

Original Article

Effects of long non-coding RNA MALAT1 on prognosis of various tumors: a meta-analysis of cohort studies

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Received September 29, 2015; Accepted December 19, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Background: Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is involved in tumor progression and may serve as a prognostic biomarker for various cancers. Objective: This meta-analysis aimed to reveal the association between MALAT1 expression and survival in solid tumors. Methods: A literature search was performed via electronic retrieval until August 2015. Different clinical outcomes of overall survival (OS) and disease-free survival (DFS) were analyzed. Pooled hazard ratios (HRs) or odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the relationship of high MALAT1 expression with survival rates and clinicopathological characteristics. Results: Fourteen studies with 1468 patients were included in this meta-analysis. MALAT1 overexpression was highly associated with OS of 1.64 (95% CI: 1.29-2.10) and DFS of 2.26 (95% CI: 1.66-3.08). MALAT1 overexpression was also significantly associated with tumor size (OR = 2.34; 95% CI = 1.14-4.79), tumor stage (OR = 1.48; 95% CI = 1.09-2.01), depth of invasion (OR = 1.49; 95% CI = 1.05-2.11), and lymph node metastasis (OR = 2.06; 95% CI = 1.19-3.58). Conclusion: MALAT1 overexpression is obviously ascribed to poor prognosis in numerous cancers, and MALAT1 may serve as a biomarker for the progression of solid tumors.

Keywords: MALAT1, lncRNA, solid tumor, prognosis, meta-analysis

Introduction

Dysregulation of gene expression plays a critical role in carcinogenesis and metastasis. With the development of sequencing and microarray for whole genome and transcriptome, at least 90% of the human genome has been actively transcribed into non-coding RNAs (ncRNAs); more than 80% of the transcribed RNAs did not code for proteins in mammals, and the protein-coding genes account for only 2% of the gene sequences [1, 2]. Although ncRNAs have been described as “noise” in the transcriptional process or “garbage” in the human body, substantial evidence has proven that ncRNAs also demonstrate important physiological functions in cell metabolism and play significant regulatory roles in some diseases [3-5].

Increasing numbers of long ncRNAs (lncRNAs) with length of more than 200 nt but frequently up to 100 kb are found comprising 80% of

ncRNAs, and have become the focus of recent studies. To date, lncRNAs are defined as “RNA molecules that may function as either primary or spliced transcripts and do not fit into known classes of small RNAs or into classes of structural RNAs” [4], suggesting that lncRNAs participate in multiple gene-regulating processes, such as chromosome silencing, genomic imprinting, transcriptional activation, post-transcriptional interference, and nuclear-cytoplasmic trafficking at various levels, which are involved in almost all physiological and pathological processes [6, 7]. However, current studies on lncRNAs remain at initial stage, and only few lncRNAs have been well characterized. Thus, further studies are needed to expand this research field and elucidate the functions and mechanisms of lncRNAs.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is one of the first lncRNAs

discovered; MALAT1 exhibits a length of 8000 nt and is also known as nuclear-enriched abundant transcript 2 [8]. MALAT1 cannot be translated into a protein because of its nuclear localization and the lack of an open coding frame with sufficient length [9]. Furthermore, MALAT1 gene is located in human chromosome 11q13.1 with a highly conserved and homologous sequence in evolution of various species, which indicates that this gene may potentially influence several physiological functions. Since the discovery of MALAT1 in 2003, several data have clarified the influence of this transcript on the progression or metastasis of different malignancies, such as lung cancer [10, 11], gastric cancer (GC) [12], hepatocellular carcinoma (HCC) [13], and gallbladder cancer [14]; data suggest that MALAT1 may serve as an independent factor for tumor prognosis. However, some studies reported that MALAT1 overexpression contributes to a poor survival outcome for non-small-cell lung cancer (NSCLC) [11], colorectal cancer [15], and HCC [16]; by contrast, several studies indicated that the high expression of MALAT1 is not associated with cancer prognosis [17, 18] or even predicting a better cancer prognosis [19]. Therefore, the real value of MALAT1 on predicting the prognosis of solid tumors remains contradictory, and a meta-analysis is necessary to evaluate the relationship between MALAT1 expression and solid tumor prognosis.

Materials and methods

Literature search

This meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses [20]. A systematic, computerized searching was performed through the PubMed, Embase, and Web of Science databases, as well as the China National Knowledge Infrastructure by using the following terms: "MALAT1 or Metastasis Associated Lung Adenocarcinoma Transcript 1", "Tumor or Cancer or Carcinoma", and "Prognosis or Survival or Outcome". No language restrictions were imposed, and literature search was conducted until August 5, 2015. Lists of references of retrieved articles and reviews were also checked to identify additional relevant studies.

Inclusion and exclusion criteria

Studies were eligible if they met the following criteria: 1) Studies reported the relationship between MALAT1 expression and tumor prognosis outcomes [i.e., overall survival (OS), or disease-free survival (DFS)]. 2) Studies used a cohort design. 3) Hazard ratios (HRs) and 95% confidence intervals (CIs) can be directly obtained or indirectly calculated from the original data. Studies were ineligible if they were reviews, conference abstracts, editorials or case reports, or non-human research, articles with insufficient data to estimate HRs and 95% CIs. If more than one publication with the same study population was identified, only the most recent data were included in the final analysis.

