The prognostic significance of long noncoding RNAs in non-small cell lung cancer: a meta-analysis

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Keywords: non-small cell lung cancer; long noncoding RNAs; prognosis; lymph node metastasis; meta-analysis

Received: November 01, 2016    Accepted: December 08, 2016    Published: December 15, 2016

ABSTRACT

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. The overall 5-year survival rate of patients is extremely low and to find a new marker is urgently needed. Numerous studies indicate that long noncoding RNAs (lncRNAs) abnormally express in cancers. However, the results have been disputed, especially in the aspects of tumor prognosis. Therefore, we performed this meta-analysis to systematically summarize the relationship between lncRNAs expression and NSCLC. A total of 34 eligible studies including 30 on overall survival, 10 on progression-free survival and 23 on clinicopathological features were identified from the databases. Our results indicated that the levels of lncRNAs were associated with the overall survival (OS; hazard ratios [HR], 1.43; 95% confidence interval [95% CI], 1.17-1.76; P < 0.001). However, there was no relationship between lncRNAs and progression-free survival (PFS; hazard ratios [HR], 1.55; 95% confidence interval [95% CI], 0.91-2.63; P = 0.11). Moreover, lncRNAs were related to lymph node metastasis (odds ratios [OR], 1.70; 95% confidence interval [95% CI], 1.03-2.80; P = 0.04), while no association was observed with other characteristics. In conclusion, our present meta-analysis indicated that lncRNAs transcription levels may serve as a promising marker for prognosis of patients with NSCLC.

INTRODUCTION

Lung cancer is one of the most common malignant cancers worldwide, making up 18.2% of all malignant tumor mortality in the world [1, 2]. Non-small cell lung cancer (NSCLC) is the most common type, accounting for about 85% of lung cancer [3]. To date, despite the effective treatments for patients have obtained, including surgical resection, systemic chemotherapy and targeted drugs, the prognosis of NSCLC remains still poor and the 5-year survival rate is only 11-15%, because the patients were diagnosed at advanced stages [4-6]. Metastasis and recurrence are the major causes of morbidity and death in NSCLC[7]. Lung cancer is a multi-factor, multi-step and complex process, which was related to many tumor-related genes[8]. In NSCLC researches, several genetic biomarkers have been used, including non-coding RNAs (ncRNAs). Therefore, to identify sensitive and specific biomarkers for prognosis of patients with NSCLC is urgently needed.

Recently, advanced techniques discovered that more than 90% of the mammalian genome can be transcribed into short or long noncoding RNAs[9]. Long non-coding RNAs (lncRNAs) are defined as noncoding RNAs longer than 200 nucleotides with no protein-coding capacity [10]. Increasing evidences have pointed that lncRNAs play tremendous roles in epigenetics and cytobiological processes, including pre-transcription, post-transcription and cell proliferation, differentiation, apoptosis, and migration [9, 11, 12]. Aberrantly expressed lncRNAs have been found in various cancers. For example, the TGF-β-activated lncRNA (lncRNA-ATB), is significantly
increased in hepatocellular carcinoma and associated with poor prognosis [13]. In 2016, Han et al [10] found that circulating long noncoding RNA GAS5 could be served as a biomarker in breast cancer to assess the surgical effects. In gastric cancer, knockdown of lncRNA X-inactive specific transcript (XIST) could reduce the mRNA and protein levels of EZH2 and suppress the colony formation and invasion ability stimulated by miR-101[14]. Meanwhile, recent studies have shown that lncRNAs could serve as potential diagnostic and prognostic biomarkers for NSCLC.

To date, there are some lncRNAs have been confirmed to aberrantly expressed in NSCLC, such as MALAT1[15], H19[16], and SPRY4-IT1[17]. In 2016, Lu et al [18] elaborated that there was a positive correlation between the expression levels of CDKN2B antisense RNA 1 (ANRIL) and c-Myc, and decreased ANRIL significantly inhibited NSCLC cell proliferation. BRAF activated non-coding RNA (BANCR) actively functioned as a regulator of epithelial-mesenchymal transition (EMT) through inducing E-cadherin expression, and decreasing N-cadherin, Vimentin. The results suggested that BANCR could be a biomarker for poor prognosis of NSCLC [19]. CAR intergenic 10 (CAR10) a novel lncRNA, could bind and stabilize transcription factor Y-box-binding protein 1 (YB-1), leading to up-regulation of the epidermal growth factor receptor (EGFR) and proliferation of lung cancer cells, and CAR10-YB-1 represented a potential therapeutic target in NSCLC [11]. Numbers of researches were done to explore the prognostic value of lncRNAs in NSCLC. However, because the sample size and research programs, single study may be inaccurate and insufficient. Thus, we conducted a meta-analysis to evaluate the value of lncRNAs in the prognosis and clinical outcomes in NSCLC through larger sample size of patients.

