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Original Article

LncRNA MALAT1 overexpression is an unfavorable prognostic factor in human cancer: evidence from a meta-analysis

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Abstract: Long non-coding RNAs (lncRNAs) have been suggested to serve as an important role in tumor development and progression. The aim of this study was to analyse the association between lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and cancer patients' overall survival. We systematically and carefully searched the studies from electronic databases and seriously identified according to eligibility criteria. The correlation between lncRNA MALAT1 expression and overall survival in human cancers was evaluated through Review Manager. A total of 8 studies which included 792 cancer patients were included in the final analysis. Meta-analysis showed that lncRNA MALAT1 overexpression was correlated with a poor overall survival and the pooled hazard ratio (HR) and corresponding 95% confidence interval (CI) was 1.94 (95% CI 1.59-2.38). From subgroup analyses, we present evidence that lncRNA MALAT1 overexpression was an unfavorable prognostic factor for patients' overall survival in non-small cell lung cancer and pancreatic cancer, the pooled HRs (95% CI) were 1.86 (95% CI 1.27-2.73) and 1.78 (95% CI 1.30-2.44), respectively. In conclusion, lncRNA MALAT1 is a potential prognostic factor in human cancers.

Keywords: Meta-analysis, lncRNA, MALAT1, prognosis, cancer, lung cancer, pancreatic cancer

Introduction

Nowadays, cancer is becoming a major cause of morbidity and mortality in most regions worldwide [1]. According to 2014 Cancer Statistics, A total of estimated 1.66 million new cancer cases and 585,720 cancer deaths occur in the United States in 2014 [2]. The 5-year survival is still low in many types of human cancers. Thus, it is urgent to identify new potential biomarker for early diagnosis, accurate prognosis prediction, and novel therapeutic target for cancer patients.

Long noncoding RNAs (lncRNAs) are generally defined as transcribed RNA molecules with a length greater than 200 nt and lacking an open reading frame of significant length (less than 100 amino acids) [3]. In the recent ten years, increasing studies have reported that the expression of lncRNAs are obviously dysregulated in varied cancers and that these lncRNAs play critical roles in tumor development, progression, and metastasis [4]. LncRNA HOTAIR (HOX transcript antisense RNA) has been thought to correlate with malignant status and serve as a convinced poor prognosis in human cancers through meta-analysis [5-7].

Recently, lncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) has been found overexpressed in almost all types of human cancers, and corrected with clinical malignant status and prognosis in cancer patients, such as lung cancer [8-10], hepatocellular carcinomas [11, 12], pancreatic cancer [13, 14], bladder cancer [15, 16], colorectal cancer [17, 18], gastric cancer [19] and osteosarcoma [20]. Moreover, the experiments in vitro showed that lncRNA MALAT1 was involved in regulation of cancer cell growth, motility and apoptosis, and induction of cell cycle arrest and epithelial-mesenchymal transition [21-25]. These studies consistently implied that lncRNA MALAT1 may act as a potential prognostic factor for cancer patients.

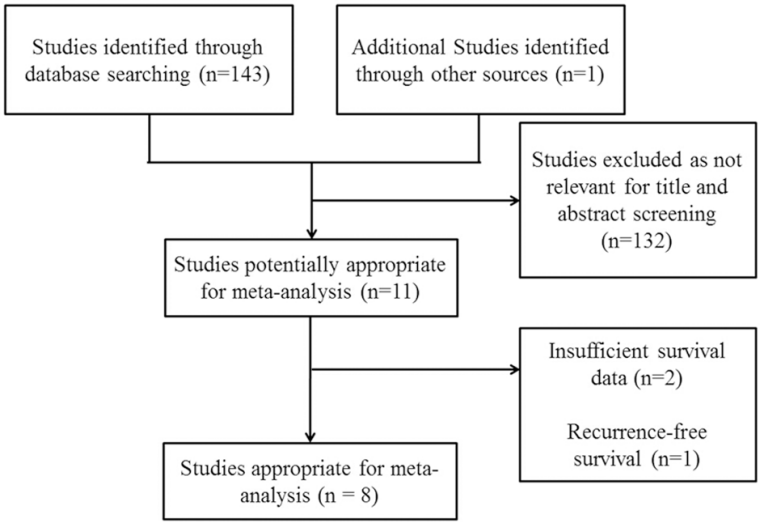

Figure 1. Flow diagram of the identification and selection of studies.