Data extraction

Information was carefully and independently extracted by two investigators (WJY and HLR) based on the inclusion and exclusion criteria stipulated above. Any disagreement was resolved through consensus. The following data were collected from each study: first author's name, year of publication, recruitment time, country of the studied population, sample size, tumor type, follow-up period, testing method of MALAT1, cut-off value, numbers of high/low MALAT1 expression, and HRs and 95% CIs for survival outcomes as applicable. Stratification into subgroups will be conducted if at least two studies reported the same outcome for the same tumor type; otherwise, they will be assigned into a subgroup named "Others." HRs and 95% CIs were preferentially obtained from the outcomes of multivariable analysis followed by univariate analysis. If no direct data were available, the HRs and 95% CIs were calculated in each study from the numbers of patients at risk and events, as well as the *P* values of log-rank statistics, or from the survival plots of Kaplan-Meier curves [21].

Quality assessment

The quality of each study included in this meta-analysis was assessed using the Newcastle Ottawa Scale (NOS) recommended by the Cochrane Non-Randomized Studies Methods Working Group [22]. Based on the NOS, studies were judged by eight items divided into three broad perspectives: selection of study groups (four items, one star each), comparability of

Meta-analysis of MALAT1 on prognosis of various tumors

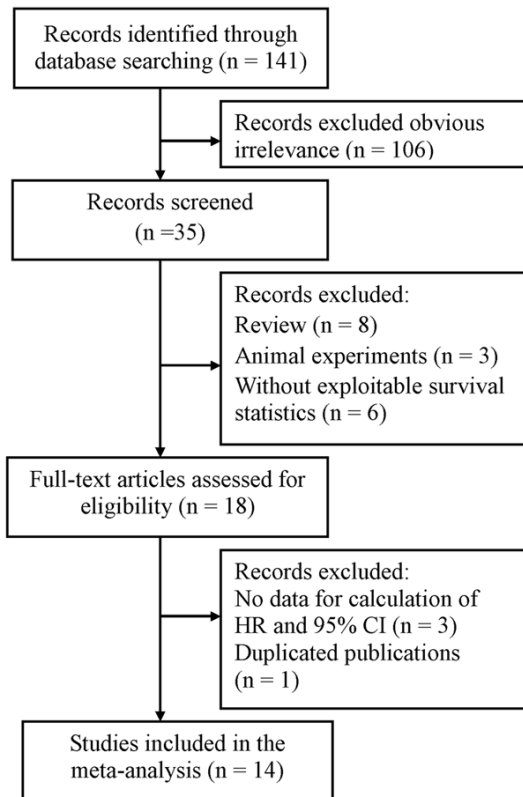


Figure 1. Flow diagram of study selection process and specific reasons for exclusion in this meta-analysis.

study groups (one item, up to two stars), and outcome of interest (three items, one star each). Stars were then added up to a total score ranging from 0 to 9. We considered studies as of high quality if they met six scores or more.

Statistical analysis

All statistical analyses were performed using STATA software version 11.0 (STATA Corporation, College Station, TX, USA). All statistical tests were two-sided. For the pooled analysis of the correlation between MALAT1 overexpression and clinicopathological parameters (age, sex, tumor size, histological grade, tumor stage, depth of invasion, lymph node metastasis, and distant metastasis), odds ratios (ORs) with their corresponding 95% CIs were combined to estimate the effects. Combined HRs and 95% CIs were used to assess the strength of the association between MALAT1 expression and different prognostic outcomes. We classified the studies into two subgroups based on different survival results (OS and DFS) to separately evaluate the effects of MALAT1 overexpression

and survival. HR > 1 indicated poor prognosis for patients with MALAT1 high expression when the 95% CI was also > 1. Statistical significance of the pooled HR was determined by Z-test, in which $P < 0.05$ was considered statistically significant.

Heterogeneity assumption was examined by chi-square test based on Q statistic and I^2 metric [23]. Heterogeneity was considered statistically significant when $P < 0.10$, which promoted the use of a random-effects model; otherwise, a fixed-effects model was used [24]. The degree of heterogeneity was quantified by the I^2 metric ($I^2 < 25\%$, no heterogeneity; $I^2 = 25\%-50\%$, moderate heterogeneity; $I^2 > 50\%$, extreme heterogeneity).

Sensitivity analysis was performed to validate the credibility of these meta-analysis outcomes. If the results did not significantly change when one study was removed, the sensitivity is low and the results are robust. Potential publication bias was evaluated statistically using Begg's and Egger's asymmetry tests [25] and visually with funnel plots. Statistical significance of Egger's test results was defined as $P < 0.10$.

Results

Characteristics of included studies

Out of the initial number of 141 studies, 14 were found eligible for this meta-analysis. The processes of identifying and selecting studies are presented in **Figure 1**. Majority the 14 studies [8, 11, 15-19, 26-32], with a total sample of 1468 patients, were almost published in 2011 or later and mainly conducted in China, whereas the others were conducted in Germany [8, 32], Japan [18], or Taiwan [29]. Twelve studies were published in English, whereas the other two were in Chinese [19, 31]. Various cancer types were recorded in our meta-analysis, including GC, HCC, and NSCLC. Quantitative real-time polymerase chain reaction was used to detect MALAT1 in all the 14 studies, and the tested specimens were all extracted from human tissues. HR estimations in 11 studies were directly extracted from original data, and three were extrapolated from survival curves [8, 11, 29]. Eleven studies reported OS as the primary outcome, whereas four trials reported data DFS [11, 15, 16, 30]. The main characteristics of these 14 studies are listed in **Table 1**.