**RESULTS**

**Study characteristics**

We searched 786 articles in the databases, as shown in the flow diagram (Figure 1). 725 records were removed after screening the titles and abstracts. Then because of no usable data or incomplete data, 27 papers were excluded. As a result, a total of 34 articles were in the current meta-analysis [3, 5, 16, 17, 19-48], including 30 on overall survival (OS) [3, 5, 16, 17, 19-43, 48], 10 on progression-free survival (PFS) [17, 19, 20, 25, 36, 37, 44-47] and 23 on clinicopathological features [5, 16, 17, 19, 20, 22-28, 30, 32-40, 46].

Table 1 summarized the main characteristics of the included 34 studies ranging from 2003 to 2016, with a maximum sample size of 192 and a minimum sample size of 38 patients. Among these studies, 32 were from China, 1 from Japan and 1 from Germany. Because the cut-off definitions were various, the cut-off values were

![Figure 1: The flow diagram indicated the process of study selection.](www.impactjournals.com/oncotarget/3958/Oncotarget)
different in these studies. Meanwhile, in the 34 studies, 23 articles performed the relationship between the expression of lncRNAs and gender[5, 16, 17, 19, 20, 22-28, 30, 32-40, 46], 16 studies referred to the smoking history[5, 16, 17, 19, 20, 22, 23, 25, 30, 32-34, 36, 38-40], 17 studies demonstrated that lncRNAs were correlated with histological classification[16, 17, 19, 20, 22-27, 30, 32-34, 36, 37, 46], 12 studies were on tumor size[16, 17, 19, 20, 22, 25, 30, 32, 33, 36-38], and 11 were about tumor-node-metastasis (TNM) [16, 17, 19, 20, 22, 25, 30, 32-34, 36, 37, 46], while 22 studies reported that lncRNAs were significantly correlated with lymph node metastasis (LNM)[5, 16, 17, 19, 20, 22, 24-28, 30, 32-40, 46] (Table 2).

Table 1: Characteristics of studies included in this meta-analysis.

| Author | Year | Country | LncRNAs | Tumor type | Method | Case number (High/Low) | Outcome | Cut-off | Follow-up months |
|--------|------|---------|---------|------------|--------|------------------------|---------|---------|-----------------|
| Hou    | 2014 | China   | Sox2ot  | NSCLC      | qRT-PCR| 47                     | OS      | Top quartile | 60              |
| Deng   | 2015 | China   | AFAP1-AS1| NSCLC      | qRT-PCR| 65/55                  | OS      | NA       | 60              |
| Li     | 2016 | China   | AGAP2-AS1| NSCLC      | qRT-PCR| 40/40                  | OS, PFS | Mean     | 40              |
| Luo    | 2014 | China   | CARLO-5  | NSCLC      | qRT-PCR| 29/33                  | OS      | Median   | 80              |
| He     | 2016 | China   | CASC2   | NSCLC      | qRT-PCR| 38/38                  | OS      | Median   | 60              |
| Sun    | 2014 | China   | BANCR   | NSCLC      | qRT-PCR| 53/60                  | OS, PFS | Fold-change | 40              |
| Han    | 2013 | China   | GAS6-AS1| NSCLC      | qRT-PCR| 25/25                  | OS      | Mean     | 60              |
| Zhang  | 2016 | China   | H19     | NSCLC      | qRT-PCR| 25/25                  | OS      | Median   | 60              |
| Lin    | 2015 | China   | ANRIL   | NSCLC      | qRT-PCR| 48/39                  | OS      | Mean     | 60              |
| Zang   | 2016 | China   | Linc01133| NSCLC      | qRT-PCR| 34/34                  | OS, PFS | Mean     | 40              |
| Xie    | 2014 | China   | HMlincRNA717| NSCLC | qRT-PCR| 49/69                  | OS      | Mean     | 80              |
| Zhao   | 2016 | China   | SBF2-AS1| NSCLC      | qRT-PCR| 80/94                  | OS      | Median   | 70              |
| Wang   | 2015 | China   | UCA1    | NSCLC      | qRT-PCR| 36/24                  | NA      | NA       | 80              |
| Lu     | 2013 | China   | MEG3    | NSCLC      | qRT-PCR| 21/21                  | OS      | Median   | 60              |
| Fang   | 2016 | China   | XIST    | NSCLC      | qRT-PCR| 38/15                  | OS      | 2.58-fold | NA              |
| Han    | 2015 | China   | PANDAR  | NSCLC      | qRT-PCR| 70/70                  | OS      | Mean     | 60              |
| Nie    | 2014 | China   | MVII    | NSCLC      | qRT-PCR| 21/21                  | OS      | Median   | 40              |
| Sun    | 2016 | China   | NEAT1   | NSCLC      | qRT-PCR| 67/29                  | OS      | 2 folds  | 40              |
| Zhang  | 2014 | China   | TUG1    | NSCLC      | qRT-PCR| 96/96                  | OS      | Median   | 60              |
| Yang   | 2014 | China   | PVT1    | NSCLC      | qRT-PCR| 65/17                  | OS      | Median   | 60              |
| Wan    | 2016 | China   | PVT1    | NSCLC      | qRT-PCR| 56/49                  | OS, PFS | Median   | 40              |
| Sun    | 2014 | China   | SPRY4-IT1| NSCLC      | qRT-PCR| 60/61                  | OS, PFS | Median   | 40              |
| Wang   | 2016 | China   | TUSC7   | NSCLC      | qRT-PCR| 56/56                  | OS, PFS | Median   | 80              |
| Nie    | 2016 | China   | UCA1    | NSCLC      | qRT-PCR| 39/73                  | OS      | Youden index | 80           |
| Zhang  | 2014 | China   | ZXF1    | NSCLC      | qRT-PCR| 43/19                  | OS      | Ratio=2  | 36              |
| Yang   | 2015 | China   | ZXF2    | NSCLC      | qRT-PCR| 20/20                  | OS      | Median   | 39              |
| Ji     | 2003 | China   | MALAT1  | NSCLC      | qRT-PCR| 70/70                  | OS      | Median   | 100             |
| Zhang  | 2015 | China   | Linc01133| LSCC | qRT-PCR| 39                     | OS      | Median   | 60              |
| Schmidt| 2011 | Germany  | MALAT1  | LSCC       | qRT-PCR| NA                    | OS      | NA       | 166             |
| Wang   | 2015 | China   | Linc01207| LAD        | qRT-PCR| 49/11                  | OS      | Fold of 5.78 | 75             |
| Cheng  | 2015 | China   | UCA1    | NSCLC      | qRT-PCR| 20/32                  | PFS     | 2-ΔCt = -0.068 | 25            |
| Pan    | 2016 | China   | BC087858| NSCLC      | qRT-PCR| 12/26                  | PFS     | 2-ΔCt = 0.142 | 40            |
| Nakagawa| 2013| Japan    | HOTAIR  | NSCLC      | qRT-PCR| 17/60                  | PFS     | 2-fold   | 50              |
| Liu    | 2013 | China   | HOTAIR  | LAD        | qRT-PCR| 22/19                  | PFS     | HSCORE=74.2 | 15             |

