78) |

Total events | 357 | 140 |

Heterogeneity: χ² = 1.16; χ² = 45.40, df = 7 (P = 0.00001); I² = 85%
Test for overall effect: Z = 2.24 (P = 0.03)

Figure S1 Forest plot of studies evaluating ORs of lncRNAs’ expression and the clinicopathological characteristics of NPC patients. (A) Gender; (B) lymph node status; and (C) TNM clinical stages.

Abbreviation: CI, confidence interval.
**A** Study or subgroup | WHO type III | WHO type II | Odds ratio | Odds ratio
| Events | Total | Events | Total | Weight (%) | M–H, fixed, 95% CI | M–H, fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bo et al (2015)24 (AFAP1-AS1) | 0 | 0 | 23 | 89 | Not estimable |
| Nie et al (2013)17 (HOTAIR) | 68 | 123 | 15 | 26 | 100.0 | 0.91 (0.39, 2.13) |
| Total (95% CI) | 123 | 115 | 100.0 | 0.91 (0.39, 2.13) |
| Total events | 68 | 38 |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.22 (P = 0.82) |

**B** Study or subgroup | T3 – T4 | T1 – T2 | Odds ratio | Odds ratio |
| Events | Total | Events | Total | Weight (%) | M–H, fixed, 95% CI | M–H, fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bo et al (2015)24 (AFAP1-AS1) | 6 | 32 | 14 | 73 | 11.2 | 0.97 (0.34, 2.81) |
| Jiang and Liu (2017)29 (HULC) | 61 | 72 | 17 | 48 | 12.4 | 10.11 (4.22, 24.21) |
| Jin et al (2016)18 (MALAT1) | 29 | 64 | 31 | 67 | 13.5 | 0.96 (0.48, 1.91) |
| Lu et al (2016)18 (NEAT1) | 29 | 64 | 31 | 67 | 13.5 | 0.96 (0.48, 1.91) |
| Nie et al (2013)17 (HOTAIR) | 51 | 77 | 40 | 83 | 13.8 | 2.11 (1.11, 4.00) |
| Sun et al (2015)25 (LET) | 12 | 35 | 22 | 33 | 11.5 | 0.26 (0.10, 0.71) |
| Tang et al (2017)26 (AFAP1-AS1) | 19 | 27 | 49 | 69 | 11.7 | 0.97 (0.37, 2.57) |
| Zou et al (2016)28 (ANRIL) | 22 | 38 | 22 | 50 | 12.5 | 1.75 (0.75, 4.10) |
| Total (95% CI) | 409 | 490 | 100.0 | 1.33 (0.69, 2.56) |
| Total events | 229 | 226 |
| Heterogeneity: $\chi^2 = 0.70; \chi^2 = 35.57, df = 7 (P < 0.00001); I^2 = 80\%$ |
| Test for overall effect: Z = 0.86 (P = 0.39) |

**C** Study or subgroup | Yes | No | Odds ratio | Odds ratio |
| Events | Total | Events | Total | Weight (%) | M–H, fixed, 95% CI | M–H, fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bo et al (2015)24 (AFAP1-AS1) | 0 | 1 | 20 | 104 | 3.9 | 1.37 (0.05, 34.97) |
| Jiang and Liu (2017)29 (HULC) | 16 | 17 | 62 | 103 | 7.3 | 10.58 (1.35, 82.89) |
| Jin et al (2016)18 (MALAT1) | 48 | 67 | 34 | 64 | 16.0 | 2.23 (1.08, 4.59) |
| Lu et al (2016)18 (NEAT1) | 48 | 67 | 34 | 64 | 16.0 | 2.23 (1.08, 4.59) |
| Nie et al (2013)17 (HOTAIR) | 59 | 115 | 32 | 45 | 15.8 | 0.43 (0.20, 0.90) |
| Sun et al (2015)25 (LET) | 5 | 14 | 30 | 54 | 11.8 | 0.32 (0.09, 1.15) |
| Tang et al (2017)26 (AFAP1-AS1) | 43 | 52 | 25 | 44 | 14.4 | 3.63 (1.43, 9.24) |
| Zou et al (2016)28 (ANRIL) | 15 | 31 | 29 | 57 | 14.8 | 0.91 (0.38, 2.17) |
| Total (95% CI) | 364 | 535 | 100 | 1.41 (0.69, 2.87) |
| Total events | 233 | 266 |
| Heterogeneity: $\chi^2 = 0.69; \chi^2 = 26.78, df = 7 (P < 0.0004); I^2 = 74\%$ |
| Test for overall effect: Z = 0.95 (P = 0.34) |