LncRNA MALAT1 overexpression in tumor cells has been shown to be an independent prognostic factor in several types of tumors, which has a favorable or unfavorable prognostic significance according to tumor types. Some studies indicated that lncRNA MALAT1 overexpression was significantly associated with a poor prognosis in non-small cell lung cancer [9, 10], hepatocellular carcinomas [12], pancreatic cancer [13], bladder cancer [16] and colorectal cancer [18], while others did not agree in lung cancer [8], gastric cancer [19] and osteosarcoma [20]. In order to identify the pathological roles of lncRNA MALAT1 in human cancers, we performed a meta-analysis aiming to evaluate the relationship between lncRNA MALAT1 expression and prognosis in patients with cancer.

Materials and methods

Search strategy

The MEDLINE, EMBASE, and Cochrane Library databases were systematically searched to October 2014. Publications with the following search words in the title, abstract or keywords were included: Long non coding RNA, LncRNA, Metastasis-associated lung adenocarcinoma transcript 1, MALAT1, Cancer, Carcinoma, Tumor and Prognosis. The studies identified through the search were independently screened by two authors (QY and LW) for inclusion. Any disagreements were arbitrated by a third author (XH). We did not limit our search by country, race, or date.

Inclusion and exclusion criteria

Studies eligible for inclusion in this meta-analysis met the following criteria: 1, Expression of lncRNA MALAT1 was evaluated in all cancers by RT-PCR or ISH; 2, Hazard ratios (HR) for overall survival related to lncRNA MALAT1 expression were provided or were extractable from the published data; 3, All patients diagnosed with malignant tumors or cancer must be confirmed by histopathologic examinations; 4, The sufficient information about study population, origin of country, and cancer type; and 5, Studies were published in English. The following criteria were used to exclude published studies: 1, Any studies that did not meet all inclusion criteria and 2, Studies of case reports, letters, and reviews without original data. When a study reporting the same patient cohort was included in several publications, the most complete study was selected.

Data extraction

Data was independently extracted by two authors (QY and LW) using the same standardized table. Data were extracted from the included studies, and the major information included the following: first's name, publication year, country, cancer type, total cases, stage, survival analysis method (multivariate or univariate), end point results, and hazard ratio with 95% confidence interval (CI). For articles with the same population resources or overlapping datasets, data were extracted and reported as a single trial. Overall survival in relation to lncRNA MALAT1 expression was estimated by the HR. If authors reported HR and 95% CI, these data were extracted from the included articles. Otherwise, HR and 95% CI were calculated as described previously [26, 27].

Statistical analysis

The meta-analysis was performed through using Cochrane Collaboration Review Manager

Table 1. Characteristics of the eligible studies

Author	Year	Country	Cancer type	Case	Tumor stage	Method	Analysis	Outcome	HR (95% CI)
Ji	2003	Germany	Non-small cell lung cancer	50	stage I	RT-PCR	Univariate	OS	1.32 (0.35-4.97)
Schmidt	2011	Germany	Non-small cell lung cancer	102	stage I-III	ISH	Univariate	OS	1.78 (1.08-2.92)
Shen	2014	China	Non-small cell lung cancer	78	stage I-IV	RT-PCR	Univariate	OS	2.20 (1.12-4.31)
Liu	2014	China	Pancreatic cancer	45	stage I-IV	RT-PCR	Multivariate	OS	1.80 (1.18-2.75)
Pang	2014	China	Pancreatic cancer	126	stage I-IV	RT-PCR	Multivariate	OS	1.76 (1.10-2.85)
Okugawa	2013	Japan	Gastirc cancer	150	stage I-IV	RT-PCR	Univariate	OS	1.54 (0.92-2.58)
Fan	2014	China	Bladder cancer	95	stage I-IV	RT-PCR	Univariate	OS	3.14 (1.51-6.53)
Zheng	2014	China	Colorectal cancer	146	stage II-III	RT-PCR	Univariate	OS	3.75 (1.74-8.07)