LncRNA: Long non-coding RNA; NSCLC: Non-small cell lung cancer; LSCC: Lung squamous cell carcinoma; LAD: Lung adenocarcinoma; qRT-PCR: Quantities reverse transcription-polymerase chain reaction; OS: Overall survival; PFS: Progression-free survival; NA: Not available

**Prognosis**

A total of 30 studies were reported that the expression levels of lncRNAs were related to OS. Hazard ratios (HRs) and 95% confidence interval (95% CI) were extracted from these studies. Analysis showed that the expression levels of lncRNAs were associated with the OS of NSCLC patients (HR = 1.43, 95%CI = 1.17-1.76, P < 0.001, random-effect) (Figure 2). Because 2 articles reported the relationship between lncRNAs and LSCC patients’ OS (HR = 1.92, 95%CI = 1.25-2.94, P = 0.003, fixed-effect) and 1 article was about LAD (HR = 2.53,
Table 2: Association between high levels of lncRNAs and characteristics of patients with NSCLC.

| Characteristics                          | Studies | Case number | Pooled OR(95% CI) | P   | Heterogeneity I² | P    | References                        |
|-----------------------------------------|---------|-------------|-------------------|-----|------------------|------|-----------------------------------|
| Gender (male vs female)                 | 23      | 2111        | 1.00 (0.83, 1.19) | 0.96| 0%               | 0.63 | [5, 16, 17, 19, 20, 22-28, 30, 32-40, 46] |
| Smoking History (never vs ever)         | 16      | 1401        | 0.91 (0.73, 1.14) | 0.43| 42%              | 0.04 | [5, 16, 17, 19, 20, 22, 23, 25, 30, 32-34, 36, 38-40] |
| Histological classification (LSCC vs LAD) | 17      | 1634        | 1.03 (0.84, 1.26) | 0.77| 39%              | 0.05 | [16, 17, 19, 20, 22-27, 30, 32-34, 36, 37, 46] |
| Tumor size (≤3 vs >3)                   | 6       | 519         | 0.45 (0.17, 1.25) | 0.13| 85%              | <0.001| [16, 25, 33, 36, 40, 41] |
| (≤5 vs >5)                              | 6       | 529         | 0.61 (0.18, 2.01) | 0.42| 90%              | <0.001| [17, 19, 23, 28, 35, 39] |
| TNM stage (I-II vs III-IV)              | 11      | 1091        | 0.63 (0.28, 1.44) | 0.27| 89%              | <0.001| [16, 17, 19, 20, 22, 25, 32, 34, 36-38] |
| Lymph node metastasis (presence vs absence) | 22      | 2036        | 1.70 (1.03, 2.80) | 0.04| 85%              | <0.001| [5, 16, 17, 19, 20, 22-28, 30, 32-40, 46] |

LSCC: Lung squamous cell carcinoma; LAD: Lung adenocarcinoma; TNM: Tumor node metastasis; I² > 50% with the random-effects model; I² < 50% with the fixed-effects model.

