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Original Article

Long noncoding RNA MALAT1 as a putative biomarker of lymph node metastasis: a meta-analysis

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Abstract: Recent studies in cancer have demonstrated that cancerous tissues have a significantly higher MALAT1 level than in noncancerous tissues. Overexpression of MALAT1 is associated with susceptibility to lymph node metastasis. This meta-analysis collected all relevant articles and explored the association of MALAT1 expression levels with lymph node metastasis in patients with carcinoma. Literature collections were conducted by searching electronic databases PubMed, Cochrane Library, Web of Science (up to January 20, 2015). The odds ratio (OR) and its corresponding 95% confidence interval (CI) were calculated to assess the strength of the association by using RevMan5.1 software. A total of 573 patients from 5 studies were included in this meta-analysis. The results showed lymph node metastasis occurred more frequently in patients with high MALAT1 expression group than in patients with low MALAT1 expression group (OR = 2.64, 95% CI 1.06-6.56, P = 0.04 random-effects model). This meta-analysis demonstrated that overexpression of MALAT1 is significantly associated with lymph node metastasis in carcinoma patients.

Keywords: MALAT1, lncRNA, lymph node metastasis, cancer, meta-analysis

Introduction

Detection of lymph node metastasis is of major prognostic significance in most cancers, and is an important part of the TNM classification system, which dictates the choice of future postoperative therapies and predicts prognosis of cancer patients [1]. In the multistep process of metastasis, invasion into the lymphatic system has generally been believed as a key step of tumor cell dissemination [2]. The exact mechanism of metastasis through lymph nodes is still unclear. Recent studies have attempted to explain the process at the genetic level. Various kinds of genomic signatures have been reported associated with lymph node and distant metastasis [3, 4]. However, most of the reports were just talking about a molecule specific to a particular tumor. A putative biomarker for predicting lymph node metastasis at the transcriptional level has not been demonstrated [5].

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), and most lack protein coding capability [6]. However, increasing evidences have been presented to suggest that lncRNAs participated in a wide range of biological pathways. LncRNAs could regulate gene expression and function, including dosage compensation, genome rearrangement, chromatin modifications, gene imprinting, alternative splicing, nuclear- cytoplasmic trafficking, cell cycle control, and inactivation of major tumor suppressor genes [7-10]. Moreover, lncRNAs play a critical role in tumor development, progression, and metastasis [11].

Metastasis associated lung adenocarcinoma transcript 1 (MALAT1), also known as non-coding nuclear enriched abundant transcript 2 (NEAT2), is a ~ 8000-nt long non-coding RNA, which is highly conserved in human [12]. A number of studies have revealed that the expression level of MALAT1 was up-regulated in cancerous tissues of a variety of cancers, such as

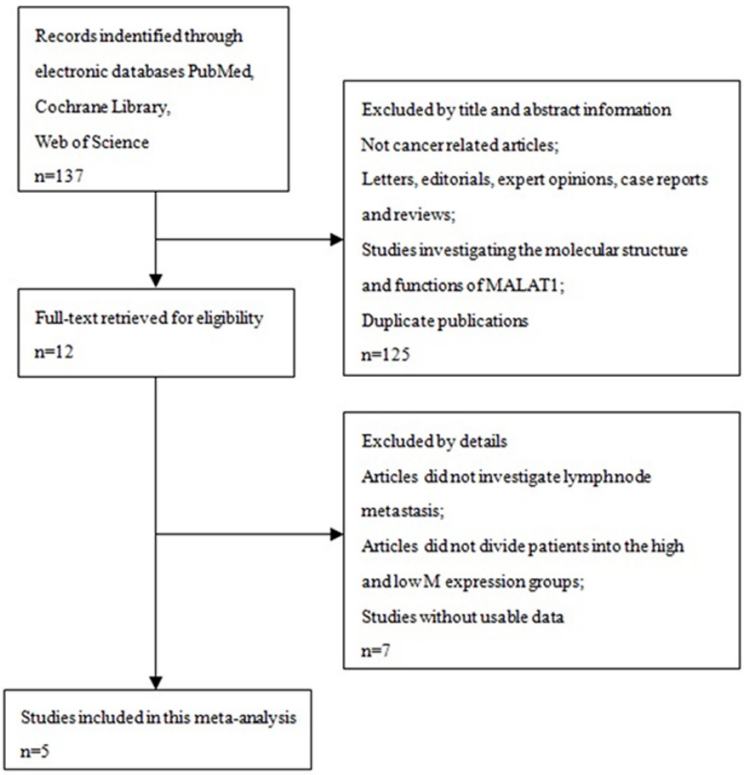

Figure 1. Flowchart presenting the steps of literature search and selection.