Meta-analysis of MALAT1 on prognosis of various tumors

Table 1. Main characteristics of 11 eligible studies in the meta-analysis

Study (authors-year)	Regions	Recruitment time	Sample size	Type of tumor	Follow up (months)	Analysis method	Specimens	Cutoff value (high/low)	Analysis of variance	HR estimation	Prognostic value	Language	Quality score
Shen et al 2015	China	NR	78	Lung cancer	NR	RT-qPCR	Tissue	NR (24/54)	Univariate	DFS: 1.73 (1.07-2.79) ^Δ	Poor	English	6
Ma et al 2015	China	NR	118	Glioma	NR	RT-qPCR	Tissue	5.18* (59/59)	Multivariate	OS: 2.29 (1.37-3.81)	Poor	English	7
Zheng et al 2014	China	2007-2009	146	Colorectal Cancer	56.2 (median)	RT-qPCR	Tissue	6.15* (73/73)	Multivariate	OS: 3.97 (1.67-9.46) DFS: 2.86 (1.66-4.94)	Poor	English	6
Fan et al 2014	China	NR	95	Bladder Cancer	NR	RT-qPCR	Tissue	NR (45/50)	Multivariate	OS: 1.26 (0.68-2.13)	NS	English	7
Zhang et al 2014	China	2006-2008	106	CCRCC	NR	RT-qPCR	Tissue	3.85* (46/60)	Multivariate	OS: 3.09 (1.81-7.03)	Poor	English	7
Pang et al 2014	China	NR	126	PC	60 (total)	RT-qPCR	Tissue	6.23* (63/63)	Multivariate	OS: 1.76 (1.10-2.82)	Poor	English	7
Cho et al 2014	Taiwan	2007-2012	36	Multiple myeloma	48 (total)	RT-qPCR	Tissue	1.5* (20/16)	Univariate	OS: 1.40 (0.73-2.71) ^Δ	NS	English	6
Okugawa et al 2014	Japan	2000-2009	150	GC	NR	RT-qPCR	Tissue	0.985* (88/62)	Univariate	OS: 1.54 (0.92-2.58)	NS	English	6
Liu et al 2014	China	2010-2011	45	PC	47 (total)	RT-qPCR	Tissue	0.1035* (26/19)	Multivariate	DFS: 1.80 (1.18-7.75)	Poor	English	7
Mu et al 2013	China	2007-2008	76	NSCLC	NR	RT-qPCR	Tissue	NR (32/44)	Multivariate	OS: 0.55 (0.27-0.99)	Protective	Chinese	7
Yang et al 2012	China	2003-2010	160	HCC	24 (median)	RT-qPCR	Tissue	1.5* (88/72)	Multivariate	OS: 1.91 (1.12-3.05)	Poor	Chinese	7
Lai et al 2012	China	2003-2005	60	HCC	18.6 (median)	RT-qPCR	Tissue	NR (33/27)	Multivariate	DFS: 3.28 (1.52-7.09)	Poor	English	6
Schmidt et al 2011	Germany	1998-2005	222	NSCLC	56 (total)	RT-qPCR	Tissue	NR (83/139)	Multivariate	OS: 1.78 (1.08-2.92)	Poor	English	7
Ji et al 2003	Germany	NR	50	NSCLC	NR	RT-qPCR	Tissue	NR (28/22)	Univariate	OS: 1.33 (1.01-1.75) ^Δ	Poor	English	6

OS overall survival, DFS Disease-free Survival, NR data were not reported, NS not significant, PC pancreatic cancer, HCC hepatocellular cancer, NSCLC non-small cell lung cancer, GC gastric cancer, CCRCC clear cell renal cell carcinoma, RT-qPCR quantitative real-time polymerase chain reaction, GAPDH glyceraldehyde 3-phosphate dehydrogenase, *normalized to GAPDH, ^Δextrapolated from survival curve.

Meta-analysis of MALAT1 on prognosis of various tumors

Table 2. Meta-analysis of Rsf-1 overexpression and clinicopathological features in solid tumors patients

Categories	Studies (no. of patients)	OR (95% CI)	I ²	P _h	Z	P
Age	9 (922)	1.01 (0.77-1.34)	0.0%	0.496	0.10	0.922
Gender	9 (922)	1.04 (0.68-1.58) ^R	49.7%	0.044	0.17	0.868
Tumor size	7 (681)	2.34 (1.14-4.79) ^R	76.6%	< 0.001	2.33	0.020
Histological grade	6 (548)	0.87 (0.58-1.31)	29.5%	0.214	0.66	0.510
Tumor stage	7 (712)	1.48 (1.09-2.01) ^R	76.1%	< 0.001	2.53	0.012
Depth of invasion	5 (542)	1.49 (1.05-2.11)	49.0%	0.098	2.23	0.026
Lymph node metastasis	7 (744)	2.06 (1.19-3.58) ^R	65.4%	0.008	2.57	0.010
Distant metastasis	7 (744)	1.23 (0.59-2.57) ^R	61.8%	0.015	0.56	0.575

All pooled HRs were calculated from fixed-effect model except for cells marked with (random^R). P_h denotes P value for heterogeneity based on Q test; P denotes P value for statistical significance based on Z test.