Figure 2: Forest plot of studies evaluating hazard ratios of lncRNAs expression and the overall survival in NSCLC. The point estimate is bounded by a 95% confidence interval, and the perpendicular line represents no increased risk for the outcome. NSCLC: Non-small cell lung cancer; LSCC: Lung squamous cell carcinoma; LAD: Lung adenocarcinoma.
95%CI = 1.36-4.71, \( P = 0.003 \), fixed-effect) in the enrolled 30 studies, we performed the subgroup analysis. From the forest plot, the increased expressions of AFAP1-AS1, XIST, Sox2ot, AGAP2-AS1, ANRIL, CARLO-5, MVIIH, UCA1, NEAT1, PVT1, ZXF2, Linc01133, ZXF1, H19, SBF2-AS1, MALAT1 and Linc01207 were associated with poor prognosis. Besides, GAS6-AS1, PANDAR, CASC2, MEG3, BANCR, SPRY4-IT1, TUSC7, HMlincRNA717 and TUG1 were correlated to poor prognosis with the decreased expression of lncRNAs in NSCLC.

In the enrolling studies, UCA1, PVT1 and MALAT1 were investigated in two researches, other lncRNAs were performed in single study. Then we conducted a meta-analysis on the relationship between the expressions of UCA1/PVT1/MALAT1 and the OS of patients with NSCLC. We found that the high levels of UCA1 were associated with a poor OS (HR = 1.49, 95% CI = 1.16-1.90, \( P = 0.002 \), fixed-effect) (Figure 3A). Meanwhile, a poor prognosis in NSCLC was found in the increased levels of PVT1 and MALAT1 (PVT1: HR = 3.05, 95% CI = 2.15-4.34, \( P < 0.001 \), fixed-effect) (MALAT1: HR = 1.66, 95% CI = 1.04-2.63, \( P = 0.03 \), fixed-effect) (Figure 3B-3C).

10 studies enrolling 807 patients indicated that lncRNAs expression was related to the PFS in NSCLC. The up-regulated expression of UCA1, AGAP2-AS1, BC087858, HOTAIR, PVT1 and Linc01133 had a relatively poor prognosis, the decreased expressions of BANCR, SPRY4-IT1 and TUSC7 were related to poor prognosis. 1 study demonstrated that the relationship between the levels of lncRNA and LAD (HR = 1.96, 95%CI = 1.01-3.80, \( P = 0.05 \), fixed-effect). However, the expression of lncRNAs was not associated with the patients’ PFS in the enrolling studies (HR = 1.55, 95% CI = 0.91-2.63, \( P = 0.11 \), random-effect) (Figure 4).

**Correlation of lncRNAs with clinicopathological characteristics**

As shown in Table 2, we performed a meta-analysis to evaluate the relationship between the transcription levels of lncRNAs and clinicopathological characteristics of patients with NSCLC. Odds ratios (OR)>1 stated that high levels of lncRNAs might be a risk factor in the features. Our results demonstrated that the high lncRNA expressions were significantly related to LNM (OR = 1.70, 95% CI = 1.03-2.80, \( P = 0.04 \), random-effect).
Unfortunately, there was no correlation in gender (OR = 1.00, 95% CI = 0.83-1.19, P = 0.96, fixed-effect), smoking history (OR = 0.91, 95% CI = 0.73-1.14, P = 0.43, fixed-effect), histological classification (OR = 1.03, 95% CI = 0.84-1.26, P = 0.77, fixed-effect), tumor size (<3 cm vs ≥3 cm: OR = 0.45, 95% CI = 0.17-1.25, P = 0.13, random-effect), (≤5 cm vs >5 cm: OR = 0.61, 95% CI = 0.18-2.01, P = 0.42, random-effect), TNM (OR = 0.63, 95% CI = 0.28-1.44, P = 0.27, random-effect) (Supplementary Figure 1).

**Publication bias and sensitivity analysis**

Begg’s test was used to evaluate the publication bias, respectively (Figure 5). In our meta-analysis, Begg’s test indicated there were no publication bias in all groups, due to all the values of P > 0.05. We used Stata11.0 software to perform sensitivity analysis to assess whether the individual studies affected the overall results. The results indicated that individual study had little influence on our final results (Figure 6), and demonstrated that our analysis was relatively stable and credible.

**DISCUSSION**

NSCLC is one of the leading causes of cancer-related death [33]. Identification of early disease indicators for prognosis is urgently required. Recently, mounting evidence demonstrated that IncRNAs dysregulation was involved in cancers [36]. H19 which was a direct target of oncogene c-Myc was an independent predictor for OS, as well as the TNM stage [16]. TUG1 was an important prognostic factor for NSCLC patients. In addition, knockdown of TUG1 was found to result in anti-apoptotic activity in NSCLC [34]. For cancer researches, most of cancer associated IncRNAs could be effective prognostic biomarkers and even therapeutic targets [43]. Therefore, we performed a meta-analysis to evaluate the association between IncRNAs and prognosis of patients with NSCLC.