OS, overall survival; HR, hazard ratio; CI, confidence interva; ISH, in situ hybridization; RT-PCR, real-time polymerase chain reaction.

5.1 software. The details of statistical analysis were shown as described previously [6]. Heterogeneity of hazard ratio was assessed by use of the χ^2 and I^2 test. When heterogeneity was significant ($I^2 > 50\%$ and $P < 0.05$ for χ^2), we used a random effects model with the DerSimonian and Laird method for the meta-analysis. Otherwise, we used a fixed effects model with the inverse variance method.

Subgroups of non-small cell lung cancer and pancreatic cancer for overall survival (OS) were performed in subgroup analyses. The sensitivity was analyzed by changing the effect model and excluding small case studies (defined as < 50 cases) to estimate confidence. Funnel plot was executed for evaluating the potential publication bias. An asymmetric plot indicates there was potential publication bias; otherwise, the plot should be shaped like a funnel.

Results

Eligible studies

Electronic database search identified a total of 143 articles by using our search criteria (**Figure 1**). After carefully reading the title and abstract 668 articles were excluded, because they did not present any data about the association of lncRNA MALAT1 expression with patients outcome. After reviewing the full text of the remaining 11 studies, we ultimately included 8 studies in the final analysis. Three studies were excluded from the final review for these reasons because of insufficient survival data (n = 2) [20, 28] and recurrence-free survival (n = 1) [12].

Study characteristics

A total of 792 cases from the 8 studies that had pathological results and clinical data were included in this meta-analysis. Publication year of selected studies ranged from 2003 to 2014. These cases of 8 studies were from different populations (five studies in China, and other two studies in Germany and Japan, respectively) and five kinds of cancers (lung cancer, gastric cancer, colorectal cancer, pancreatic cancer, and bladder carcinoma). LncRNA MALAT1 expression was evaluated by RT-PCR (n = 7) or ISH (n = 1). Six studies calculated HR and 95% CI by univariate analysis; the other two studies used multivariate analysis. **Table 1** shows the main characteristics of all of the studies.

Meta-analysis

There was obvious heterogeneity among those 8 studies ($I^2 = 0\%$). Thus, the fixed effects model was used to calculate the pooled HR with corresponding 95% CI. Meta-analysis of those 8 studies showed that lncRNA MALAT1 expression was obviously associated with poor overall survival outcome in various cancers, with the pooled HR of 1.94 (95% CI 1.59-2.38) (**Figure 2**).

No significant heterogeneity was observed in the studies on non-small cell cancer ($I^2 = 0\%$) and pancreatic cancer ($I^2 = 0\%$). The fixed effects model was used to calculate the pooled HR (95% CI) in subgroups of non-small cell cancer and pancreatic cancer. The result indicated that pooled HRs (95% CI) were 1.86 (95% CI 1.27-2.73) for non-small cell lung cancer patients and 1.78 (95% CI 1.30-2.44) for pancreatic cancer (**Figure 3**).