Table 3. Main results of the meta-analysis

Survival	Categories	No. of studies	No. of patients	HR (95% CI)	I ²	P _h	Z	P	Egger's test		Begg's test		
									t	P	Z	P	
OS	All	11	1285	1.644 (1.289-2.098) ^R	57.4%	0.009	4.00	< 0.001	0.95	0.365	0.93	0.350	
	Cancer type												
	NSCLC	3	348	1.150 (0.670-1.974) ^R	75.8%	0.016	0.51	0.613	0.57	0.673	0.00	1.000	
	Others	8	937	1.875 (1.535-2.290)	20.5%	0.267	6.16	< 0.001	0.62	0.536	1.41	0.207	
	Ethnicity												
	China	7	827	1.775 (1.175-2.681) ^R	71.1%	0.002	2.73	0.006	0.90	0.368	0.30	0.774	
	Abroad	4	458	1.440 (1.171-1.770)	0.0%	0.779	3.45	0.001	-0.34	1.000	1.18	0.361	
	Analysis method												
	Multivariate	8	1049	1.771 (1.249-2.512) ^R	66.3%	0.004	3.21	0.001	1.11	0.266	0.31	0.765	
	Univariate	3	236	1.377 (1.097-1.729)	0.0%	0.885	2.76	0.006	0.00	1.000	1.09	0.473	
Sample size													
≥ 100	7	1028	2.014 (1.639-2.473)	0.0%	0.451	6.67	< 0.001	1.80	0.072	4.02	0.010		
< 100	4	257	1.116 (0.770-1.619) ^R	52.5%	0.097	0.58	0.562	0.34	0.734	0.86	0.480		
DFS	All	4	329	2.260 (1.661-3.075)	1.1%	0.386	5.19	< 0.001	0.34	0.734	0.38	0.740	

All pooled HRs were calculated from fixed-effect model except for cells marked with (random^R). P_h denotes P value for heterogeneity based on Q test; P denotes P value for statistical significance based on Z test.

Correlation of MALAT1 expression with clinicopathological parameters

The correlations of MALAT1 expression with clinicopathological characteristics are presented in **Table 2**. Relationships existed between MALAT1 overexpression and some phenotypes of tumor progression, such as tumor size (pooled OR = 2.34; 95% CI = 1.14-4.79; P = 0.020; random effects), tumor stage (pooled OR = 1.48; 95% CI = 1.09-2.01; P = 0.012; random effects), depth of invasion (pooled OR = 1.49; 95% CI = 1.05-2.11; P = 0.026; fixed effects), and lymph node metastasis (pooled OR = 2.06; 95% CI = 1.19-3.58; P = 0.010; random effects), which suggested that MALAT1 may demonstrate a promoting effect on tumor progression. However, when age (pooled OR = 1.01; 95% CI = 0.77-1.34; P = 0.922; fixed

effects), gender (pooled OR = 1.04; 95% CI = 0.68-1.58; P = 0.868; random effects), histological grade (pooled OR = 0.87; 95% CI = 0.58-1.31; P = 0.510; fixed effects), and distant metastasis (pooled OR = 1.23; 95% CI = 0.59-2.57; P = 0.575; random effects) were considered, no significant association existed.

Effect of MALAT1 expression on survival

The main results of the analysis on the relationship between MALAT1 overexpression and survival are summarized in **Table 3**, and the forest plots for the overall association between MALAT1 overexpression and survivals are shown in **Figure 2**. Summary of the reported HRs for OS from the 11 individual studies with a total of 1285 patients suggested that high MALAT1 expression indicated a poor prognosis for OS (HR = 1.64; 95% CI, 1.29-2.10; P <

Meta-analysis of MALAT1 on prognosis of various tumors

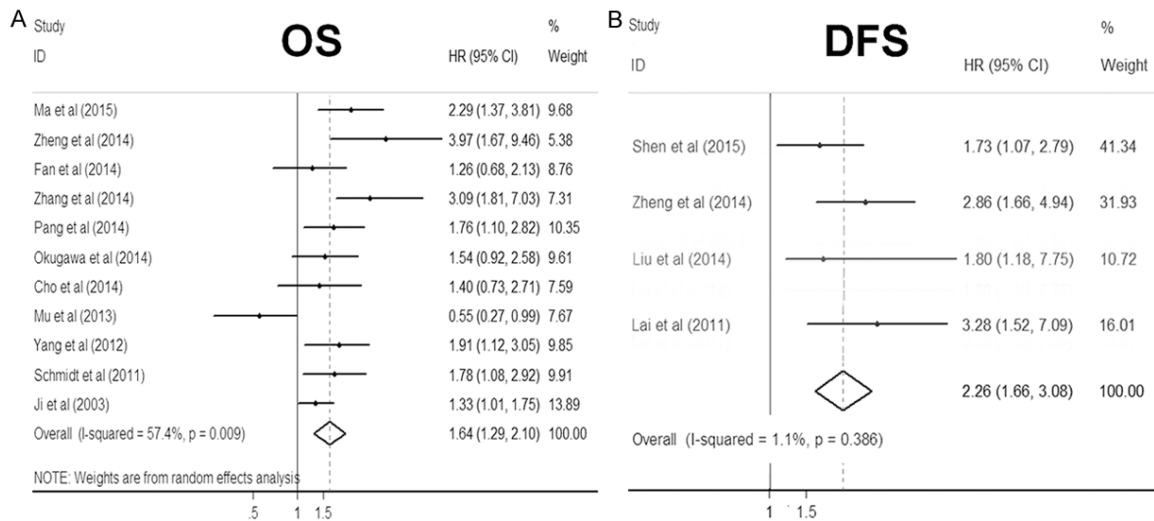


Figure 2. Forest plots of overall association between MALAT1 expression and survival in solid tumors. A. Forest plot for pooled OS estimation. B. Forest plot for pooled DFS estimation.