Accumulating studies elaborated that the association between IncRNAs and NSCLC. In 2013, Lu et al [29] suggested that MEG3 could be considered as a negative prognostic factor for NSCLC patients and an indicative of poor survival rates. Meantime, the decreased levels of CASC2 predicted a poor prognosis and could be as an independent predictor for OS [22]. In our meta-analysis, we assessed the prognostic role of IncRNAs in NSCLC. Our results indicated that high expressions of IncRNAs represented a risk factor for OS in NSCLC. From these results, IncRNAs could be as biomarkers for the prognosis of NSCLC. Previous study indicated that TUSC7 acted as a growth suppressor in NSCLC through inhibiting the p21/p27, and low TUSC7 expression had a shorter PFS. Unfortunately, there was no relationship between IncRNAs expression and PFS in our meta-analysis. Therefore,

| Study or Subgroup | log(Hazard Ratio) | SE | Weight | Hazard Ratio  | Hazard Ratio  |
|-------------------|------------------|----|--------|---------------|---------------|
|                   | IV, Random, 95% CI |     |        | IV, Random, 95% CI |     |
| 3.1.1 NSCLC       |                 |    |        |               |               |
| Cheng 2015 (UCA1) | 1.1777           | 0.5186 | 8.5%   | 3.25 [1.17, 8.97] | 3.25 [1.17, 8.97] |
| Li 2016 (AGAP2-AS1) | 1.2302           | 0.3135 | 10.6%  | 3.42 [1.85, 6.33] | 3.42 [1.85, 6.33] |
| Nakagawa 2013 (HOTAIR) | 1.0787         | 0.5314 | 8.4%   | 2.94 [1.04, 8.33] | 2.94 [1.04, 8.33] |
| Pan 2016 (SC087958) | 0.9203           | 0.5901 | 8.4%   | 2.51 [0.89, 7.09] | 2.51 [0.89, 7.09] |
| Sun 2014 (BANCR) | -0.7985         | 0.3704 | 10.0%  | 0.45 [0.22, 0.93] | 0.45 [0.22, 0.93] |
| Sun 2014 (SPRY4-IT1) | -0.6301        | 0.2638 | 11.0%  | 0.44 [0.26, 0.73] | 0.44 [0.26, 0.73] |
| Wan 2016 (PVT1) | 0.8675           | 0.275 | 10.9%  | 2.38 [1.39, 4.08] | 2.38 [1.39, 4.08] |
| Wang 2016 (TUSC7) | -0.3683         | 0.0856 | 12.2%  | 0.70 [0.59, 0.82] | 0.70 [0.59, 0.82] |
| Zang 2016 (Linc01133) | 0.9163         | 0.4023 | 9.7%   | 2.50 [1.14, 5.50] | 2.50 [1.14, 5.50] |
| Subtotal (95% CI) | 89.7%           | 1.51 | 0.85, 2.67 |               |               |

Heterogeneity: Tau² = 0.63; Chi² = 71.96, df = 8 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.40 (P = 0.16)

3.1.2 LAD

| Study or Subgroup | log(Hazard Ratio) | SE | Weight | Hazard Ratio  | Hazard Ratio  |
|-------------------|------------------|----|--------|---------------|---------------|
|                   | IV, Random, 95% CI |     |        | IV, Random, 95% CI |     |
| Liu 2013 (HOTAIR) | 0.6729           | 0.3378 | 10.3%  | 1.96 [1.01, 3.80] | 1.96 [1.01, 3.80] |
| Subtotal (95% CI) |                 |     |        |               |               |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)

Total (95% CI) 100.0% 1.55 [0.91, 2.63]

Heterogeneity: Tau² = 0.60; Chi² = 77.41, df = 9 (P < 0.00001); I² = 88%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.56). I² = 0%

Figure 4: Forest plot of studies evaluating hazard ratios of IncRNAs expression and the progression-free survival in NSCLC. The point estimate is bounded by a 95% confidence interval, and the perpendicular line represents no increased risk for the outcome. NSCLC: Non-small cell lung cancer; LAD: Lung adenocarcinoma.
Figure 5: Begg’s test for publication bias. A. overall survival; B. progression-free survival; C. lymph node metastasis; D. gender; E. smoking history; F. histological classification; G. tumor size (≤3 vs >3); H. tumor size (≤5 vs >5); I. TNM stage.
Figure 6: Sensitivity analyses of the studies. A. overall survival; B. progression-free survival; C. lymph node metastasis; D. gender; E. smoking history; F. histological classification; G. tumor size (≤3 vs >3); H. tumor size (≤5 vs >5); I. TNM stage.
Therefore, another limitation was the lack of diagnosis the diagnostic studies about lncRNAs are not enough. Unstable, especially in cancer patients [50]. Meantime, of RNases, circulating RNA has been thought to be for the diagnosis of NSCLC. However, due to the presence in NSCLC plasma and could be considered as a biomarker 2016, Liang evaluate their diagnostic significance in NSCLC[49]. In our studies were Chinese, which also might affect the more studies. What is more, most of the population in our studies were Chinese, which also might affect the results. Recently, circulating lncRNAs were detected to evaluate their diagnostic significance in NSCLC[49]. In 2016, Liang et al[49] indicated that GAS5 was decreased in NSCLC plasma and could be considered as a biomarker for the diagnosis of NSCLC. However, due to the presence of RNases, circulating RNA has been thought to be unstable, especially in cancer patients [50]. Meantime, the diagnostic studies about lncRNAs are not enough. Therefore, another limitation was the lack of diagnosis about lncRNAs in our meta-analysis.