Figure S2 Forest plot of studies evaluating ORs of lncRNAs’ expression and the clinicopathological characteristics of NPC patients. (A) histological classification; (B) tumor classification; and (C) metastasis. **Abbreviations:** CI, confidence interval; WHO, World Health Organization; M–H, Mantel Haenszel test.
Figure S3 Egger’s test for publication bias.
Notes: (A) Overall survival; (B) disease-free survival; (C) recurrence-free survival; (D) gender; (E) tumor classification; (F) lymph node status; (G) metastasis; (H) TNM stage.
Table S1 Characteristics of studies (included and excluded) in this meta-analysis

| Author            | Year | lncRNAs       | Biotype (Ensembl/length(bp)) | Method       | Case number (high/low) | Outcome               | Cut-off | Follow-up months |
|-------------------|------|---------------|-------------------------------|--------------|------------------------|-----------------------|---------|-----------------|
| Nie et al         | 2013 | HOTAIR        | Antisense RNA/2421            | qRT-PCR and ISH | 91/69                  | OS, DFS, and RFS      | SI=6    | Median of 69    |
| Zhang et al       | 2013 | LINC00312     | Misc RNA/2887                 | qRT-PCR and ISH | 169/160                | OS and DFS            | NA      | 100             |
| Bo et al          | 2015 | AFAP1-AS1     | Antisense RNA/6795            | qRT-PCR and ISH | 23/55                  | OS and RFS            | SI 1.5-Fold | 120             |
| Sun et al         | 2015 | LET           | Sense intronic/2283           | qRT-PCR      | 34/34                  | OS and RFS            | Median   | 100             |
| Zhang et al       | 2015 | LOC84740      | NA                            | qRT-PCR      | 23/82                  | DFS                   | Fold-change | 48              |
| Zhang et al       | 2015 | ENST00000498296| Processed pseudogene/909     | qRT-PCR      | 64/42                  | DFS                   | Fold-change | 48              |
| Zhang et al       | 2015 | AL359062      | NA/1762                       | qRT-PCR      | 58/48                  | DFS                   | Fold-change | 48              |
| Zhang et al       | 2015 | ENST00000438550| Processed pseudogene/371     | qRT-PCR      | 81/25                  | DFS                   | Fold-change | 48              |
| Jin et al         | 2016 | MALAT1        | lincRNA/8708                  | qRT-PCR and ISH | 66/65                  | OS                    | SI=6    | 60              |
| Lu et al          | 2016 | NEAT1         | lincRNA/22743                 | qRT-PCR and ISH | 66/65                  | OS                    | SI=6    | 60              |
| Song et al        | 2016 | XIST          | lincRNA/19275                 | qRT-PCR      | 76/32                  | OS                    | 2.31-Fold | 140             |
| Song and          | 2016 | EWSAT1        | lincRNA/2498                  | qRT-PCR      | 76/32                  | OS                    | 2.36-Fold | 140             |
| Yin               | 2016 | ANRIL         | Antisense RNA/3835            | qRT-PCR      | 44/44                  | OS and DFS            | Median   | 100             |
| Guo et al         | 2017 | LINC0086      | Protein coding/5230           | qRT-PCR and ISH | 44/68                  | OS                    | NA      | 80              |
| Jiang and Liu     | 2017 | HULC          | lincRNA/556                   | qRT-PCR      | 78/42                  | OS                    | 2.5-Fold | 50              |
| Liu et al         | 2017 | PCAT7         | Retained intron/1164          | qRT-PCR      | 38/12                  | OS                    | NA      | 140             |
| Su et al          | 2017 | CASC9         | lincRNA/1164                  | qRT-PCR      | 45/45                  | OS                    | 2.5-Fold | 60              |
| Sun et al         | 2017 | LOC100129148  | Misc RNA/461                  | qRT-PCR      | 39/43                  | OS                    | Mean     | 80              |
| Tang et al        | 2017 | AFAP1-AS1     | Antisense RNA/6795            | qRT-PCR and ISH | 68/28                  | OS                    | NA      | 120             |
| Wang et al        | 2017 | NEAT1         | lincRNA/22743                 | qRT-PCR and AM | 39/31                  | OS                    | 2-Fold   | 50              |
| Yang et al        | 2017 | LINC00420     | Misc RNA/694                  | qRT-PCR and ISH | 65/45                  | OS                    | 1.2-Fold | 125             |
| Kong et al        | 2018 | LINC00460     | lincRNA/739                   | qRT-PCR      | 25/25                  | OS                    | Median   | 140             |

Note: Bold fonts represent the included studies.

Abbreviations: AM, affymetrix microarray; DFS, disease-free survival; ISH, in situ hybridization; lincRNA, long intergenic noncoding RNA; lncRNAs, long noncoding RNAs; NA, not available; NPC, nasopharyngeal carcinoma; OS, overall survival; qRT-PCR, quantitative real time polymerase chain reaction; RFS, recurrence-free survival; SI, staining index.

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