Sensitivity analysis suggested that changing the effect model had no effect on pooled HR and did not change the strength of the association between lncRNA MALAT1 expression and overall survival for patients with cancers. The

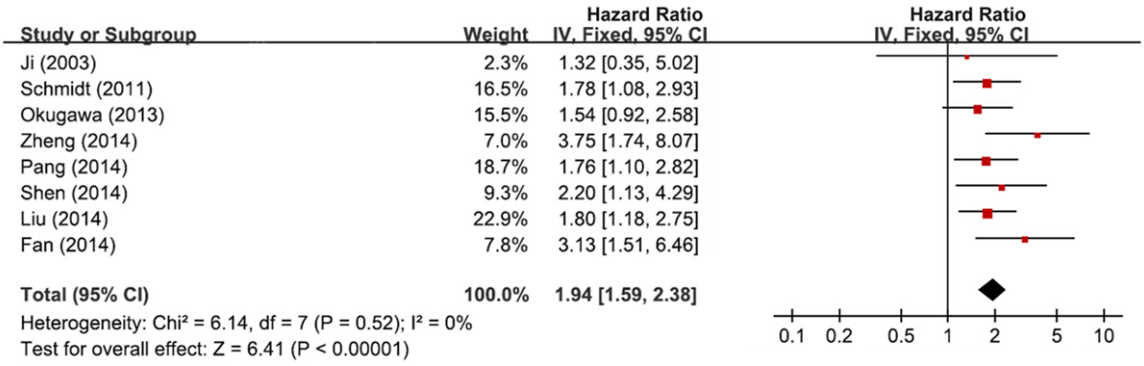

Figure 2. Forest plot for the correlation between lncRNA MALAT1 expression and overall survival of patients with human cancers.

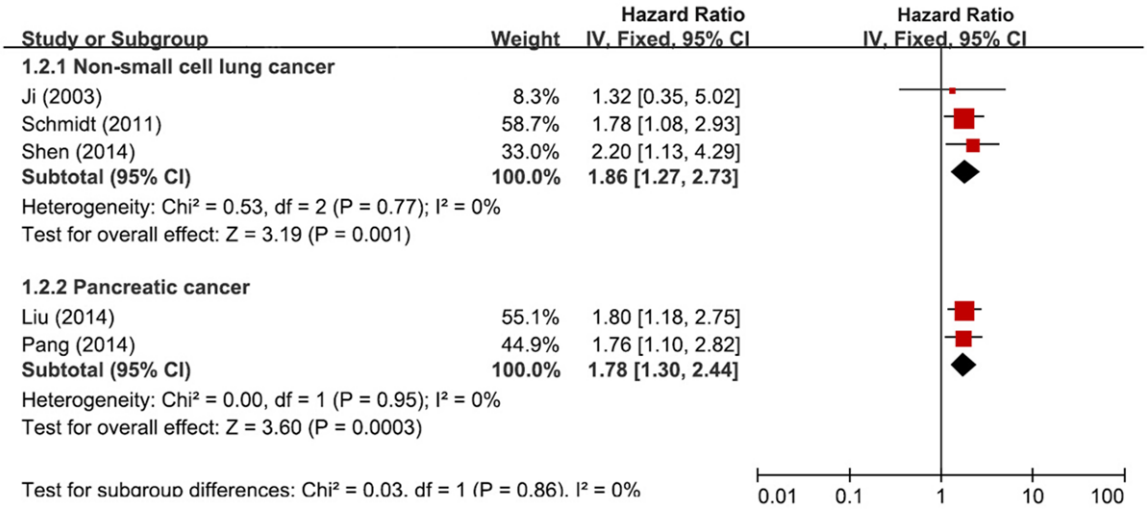

Figure 3. Forest plot of subgroup analysis showed the correlation of lncRNA MALAT1 expression with overall survival in non-small cell lung cancer and pancreatic cancer.

HRs (95% CI) were 1.94 (95% CI 1.59-2.38) for changing the effect model and 2.03 (95% CI 1.58-2.61) for excluding small case studies. Publication bias of this meta-analysis was evaluated by funnel plot. No evidence of asymmetry was observed in the funnel plots (**Figure 4**).