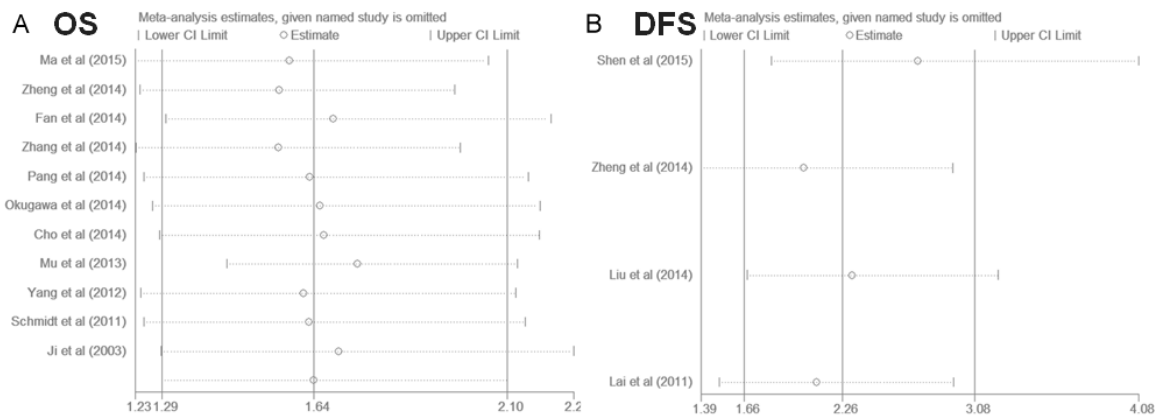


Figure 3. Effects of individual studies on pooled hazard ratios (HRs) for MALAT1 expression and survival in solid tumors. A. Result of sensitivity analysis for pooled OS estimation. B. Result of sensitivity analysis for pooled DFS estimation.

0.001; random effects) with a moderate heterogeneity ($I^2 = 57.4\%$, $P_h = 0.009$). When the eligible studies were stratified into subgroup analyses, a significant correlation was observed in studies published in China (HR = 1.78; 95% CI, 1.18-2.68; $P = 0.006$; random effects) or those published abroad (HR = 1.44; 95% CI, 1.17-1.77; $P = 0.001$; fixed effects), as well as in multivariate analysis (HR = 1.77; 95% CI, 1.25-2.51; $P = 0.001$; random effects) and univariate analysis (HR = 1.38; 95% CI, 1.10-1.73; $P = 0.006$; fixed effects). However, when the subgroup analyses were conducted in terms of tumor types and sample sizes, the negative role of MALAT1 in predicting cancer prognosis was

obvious in other cancer types (HR = 1.88; 95% CI, 1.54-2.29; $P < 0.001$; fixed effects), and studies with number of cases ≥ 100 (HR = 2.01; 95% CI, 1.64-2.47; $P < 0.001$; fixed effect), but not in NSCLC (HR = 1.15; 95% CI, 0.67-1.97; $P = 0.613$; random effects), nor those with number of cases < 100 (HR = 1.12; 95% CI, 0.77-1.62; $P = 0.562$; random effects).

Four studies comprising 329 patients reported DFS as the primary endpoint, upregulation of MALAT1 was associated with worse DFS (HR = 2.26; 95% CI, 1.66-3.08; $P < 0.001$; fixed effects), and significant heterogeneity did not exist ($I^2 = 1.1\%$, $P_h = 0.386$).

Meta-analysis of MALAT1 on prognosis of various tumors

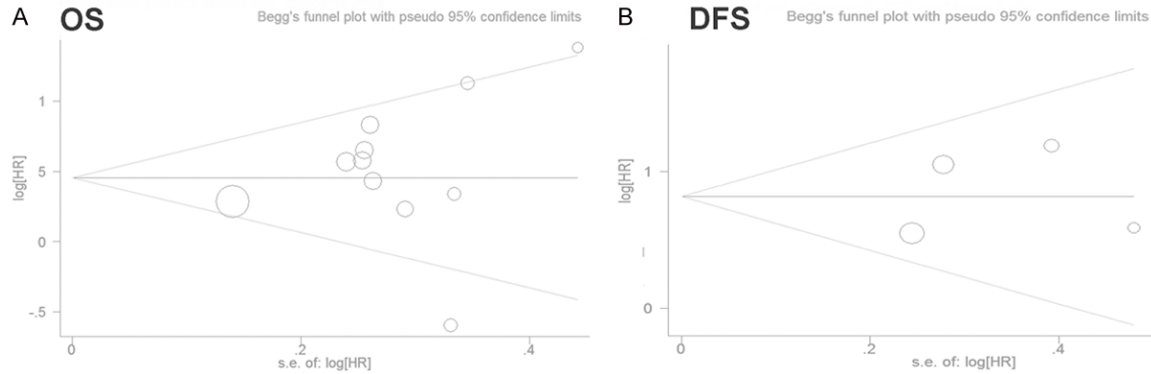


Figure 4. Begg's funnel plots of overall relationship between MALAT1 expression and survival in solid tumors. A. Begg's funnel plot of publication-bias analysis for pooled OS estimation. B. Begg's funnel plot of publication-bias analysis for pooled DFS estimation.

Sensitivity analysis and publication bias

Sensitivity analysis of pooled OS and pooled DFS is presented in **Figure 3**. Notably, the corresponding overall HR estimated by OS or DFS did not change significantly when each study was omitted individually. These results suggest that no individual study affected the meta-analysis results, and the outcomes of this meta-analysis were robust.

Neither Egger's test nor Begg's test showed obvious publication bias for the pooled HR estimations of OS (Egger's test, $t = 0.95$, $P = 0.365$; Begg's test, $Z = 0.93$, $P = 0.350$) or DFS (Egger's test, $t = 0.34$, $P = 0.734$; Begg's test, $Z = 0.38$, $P = 0.740$) (**Table 3**). The shapes of the funnel plots (**Figure 4**) also did not show apparent evidence of asymmetry, indicating that our results were statistically credible.