In summary, our meta-analysis was firstly to evaluate the expressions of lncRNAs and clinical values of patients with NSCLC. Furthermore, the result indicated that the level transcription was related to LNM. Despite these limitations, there was a relationship between lncRNAs levels and OS in NSCLC, which demonstrated that lncRNAs could be potential prognostic markers for NSCLC. However, large-scale and comprehensive researches were needed to illuminate our results.

MATERIALS AND METHODS

Publication search

We searched the databases PubMed, Embase and Web of Science for studies published up to October 2016 to obtain relevant articles for the meta-analysis. The search strategy used both medical subject heading terms and free-text words to increase the sensitivity of the search. We mainly searched three key aspects “lncRNA”, “cancer”, and “lung”, the detail search strategy was following: “Long noncoding RNA”, “lncRNA”, “LincRNA”, “Long intergenic non-coding RNA” and “NSCLC”, “non-small cell lung cancer”, “LAD”, “lung adenocarcinoma”, “LSCC”, “lung squamous cell cancer”. Meanwhile, the article covered was limited to human and English.

Inclusion and exclusion criteria

In this meta-analysis, eligible studies had to meet the following standards: patients in the study were diagnosed with lung cancer; researches were association between lncRNAs and lung cancer; the prognostic value of lncRNAs was investigated; the relationship between lncRNAs expression and overall survival or progression-free survival was performed; sufficient published data were provided to calculate hazard ratios and 95% confidence interval. If there were duplicated data, we chose the most complete data or the most recent one. Exclusion criteria were as follow: studies without usable or insufficient data; case reports, reviews, letters and conference abstracts.

Data extraction

Two investigators extracted relevant data from the eligible studies independently, including the first author, year of publication, country, the lncRNAs, tumor type, method, case number, cut-off value and follow-up months.
Statistical analysis

HRs and 95% CIs were used to assess the association between lncRNAs and survival in NSCLC. An observed HR > 1 implied a worse survival for the group with elevated lncRNAs expression. Conversely, HR < 1 implied a worse survival for the group with decreased lncRNAs expression [51]. Meanwhile, Odds ratios and 95% CI were used to evaluate the relationship between lncRNAs and clinicopathological features in these inclusive articles. The features included gender, lymph node status, tumor sizes, histological classification, smoking history and TNM. We used Revman5.3 Software (Revman, the Cochrane Collaboration) to perform the meta-analysis and evaluate heterogeneity between studies by Cochrane Q-test and P-values. If heterogeneity was present ($P \geq 0.50$ or $P \leq 0.05$), random-effect model was used to calculate pooled HRs or ORs. If not, the fixed-effect model was more appropriate [52, 53]. The Stata11.0 Software (Stata, College Station) was performed to evaluate the sensitivity and publication bias of the studies. Publication bias was evaluated by Begg’s test, $P < 0.05$ was considered statistically significant.