esophageal squamous cell carcinoma [13], gastric cancer [14], pancreatic cancer [15], hepatocellular cancer [16], colorectal cancer [17], prostate cancer [18] and cervical cancer [19]. In addition, regulating the expression of MALAT1 in vitro had a significant impact on the viability, proliferation, and invasion of tumor cells. We collected all relevant articles and carried out a meta-analysis to explore the relationship between MALAT1 expression levels with lymph node metastasis and furthermore to determine whether MALAT1 can be used as a putative biomarker for lymph node metastasis.

Methods

Literature search strategies

Articles up to January 20, 2015, which related to the long noncoding RNA MALAT1 serving as a putative biomarker for lymph node metastasis, were searched in several computerized databases, including PubMed, Cochrane Library, Web of Science and Chinese National Knowledge Infrastructure (CNKI). The search terms we used were listed as follows: MALAT1 or MALAT-1 or Metastasis associated lung adenocarcinoma transcript 1 and cancer or carcinoma or neoplasms or tumor and lymph node metastasis. Besides, the reference lists are manually viewed to obtain additional relevant articles.

Inclusion and exclusion criteria

Inclusion criteria are the following: (1) articles investigating the roles of MALAT1 in the development of cancer, (2) the expression levels of MALAT1 in primary cancerous tissues were measured, (3) patients were grouped according to the expression levels of MALAT1, (4) related clinicopathologic parameters were described, (5) studies containing sufficient data for the computation of odds ratios (OR) and corresponding 95% confidence intervals (CI). Exclusion criteria are the following: (1) studies investigating the molecular structure and functions of MALAT1; (2) letters, expert opinions, editorials, reviews and case reports; (3) duplicate publications; (4) studies without usable data.

Date extraction and quality assessment

Two investigators (HZ and QJC) extracted data from the eligible studies independently, according to the inclusion and exclusion criteria above. For disagreements, a consensus was reached by a third investigator (WL). The following information was collected from each eligible study: first author, publication date, country of origin, ethnicity, tumor type, total number of patients, number of high MALAT1 expression group and low MALAT1 expression group, number of patients with lymph node metastasis in each group, and detection method of MALAT1 expression levels. Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was used to evaluate the quality of included publications.

Statistical methods

All statistical analyses used RevMan5.1 software and Stata SE12.0 (Stata Corporation). To

Table 1. Characteristics of the eligible studies in this meta-analysis

First author	Year	Country	Cancer type	Total number	MALAT1 expression				MALAT1 Detection method
					High	High with LNM	Low	Low with LNM	
Er-Jun	2014	China	PC	126	63	46	63	22	qRT-PCR
Hai-min	2014	China	ccRCC	106	22	13	60	6	qRT-PCR
Yoshinaga	2014	USA	GC	150	88	66	62	39	qRT-PCR
Hong-Tu	2014	China	CC	146	73	19	73	23	qRT-PCR
Jiang-Hua	2014	China	PC	45	26	15	19	8	qRT-PCR

LNM lymph node metastasis, PC pancreatic cancer, ccRCC clear cell renal cell carcinoma, GC gastric cancer, CC colorectal cancer.

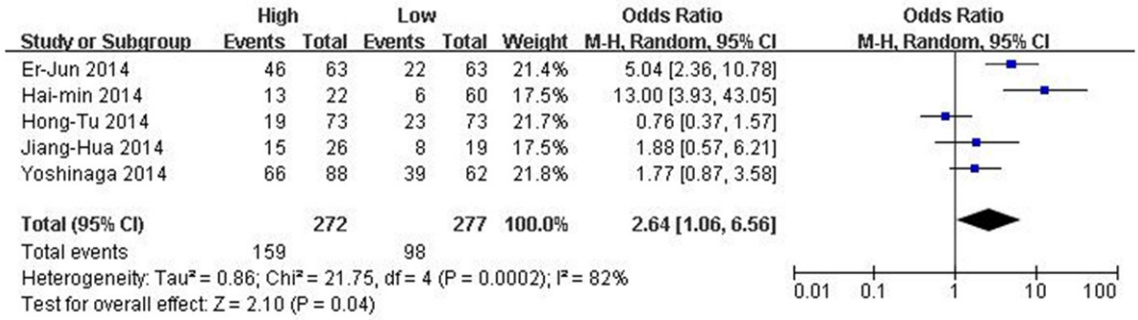

Figure 2. Forest plot for the association between MALAT1 expression levels with lymph node metastasis. Forest plot of OR was assessed for the difference in the incidence of lymph node metastasis between high MALAT1 expression group and low MALAT1 expression group (OR = 2.64, 95% CI = 1.06-6.56, P = 0.04 random-effects model).