Discussion

The invasion and metastasis of solid tumors comprise an extremely complex process involving an interplay among multiple cytokines, signal pathways, and other factors; invasion and metastasis of solid tumors mainly cause of death in patients. Thus, searching for sensitive and specific biomarkers for early tumor detection and accurate prognosis, as well as targets for more efficient treatment, is valuable. MALAT1 was upregulated in many solid tumors, including lung cancer [8], bladder cancer [17], HCC [33], and colorectal cancer [34]. MALAT1 can promote tumor cell proliferation and migration, which implies its participation in human cancer development [9]. High level expression of MALAT1 in tissues with cancer metastasis

suggested that this transcript may significantly affect tumor progression [35]. However, the prognostic role of MALAT1 on solid tumors remains uncertain. Considering meta-analysis can provide an overall and precise evaluation of several individual studies for a specified outcome, we conducted this first meta-analysis to explore the prognostic values of lncRNA MALAT1 in solid tumors.

In this meta-analysis, we included 14 cohort studies and classified these into two subgroups based on the reported survival outcomes. In both OS and DFS subgroups, the overexpression of MALAT1 is highly related with shorter survival, which suggested that MALAT1 is a marker for poor prognosis in patients with solid tumors. When the trials in the OS subgroup were further stratified for various characteristics, the high level of MALAT1 expression was significantly associated with worse prognosis, as shown in the results of either multivariate or univariate analysis, which indicated that MALAT1 may serve as an independent, negative biomarker for OS. Furthermore, when the studies in OS subgroup were analyzed by ethnicity, worse OS was presented in patients with high MALAT1 expression in China and abroad, which revealed that the effects of MALAT1 on cancer development showed no racial and environmental influence. In addition, MALAT1 showed obvious effects on poor OS in patients with cancer type other than NSCLC, although MALAT1 was originally found in patients with lung cancer. Of the three cohorts reporting the relationship of MALAT1 and NSCLC, we noted that two reported MALAT1 genes as tumor-promoting factors [8, 32], whereas one was regard-

ed as a tumor suppressor [19]. Thus, the influence of MALAT1 on NSCLC remains controversial, and conclusion should be made with caution because only 348 patients were included in these studies.

Moreover, significant correlations were found between MALAT1 high expression and some clinicopathological features, such as tumor size, tumor stage, depth of invasion, and lymph node metastasis, which revealed that MALAT1 may boost tumor progression and aggressiveness. MALAT1 was originally found as a metastasis-related gene in NSCLC. Tano et al. [36] found that after MALAT1 was interfered by siRNA, four different genes (CTHRC1, CCT4, HMMR, and ROD1) related to cell mobility were found by comparing the pre- and post-interference gene expression screening, and knock-down of any of the above-mentioned genes can significantly suppress the migration of lung cancer cells; this indicated that MALAT1 can control the migration ability of lung cancer cells by regulating mobility-related genes. Moreover, epithelial-mesenchymal transition (EMT) is a key step of tumor metastasis, and loss of expression of E-cadherin is one of the landmark events [37]. In bladder cancer, MALAT1 can suppress the expression of E-cadherin, promote EMT, and finally assist tumor metastasis [17, 38]. Furthermore, MALAT1 advances the cell differentiation and the cell proliferation in gastric cancer by recruiting and regulating SF2/ASF which plays a vital role in inflammatory diseases and human tumors by alternative splicing [12]. Above all, we can learn that MALAT1 can affect the occurrence and development of different tumors by a variety of pathways; however, the mechanisms remain unclear. Thus, more studies should be conducted to explore its biological functions.

Although this meta-analysis showed some advantages through an overall and consistent estimation, a few limitations should be acknowledged. First, the heterogeneities of some pooled results were moderate or even extreme, and subgroup analyses cannot identify the source of heterogeneity. Second, the number of included studies and the total sample size were relatively small. Third, prognosis is a comprehensive final result reflected by multiple factors, for instance, tumor types, therapeutic regimen, tumor location, and histological types. Nevertheless, we failed to assess these poten-

tial confounders in individual studies. Fourth, the inconsistency in cut-off values and experimental designs may in part a source of the inter-study heterogeneity. Finally, the HRs in some studies in our meta-analysis was calculated from the survival curves, which may lead to some minor differences from the actual HRs [22].

In conclusion, lncRNA MALAT1 overexpression is associated with a poor survival rate on OS as well as DFS in many cancer types, and MALAT1 may be an independent biomarker for indicating aggressive tumor development and poor prognosis in solid tumors. However, one should take caution to interpreting these results due to the limitations in this current meta-analysis, and large scale, high-quality clinical investigations are still needed to further confirm these results.

Acknowledgements

This study was funded by the Scientific and Technological Innovation Project of Educational Commission of Guangdong Province (Grant No. 2013KJ CX0092).

Disclosure of conflict of interest

None.

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References

- [1] ENCODE Project Consortium, Birney E, Stamatoyannopoulos JA, Dutta A, Guigo R, Gingeras TR, Margulies EH, Weng Z, Snyder M, Dermitzakis ET, Thurman RE, Kuehn MS, Taylor CM, Neph S, Koch CM, Asthana S, Malhotra A, Adzhubei I, Greenbaum JA, Andrews RM, Flicek P, Boyle PJ, Cao H, Carter NP, Clelland GK, Davis S, Day N, Dhami P, Dillon SC, Dorschner MO, Fiegler H, Giresi PG, Goldy J, Hawrylycz M, Haydock A, Humbert R, James KD, Johnson BE, Johnson EM, Frum TT, Rosenzweig ER, Karnani N, Lee K, Lefebvre GC, Navas PA, Neri F, Parker SC, Sabo PJ, Sandstrom R, Shafer A, Vetrie D, Weaver M, Wilcox S, Yu M, Collins FS, Dekker J, Lieb JD, Tullius TD, Crawford GE, Sunyaev S, Noble WS, Dunham I, Denoeud F, Rey-