ACKNOWLEDGMENTS

This study was supported by the National Basic Research Program of China (973 Program) (2012CB720605), 2012 US-China Biomedical Cooperation Projection (81261120403/H09298).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Torre LA, Siegel RL, Jemal A. Lung Cancer Statistics. Adv Exp Med Biol. 2016; 893: 1-19. doi: 10.1007/978-3-319-24223-1_1.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127: 2893-917. doi: 10.1002/ijc.25516.
3. Hou Z, Zhao W, Zhou J, Shen L, Zhan P, Xu C, Chang C, Bi H, Zou J, Yao X, Huang R, Yu L, Yan J. A long noncoding RNA Sox2ot regulates lung cancer cell proliferation and is a prognostic indicator of poor survival. Int J Biochem Cell Biol. 2014; 53: 380-8. doi: 10.1016/j.biocel.2014.06.004.
4. Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol. 2008; 3: 819-31. doi: 10.1097/JTO.0b013e3181020eb.
5. Deng J, Liang Y, Liu C, He S, Wang S. The up-regulation of long non-coding RNA AFAP1-AS1 is associated with the poor prognosis of NSCLC patients. Biomed Pharmacother. 2015; 75: 8-11. doi: 10.1016/j.biopha.2015.07.003.
6. Reed MF, Molloy M, Dalton EL, Howington JA. Survival after resection for lung cancer is the outcome that matters. Am J Surg. 2004; 188: 598-602. doi: 10.1016/j.amjsurg.2004.07.037.
7. Wu Y, Lyu H, Liu H, Shi X, Song Y, Liu B. Downregulation of the long noncoding RNA GAS5-AS1 contributes to tumor metastasis in non-small cell lung cancer. Sci Rep. 2016; 6: 31093. doi: 10.1038/srep31093.
8. Minna JD, Roth JA, Gazdar AF. Focus on lung cancer. Cancer Cell. 2002; 1: 49-52.
9. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. Cell. 2009; 136: 629-41. doi: 10.1016/j.cell.2009.02.006.
10. Han L, Ma P, Liu SM, Zhou X. Circulating long noncoding RNA GAS5 as a potential biomarker in breast cancer for assessing the surgical effects. Tumour Biol. 2016; 37: 6847-54. doi: 10.1007/s13277-015-4568-7.
11. Wei MM, Zhou YC, Wen ZS, Zhou B, Huang YC, Wang GZ, Zhao XC, Pan HL, Qu LW, Zhang J, Zhang C, Cheng X, Zhou GB. Long non-coding RNA stabilizes the Y-box-binding protein 1 and regulates the epithelial growth factor receptor to promote lung carcinogenesis. Oncotarget. 2016; 7: 59556-59571. doi: 10.18632/oncotarget.10006.
12. Jing W, Zhu M, Zhang XW, Pan ZY, Gao SS, Zhou H, Qiu SL, Liang CZ, Tu JC. The Significance of Long Noncoding RNA H19 in Predicting Progression and Metastasis of Cancers: A Meta-Analysis. Biomed Res Int. 2016; 2016: 5902678. doi: 10.1155/2016/5902678.
13. Yuan JH, Yang F, Wang F, Ma JZ, Guo YJ, Tao QF, Liu F, Pan W, Wang TT, Zhou CC, Wang SB, Wang YZ, Yang Y, et al. A long noncoding RNA activated by TGF-beta promotes the invasion-metastasis cascade in hepatocellular carcinoma. Cancer Cell. 2014; 25: 666-81. doi: 10.1016/j.ccr.2014.03.010.
14. Chen DL, Ju HQ, Lu YX, Chen LZ, Zeng ZL, Zhang DS, Luo HY, Wang F, Qiu MZ, Wang DS, Xu ZD, Zhou ZW, Pelicano H, et al. Long non-coding RNA XIST regulates gastric cancer progression by acting as a molecular sponge of miR-101 to modulate EZH2 expression. J Exp Clin Cancer Res. 2016; 35: 142. doi: 10.1186/s13046-016-0420-1.
15. Li J, Wang J, Chen Y, Li S, Jin M, Wang H, Chen Z, Yu W. LncRNA MALAT1 exerts oncogenic functions in lung adenocarcinoma by targeting miR-204. Am J Cancer Res. 2016; 6: 1099-107.
16. Zhang E, Li W, Yin D, De W, Zhu L, Sun S, Han L. c-Myc-regulated long non-coding RNA H19 indicates a poor prognosis and affects cell proliferation in non-small-cell lung cancer. Tumour Biol. 2016; 37: 4007-15. doi: 10.1007/s13277-015-4185-5.
17. Sun M, Liu XH, Lu KH, Nie FQ, Xia R, Kong R, Yang JS,
26. Xie X, Liu HT, Mei J, Ding FB, Xiao HB, Hu FQ, Hu R, Wang MS. LncRNA HMlincRNA717 represses KLF2 and P21 and E-cadherin transcription through binding with EZH2 and LSD1 in non-small-cell lung cancer cells. Cell Death Dis. 2016; 7: e2225. doi: 10.1038/cddis.2016.126.

23. Han L, Kong R, Yin DD, Zhang EB, Xu TP, De W, Shu YQ. Low expression of long non-coding RNA GAS6-AS1 indicates a poor prognosis and regulates cell proliferation in non-small cell lung cancer. Tumour Biol. 2016; 37: 9503-10. doi: 10.1007/s13277-014-2442-7.

20. Li W, Sun M, Zang C, Ma P, He J, Zhang M, Huang Z, Ding Y, Shu Y. Upregulated long non-coding RNA AGAP2-AS1 represses LATS2 and KLF2 expression through interacting with EZH2 and LSD1 in non-small-cell lung cancer cells. Cell Death Dis. 2016; 7: e2225. doi: 10.1038/cddis.2016.126.

18. Luo J, Tang L, Zhang J, Ni J, Zhang HP, Zhang L, Xu JF, Zheng D. Long non-coding RNA CARLO-5 is a negative prognostic factor and exhibits tumor pro-oncogenic activity in non-small cell lung cancer. Tumour Biol. 2014; 35: 11541-9. doi: 10.1007/s13277-014-1955-4.

15. Lu KH, Li W, Liu XH, Sun M, Zhang ML, Wu WQ, Xie L, Xia R, Shu YQ, De W. Low expression of long non-coding RNA MVIH indicates a poor prognosis for non-small cell lung cancer and promotes cell proliferation and invasion. Tumour Biol. 2014; 35: 7587-94. doi: 10.1007/s13277-014-2009-7.