Discussion

Long ncRNAs (lncRNAs) are broadly defined as transcribed RNA molecules greater than 200 nt in length, and most lack protein coding capability [3]. LncRNAs transcribe from intronic and intergenic regions of the human genome and lack an open reading frame of significant length (less than 100 amino acids), so they were described as transcriptional "noise" in the past decades. Recently, more and more studies reported that lncRNAs involve in tumor development and progression by regulating cell growth, metastasis, and apoptosis [4, 29]. In glioma, MEG3 (maternally expressed gene 3) has been showed to be obviously decreased in glioma tissues compared with adjacent normal brain tissues. Furthermore, the overexpression of the lncRNA MEG3 significantly suppressed glioma cell proliferation and promotes apoptosis [30]. In addition, lncRNA H19 was obviously increased in primary pancreatic ductal adenocarcinoma tissues and knockdown of H19 significantly suppressed migration, invasion, and the process of epithelial-mesenchymal transition (EMT) through mediating let-7 and its target HMGA2 [31]. Moreover, lncRNA HOTAIR (HOX transcript antisense RNA) has been thought to correlate with malignant status and

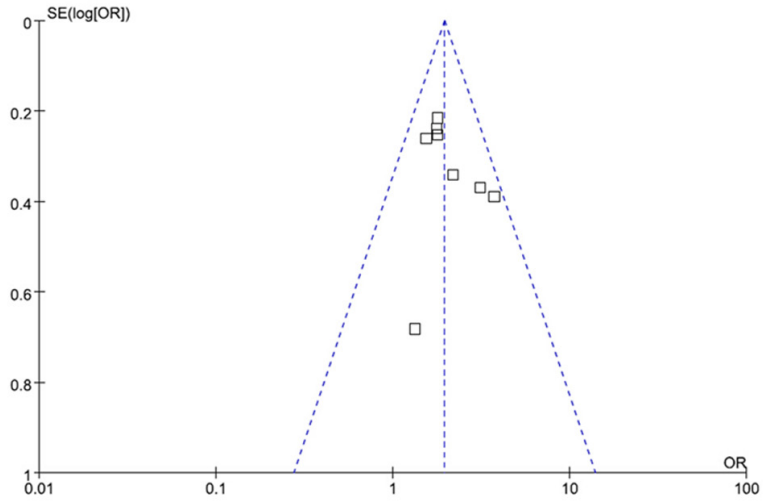

Figure 4. Funnel plot for identifying publication bias in the correlation between lncRNA MALAT1 expression and overall survival of patients with human cancers.

serve as a convinced poor prognosis in human cancers through meta-analysis [5-7].

LncRNA MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript1), one of the first lncRNAs identified in lung metastasis, is a highly conserved nuclear long noncoding RNA with a length of more than 8000nt and locates on chromosome 11q13 [32]. In comparison to benign tumor or normal tissue, lncRNA MALAT1 overexpression was observed in most types of human cancer [32]. In pancreatic cancer, recent studies showed that the expression of lncRNA MALAT1 was significantly increased in pancreatic cancer samples compared adjacent non-cancerous tissues, and knocking down of lncRNA MALAT1 expression inhibited cell growth, mobility and the process of epithelial-mesenchymal transition, and induce cell apoptosis and cell cycle arrest in vitro [13, 14]. Similarly, lncRNA MALAT-1 expression was overexpressed in colorectal cancer tissue and obviously regulated the biological function of proliferation, cell cycle, migration and invasion in colorectal cancer cells [17, 18]. Moreover, Lai el al.'s study demonstrated that lncRNA MALAT1 was increased in hepatocellular carcinoma clinical sample and cell lines, and down-regulated lncRNA MALAT1 expression in HepG2 cells suppressed cell viability, motility, and invasiveness and elevated the sensitivity to apoptosis [12]. These studies consistently suggest that lncRNA MALAT1 may serve as an important prognostic factor in cancer patients.