Meta-analysis of MALAT1 on prognosis of various tumors

- mond A, Kapranov P, Rozowsky J, Zheng D, Castelo R, Frankish A, Harrow J, Ghosh S, Sandelin A, Hofacker IL, Baertsch R, Keefe D, Dike S, Cheng J, Hirsch HA, Sekinger EA, Lagarde J, Abril JF, Shahab A, Flamm C, Fried C, Hacker-müller J, Hertel J, Lindemeyer M, Missal K, Tanzer A, Washietl S, Korb J, Emanuelsson O, Pedersen JS, Holroyd N, Taylor R, Swarbreck D, Matthews N, Dickson MC, Thomas DJ, Weirauch MT, Gilbert J, Drenkow J, Bell I, Zhao X, Srinivasan KG, Sung WK, Ooi HS, Chiu KP, Foisac S, Alioto T, Brent M, Pachter L, Tress ML, Valencia A, Choo SW, Choo CY, Ucla C, Manzano C, Wyss C, Cheung E, Clark TG, Brown JB, Ganesh M, Patel S, Tammana H, Chrast J, Henriksen CN, Kai C, Kawai J, Nagalakshmi U, Wu J, Lian Z, Lian J, Newburger P, Zhang X, Bickel P, Mattick JS, Carninci P, Hayashizaki Y, Weissman S, Hubbard T, Myers RM, Rogers J, Stadler PF, Lowe TM, Wei CL, Ruan Y, Struhl K, Gerstein M, Antonarakis SE, Fu Y, Green ED, Karaöz U, Siepel A, Taylor J, Liefer LA, Wetterstrand KA, Good PJ, Feingold EA, Guyer MS, Cooper GM, Asimenos G, Dewey CN, Hou M, Nikolaev S, Montoya-Burgos JI, Löytynoja A, Whelan S, Pardi F, Massingham T, Huang H, Zhang NR, Holmes I, Mullikin JC, Ureta-Vidal A, Paten B, Srinivasan M, Church D, Rosenbloom K, Kent WJ, Stone EA; NISC Comparative Sequencing Program; Baylor College of Medicine Human Genome Sequencing Center; Washington University Genome Sequencing Center; Broad Institute; Children's Hospital Oakland Research Institute, Batzoglou S, Goldman N, Hardison RC, Haussler D, Miller W, Sidow A, Trinklein ND, Zhang ZD, Barrera L, Stuart R, King DC, Ameur A, Enroth S, Bieda MC, Kim J, Bhinge AA, Jiang N, Liu J, Yao F, Vega VB, Lee CW, Ng P, Shahab A, Yang A, Moqtaderi Z, Zhu Z, Xu X, Squazzo S, Oberley MJ, Inman D, Singer MA, Richmond TA, Munn KJ, Rada-Iglesias A, Wallerman O, Komorowski J, Fowler JC, Couttet P, Bruce AW, Dovey OM, Ellis PD, Langford CF, Nix DA, Euskirchen G, Hartman S, Urban AE, Kraus P, Van Calcar S, Heintzman N, Kim TH, Wang K, Qu C, Hon G, Luna R, Glass CK, Rosenfeld MG, Aldred SF, Cooper SJ, Halees A, Lin JM, Shulha HP, Zhang X, Xu M, Haidar JN, Yu Y, Ruan Y, Iyer VR, Green RD, Wadelius C, Farnham PJ, Ren B, Harte RA, Hinrichs AS, Trumbower H, Clawson H, Hillman-Jackson J, Zweig AS, Smith K, Thakkarapallayil A, Barber G, Kuhn RM, Karolchik D, Armengol L, Bird CP, de Bakker PI, Kern AD, Lopez-Bigas N, Martin JD, Stranger BE, Woodroffe A, Davydov E, Dimas A, Eyras E, Hallgrímsson IB, Huppert J, Zody MC, Abecasis GR, Estivill X, Bouffard GG, Guan X, Hansen NF, Idol JR, Maduro VV, Maskeri B, McDowell JC, Park M, Thomas PJ, Young AC, Blakesley RW, Muzny DM, Sodergren E, Wheeler DA, Worley KC, Jiang H, Weinstock GM, Gibbs RA, Graves T, Fulton R, Mardis ER, Wilson RK, Clamp M, Cuff J, Gnerre S, Jaffe DB, Chang JL, Lindblad-Toh K, Lander ES, Koriabine M, Nefedov M, Osoegawa K, Yoshinaga Y, Zhu B, de Jong PJ. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature* 2007; 447: 799-816.
- [2] Esteller M. Non-coding RNAs in human disease. *Nat Rev Genet* 2011; 12: 861-874.
- [3] Ebisuya M, Yamamoto T, Nakajima M, and Nishida E. Ripples from neighbouring transcription. *Nat Cell Biol* 2008; 10: 1106-1113.
- [4] Mercer TR, Dinger ME, and Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet* 2009; 10: 155-159.
- [5] Deng Q, Sun H, He B, Pan Y, Gao T, Chen J, Ying H, Liu X, Wang F, Xu Y, Wang S. Prognostic value of long non-coding RNA HOTAIR in various cancers. *PLoS One* 2014; 9: e110059.
- [6] Kung JT, Colognori D and Lee JT. Long noncoding RNAs: past, present, and future. *Genetics* 2013; 193: 651-669.
- [7] Yoon JH, Abdelmohsen K, and Gorospe M. Posttranscriptional gene regulation by long noncoding RNA. *J Mol Biol* 2103; 425: 3723-3730.
- [8] 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, Müller-Tidow C. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* 2003; 22: 8031-8041.
- [9] Gutschner T, Hammerle M, and Diederichs S. MALAT1-a paradigm for long noncoding RNA function in cancer. *J Mol Med* 2013; 91: 791-801.
- [10] Gutschner T, Hammerle M, Eissmann M, Hsu J, Kim Y, Hung G, Revenko A, Arun G, Stentrup M, Gross M, Zörnig M, MacLeod AR, Spector DL, Diederichs S. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. *Cancer Res* 2013; 73: 1180-1189.
- [11] Shen LQ, Chen L, Wang YS, Jiang XC, Xia HP, and Zhuang ZX. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. *J Neurooncol* 2015; 121: 101-108.
- [12] Wang J, Su L, Chen X, Li P, Cai Q, Yu B, Liu B, Wu W, Zhu Z. MALAT1 promotes cell proliferation in gastric cancer by recruiting SF2/ASF. *Biomed Pharmacother* 2014; 68: 557-564.
- [13] Li G, Zhang H, Wan X, Yang X, Zhu C, Wang A, He L, Miao R, Chen S, Zhao H. Long noncoding RNA plays a key role in metastasis and progno-