28. Wang HM, Lu JH, Chen WY, Gu AQ. Upregulated IncRNA-UCA1 contributes to progression of lung cancer and is closely related to clinical diagnosis as a predictive biomarker in plasma. Int J Clin Exp Med. 2015; 8: 11824-30.

29. Lu KH, Li W, Liu XH, Sun M, Zhang ML, Wu WQ, Xie WP, Hou YY. Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. BMC Cancer. 2013; 13: 461. doi: 10.1186/1471-2407-13-461.

30. Fang J, Sun CC, Gong C. Long noncoding RNA XIST acts as an oncogene in non-small cell lung cancer by epigenetically repressing KLF2 expression. Biochem Biophys Res Commun. 2016; 478: 811-7. doi: 10.1016/j.bbrc.2016.08.030.
39. Zhang L, Zhou XF, Pan GF, Zhao JP. Enhanced expression of long non-coding RNA ZXF1 promoted the invasion and metastasis in lung adenocarcinoma. Biomed Pharmacother. 2014; 68: 401-7. doi: 10.1016/j.biopha.2014.03.001.

40. Yang ZT, Li Z, Wang XG, Tan T, Yi F, Zhu H, Zhao JP, Zhou XF. Overexpression of Long Non-Coding RNA ZXF2 Promotes Lung Adenocarcinoma Progression Through c-Myc Pathway. Cell Physiol Biochem. 2015; 35: 2360-70. doi: 10.1159/000374038.

41. Zhang J, Zhu N, Chen X. A novel long noncoding RNA LINCO1133 is upregulated in lung squamous cell cancer and predicts survival. Tumour Biol. 2015; 36: 7465-71. doi: 10.1007/s13277-015-3460-9.

42. Schmidt LH, Spieker T, Koschmieder S, Schaffers S, Humberg J, Jungen D, Bulk E, Hascher A, Wittmer D, Marra A, Hillejan L, Wiebe K, Berdel WE, et al. The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. J Thorac Oncol. 2011; 6: 1984-92. doi: 10.1097/JTO.0b013e3182318eaa.

43. Wang G, Chen H, Liu J. The long noncoding RNA LINCO1207 promotes proliferation of lung adenocarcinoma. Am J Cancer Res. 2015; 5: 3162-73.

44. Cheng N, Cai W, Ren S, Li X, Wang Q, Pan H, Zhao M, Li J, Zhang Y, Zhao C, Chen X, Fei K, Zhou C, et al. Long non-coding RNA UCA1 induces non-T790M acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway in EGFR-mutant non-small cell lung cancer. Oncotarget. 2015; 6: 23582-93. doi: 10.18632/oncotarget.4361.

45. Pan H, Jiang T, Cheng N, Wang Q, Ren S, Li X, Zhao C, Zhang L, Cai W, Zhou C. Long non-coding RNA BC087858 induces non-T790M mutation acquired resistance to EGFR-TKIs by activating PI3K/AKT and MEK/ERK pathways and EMT in non-small-cell lung cancer. Oncotarget. 2016; 7: 49948-49960. doi: 10.18632/oncotarget.10521.

46. Nakagawa T, Endo H, Yokoyama M, Abe J, Tamai K, Tanaka N, Sato I, Takahashi S, Kondo T, Satoh K. Large noncoding RNA HOTAIR enhances aggressive biological behavior and is associated with short disease-free survival in human non-small cell lung cancer. Biochem Biophys Res Commun. 2013; 436: 319-24. doi: 10.1016/j.bbrc.2013.05.101.

47. Liu Z, Sun M, Lu K, Liu J, Zhang M, Wu W, De W, Wang Z, Wang R. The long noncoding RNA HOTAIR contributes to cisplatin resistance of human lung adenocarcinoma cells via downregualtion of p21(WAF1/CIP1) expression. PLoS One. 2013; 8: e77293. doi: 10.1371/journal.pone.0077293.

48. Ji P, Diederichs S, Wang W, Boing S, Metzger R, Schneider PM, Tidow N, Brandt B, Buerger H, Bulk E, Thomas M, Berdel WE, Serve H, et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene. 2003; 22: 8031-41. doi: 10.1038/sj. onc.1206928.

49. Liang W, Lv T, Shi X, Liu H, Zhu Q, Zeng J, Yang W, Yin J, Song Y. Circulating long noncoding RNA GAS5 is a novel biomarker for the diagnosis of nonsmall cell lung cancer. Medicine (Baltimore). 2016; 95: e4608. doi: 10.1097/md.0000000000004608.

50. Tsui NB, Ng EK, Lo YM. Stability of endogenous and added RNA in blood specimens, serum, and plasma. Clin Chem. 2002; 48: 1647-53.

51. Chen J, Chen Y, Gu L, Gu L, Li X, Gao Y, Lyu X, Chen L, Luo G, Wang L, Xie Y, Duan J, Peng C, Ma X. LncRNAs act as prognostic and diagnostic biomarkers in renal cell carcinoma: a systematic review and meta-analysis. Oncotarget. 2016; 7: 74325-74336. doi: 10.18632/oncotarget.11101.

52. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177-88.

53. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959; 22: 719-48.