determine the heterogeneity among the included studies, chi-square-based Q test and I^2 statistics were used. For the Q test, a *P* value less than 0.05 indicated significant heterogeneity; for the I^2 statistics, an I^2 value greater than 50% was considered severe heterogeneity. The potential publication bias was assessed using a "funnel plot" and the Begg's test. The fixed effects model was adopted in the initial calculation of odds ratio with corresponding 95% CIs. If there was a significant statistical heterogeneity among the studies, the random-effects model was applied for the analysis. By comparing the incidence of lymph node metastasis between high MALAT1 expression group and low MALAT1 expression group, we tried to make a thorough inquiry on the relationship between MALAT1 expression levels with lymph node metastasis.

Results

Studies characteristics

A total of five studies were identified as eligible according to the criteria for selection [20-24] (**Figure 1**). These studies included a total of 573 patients. The mean patient sample size was 114.6 (range 45 to 150). Four studies came from China and one study from America. All the research methods were qRT-PCR. Among the five studies, two focused on pancreatic cancer, one on clear cell renal cell carcinoma, and one on gastric cancer. All cancerous specimens were well preserved before RNA extraction. No patient received chemotherapy or radiotherapy before surgery. All the diagnoses of lymph node metastasis were based on pathology. QUADAS-2 system was to assess the qualities of included articles, and the assessment results turned out to be from moderate to high.

In the five studies, a total of four kinds of methods were used to divide high MALAT1 expression group and low MALAT1 expression group: (1) using qRT-PCR (quantitative real-time PCR) to measure the expression levels of MALAT1 in cancerous tissues (high MALAT1 group-MALAT1 expression ratio ≥ median value 6.23, low MALAT1 group-MALAT1 expression ratio < median value 6.23); (2) also using qRT-PCR to measure the expression levels of MALAT1 in

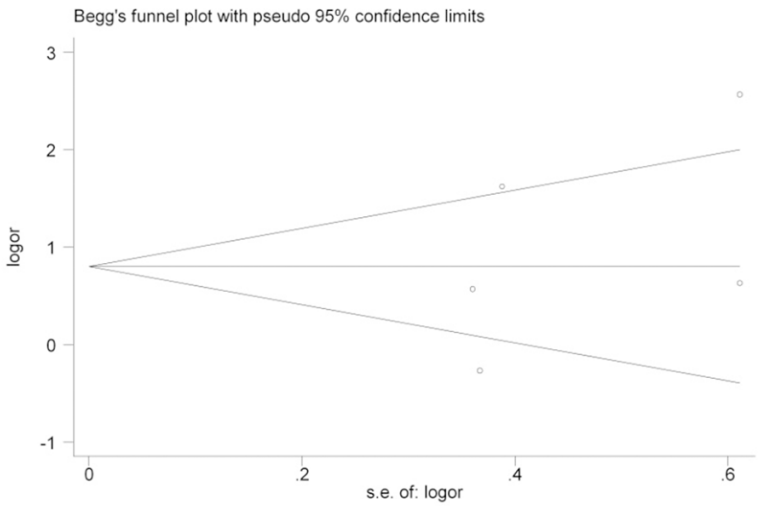

Figure 3. Funnel plot analysis of potential publication bias.

cancerous tissues (high MALAT1 group-MALAT1 expression ratio mean value, low MALAT1 group-MALAT1 expression ratio < mean value; (3) using qRT-PCR to measure the expression levels of MALAT1 in cancerous and noncancerous tissues (MALAT1 expression value of 0.985 was used as a cutoff value based on ROC analyses with Youden's index, and the expression levels of MALAT1 were defined as high (cutoff value ≥ 0.985) or low (cutoff value ≥ 0.985); (4) using qRT-PCR to measure the expression levels of MALAT1 in cancerous and noncancerous tissues (high MALAT1 group-MALAT1 expression level in cancerous tissues ≥ 2.26 fold the level in noncancerous tissues, low MALAT1 group-0MALAT1 expression level in cancerous < 2.26 fold the level in noncancerous tissues). The main characteristics of the eligible studies were summarized in **Table 1**.