In the past ten years, lncRNA MALAT1 overexpression has been suggested to be an independent predictor of overall survival in various human cancers, which has a favorable or unfavorable prognostic significance according to the type of cancer. In gastric cancer, Okugawa et al. reported that lncRNA MALAT1 expression was elevated in cancerous tissue and correlated with peritoneal metastasis in patients with gastric cancer, but patients with high-expression of lncRNA MALAT1 did not associate with unfavorable prognoses [19]. Meanwhile, Fellenberg et al. indicated that lncRNA MALAT1 expression markedly associated with response to chemotherapy in osteosarcoma patients, but no significant association of lncRNA MALAT1 expression and overall survival was found in univariate analysis [20]. Conversely, there was more evidence suggesting that overexpression of lncRNA MALAT1 was unfavorable prognosis factor in non-small cell lung cancer [9, 10], hepatocellular carcinomas [12], pancreatic cancer [13], bladder cancer [16] and colorectal cancer [18]. In pancreatic cancer, the expression of lncRNA MALAT1 was detected in 45 clinical pancreatic duct adenocarcinoma samples and 25 adjacent non-cancerous samples and found that lncRNA MALAT1 was increased in cancer tissues and correlated with advanced clinical stage, large tumor size, and poor overall survival [13]. Similarly, Zheng et al.'s study showed that the expression level of lncRNA MALAT1 was higher in colorectal cancer tissues than those in paired non-cancerous tissues, and might act a convinced poor prognostic biomarker for stage II/III colorectal cancer patients' disease-free survival and overall survival [18]. These results were consistent with relevant studies reported in non-small cell lung cancer and bladder cancer [9, 10, 16].

In order to evaluate the prognostic value of lncRNA MALAT1 in human cancer, we conduct a meta-analysis to analyze the association between lncRNA MALAT1 and human cancer. In the meta-analysis of 8 studies containing 792 cases, we found that lncRNA MALAT1 expres-

sion was obviously associated with unfavorable overall survival in varied cancers, with the pooled HR of 1.94 (95% CI 1.59-2.38). Among those 8 studies, only a study showed that there were no statistically significant difference between lncRNA MALAT1 expression and overall survival in gastric cancer. In the study reported by Okugawa et al. [19], the borderline significance between high lncRNA MALAT1 expression and poor overall survival might be attributed to the absence of sufficient samples. Moreover, Sensitivity analysis indicated that the result was stable through excluding small case studies and changing the effect model. Thus, we thought lncRNA MALAT1 is a significant potential prognostic factor for cancer patients.

Furthermore, the subgroup analysis was performed to identify the heterogeneity of tumor types. The subgroup analysis showed that there was no significant subgroup difference between non-small cell lung cancer and pancreatic cancer (I^2 = 0%). The lncRNA MALAT1 overexpression was significantly correlated with unfavorable overall survival in non-small cell lung cancer (HR 1.86, 95% CI 1.27-2.73) and in pancreatic cancer (HR 1.78, 95% CI 1.30-2.44). Therefore, the results suggested that lncRNA MALAT1 expression is an independent prognostic factor in non-small cell lung cancer and pancreatic cancer.

The meta-analysis may have some potential limitations. On the one hand, although 792 cases of 8 studies were included in this meta-analysis, well-designed and large cases clinical studies for each cancer were insufficient. On the other hand, there was statistical heterogeneity in this meta-analysis may be attributed to the differences of evaluation criterions of lncRNA MALAT1 expression, population, disease stages, and tumor types.

In conclusion, lncRNA MALAT1 overexpression was significantly correlated with unfavorable overall survival in most types of cancers. LncRNA MALAT1 may be considered to serve as a credible prognostic factor in human cancers. In the future, more studies will be necessary to verify and strengthen the role of lncRNA MALAT1 in human cancers.

Disclosure of conflict of interest

None.

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