Meta-analysis results

There was a significant heterogeneity among the studies (I^2 = 82%, P = 0.0002), and then the random-effects model was adopted (**Figure 2**). The odds ratios, expressed as high MALAT1 expression group versus low MALAT1 expression group, was 2.64 (CI 95% 1.06-6.56, P = 0.04 random-effects model). Through comparing the incidence of lymph node metastasis between high MALAT1 expression group and low MALAT1 expression group, we found that there was a significant difference in the incidence of lymph node metastasis between the two groups. This result demonstrated that patients detected with high MALAT1 expression in cancerous tissues were more prone to lymph node metastasis.

Publication bias

We used a funnel plot to test for publication bias (**Figure 3**). No significant publication bias was observed. Bias was assessed statistically using the Begg's test; still, the results of Begg's test (Pr > |z| = 0.462) revealed no publication bias (P > 0.05).

Discussion

LncRNAs, which are non-coding RNAs greater than 200 nt in length, were first described by Brockdorff et al [25]. Since then, especially in recent years, an increasing number of studies have reported that lncRNAs are involved in the progression of diverse diseases, especially cancers [26].

Emerging studies have proved that unique lncRNAs are associated with the development and progression of cancer through diverse pathways, including regulation of the cell cycle [27], metastasis, apoptosis, chemotherapy resistance, autophagy, and epigenetic regulation [28-32] in tumor tissues or malignant cell lines. A great number of lncRNAs can be commonly detected in various tumors, such as HOTAIR, CCAT1, ANRIL, SRHC, and MALAT1 [33-37]. Thus, lncRNAs have opened a new field of cancer genomics.

MALAT1 is a ~8000-nt long lncRNA, which is located on chromosome 11q13.1. It regulates the expression of metastasis-associated genes [38]. It also positively regulates cell motility via the transcriptional and/or post-transcriptional regulation of motility-related genes [39]. Research report indicated that MALAT1 regulated gene expression and also post-transcriptionally modified primary transcripts [40]. In addition, functional domain study also showed that 3' end of MALAT1 played a crucial role in cell proliferation, invasion and migration [41]. MALAT1 was highly expressed in lung, pancreas and multiple types of cancers [42].

To date, there have been many studies focusing on the expression levels of MALAT1 in paired

primary cancerous tissues and adjacent non-cancerous tissues. Overexpression of MALAT1 was significantly associated with high-risk grade, metastasis and survival of cancer patients. In addition, knocking down MALAT1 obviously inhibited cell proliferation, migration, and invasion, and regulated MMPs, stemness, and EMT-associated genes expression [43]. However, the precise mechanism of how MALAT1 promotes tumor cell invasion and migration is unclear. Ren S et al. [44] found that silencing MALAT1 resulted in the inhibition of CRPC cell growth and metastasis in vivo. Previous studies have shown that the up-regulation of the expression levels of matrix metalloproteinases (MMPs) is a key step for promoting cell invasion [45]. Knockdown of MALAT1 inhibited the proliferation and invasion of human osteosarcoma cell and suppressed its metastasis in vitro and vivo, and the expression of matrix metallopeptidase 9 (MMP-9) was significantly inhibited in MALAT1-deleted cells. Moreover, Dong et al. [46] found that that MALAT1 might suppress the tumor growth and metastasis via PI3K/AKT signaling pathway [46].

This meta-analysis explored the relationship between MALAT1 expression levels with lymph node metastasis. The meta-analysis results showed that the incidence of lymph node metastasis in patients detected with high MALAT1 expression was higher than that in patients with low MALAT1 expression. Nevertheless, it is still necessary to conduct larger-size and better design studies to confirm our results. In addition, the major limitation of this meta-analysis was that patients included in our study were most of Asians, only one study was from America. Because of this, our finding may just represent patients from Asia. Another limitation was that there was a high heterogeneity among the studies (I^2 = 82%, P = 0.0002), it may be due to the different methods used to divide high MALAT1 expression group and low MALAT1 expression group. Therefore, we suggest that setting up a unified criterion for the division of MALAT1 expression groups is important for further researches.

In conclusion, as a novel minimally invasive biomarker for lymph node metastasis, MALAT1 shows great potential in lymph node metastasis for cancer and warrants further study to explore its clinical application.

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Disclosure of conflict of interest

None.

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