Meta-analysis of MALAT1 on prognosis of various tumors

- sis of hepatocellular carcinoma. *Biomed Res Int* 2014; 2014: 780521.
- [14] Wu XS, Wang XA, Wu WG, Hu YP, Li ML, Ding Q, Weng H, Shu YJ, Liu TY, Jiang L, Cao Y, Bao RF, Mu JS, Tan ZJ, Tao F, Liu YB. MALAT1 promotes the proliferation and metastasis of gallbladder cancer cells by activating the ERK/MAPK pathway. *Cancer Biol Ther* 2014; 15: 806-814.
- [15] Zheng HT, Shi DB, Wang YW, Li XX, Xu Y, Tripathi P, Gu WL, Cai GX, Cai SJ. High expression of lncRNA MALAT1 suggests a biomarker of poor prognosis in colorectal cancer. *Int J Clin Exp Pathol* 2014; 7: 3174-3181.
- [16] Lai MC, Yang Z, Zhou L, Zhu QQ, Xie HY, Zhang F, Wu LM, Chen LM, Zheng SS. Long non-coding RNA MALAT-1 overexpression predict tumor recurrence of hepatocellular carcinoma after liver transplantation. *Med Oncol* 2012; 29: 1810-1816.
- [17] Fan Y, Shen B, Tan MY, Mu XY, Qin Y, Zhang F, Liu Y. TGF- β -induced upregulation of MALAT1 promotes bladder cancer metastasis by associating with suz12. *Clin Cancer Res* 2014; 20: 1531-1541.
- [18] Okugawa Y, Toiyama Y, Hur K, Toden S, Saigusa S, Tanaka K, Inoue Y, Mohri Y, Kusunoki M, Bolland CR, Goel A. Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. *Carcinogenesis* 2014; 35: 2731-2739.
- [19] Mu YY. Expression of the long noncoding MALAT-1 RNA in NSCLC tissues and its clinical significance, MS, Dissertation, Henan University, 2013.
- [20] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; 6: e1000100.
- [21] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; 8: 16.
- [22] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M. The Newcastle-Ottawa Scale(NOS) for assessing the quality of non-randomised studies in meta-analyses, Ottawa Health Research Institute Web site, 2012.
- [23] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-560.
- [24] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22: 719-748.
- [25] Egger M, Davey SG, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-634.
- [26] Ma KX, Wang HJ, Li XR, Li T, Su G, Yang P, Wu JW. Long noncoding RNA MALAT1 associated with the malignant status and poor prognosis in glioma. *Tumor Biol* 2015; 36: 3355-3359.
- [27] Zhang HM, Yang FQ, Chen SJ, Che JP and Zheng JH. Upregulation of long non-coding RNA MALAT1 correlates with tumor progression and poor prognosis in clear cell renal cell carcinoma. *Tumor Biol* 2014; 36: 2947-2955.
- [28] Pang EJ, Yang R, Fu XB and Liu YF. Overexpression of long non-coding RNA MALAT1 is correlated with clinical progression and unfavorable prognosis in pancreatic cancer. *Tumor Biol* 2014; 36: 2403-2407.
- [29] Cho SF, Chang YC, Chang CS, Lin SF, Liu YC, Hsiao HH, Chang JG, Liu TC. MALAT1 long non-coding RNA is overexpression in multiple myeloma and may serve as a marker to predict disease progression. *BMC Cancer* 2104; 14: 809.
- [30] Liu JH, Chen G, Dang YW, Li CJ and Luo DZ. Expression and prognostic significance of lncRNA MALAT1 in pancreatic cancer tissues. *Asian Pac J Cancer Prev* 2104; 15: 2971-2977.
- [31] Yang Z. Molecular biomarkers for predicting tumor recurrence and prognosis in hepatocellular carcinoma after liver transplantation. Ph. D. Dissertation, Zhejiang University 2012.
- [32] Schmidt LH, Spieker T, Koschmieder S, Humberg J, Jungen D, Bulk E, Hascher A, Wittmer D, Marra A, Hillejan L, Wiebe K, Berdel WE, Wiewrodt R, Muller-Tidow C. The long noncoding MALAT1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. *J Thorac Oncol* 2011; 6: 1984-1992.
- [33] Lin R, Maeda S, Liu C, Karin M and Edgington TS. A large noncoding RNA is a marker for murine hepatocellular carcinoma and a spectrum of human carcinomas. *Oncogene* 2007; 26: 851-858.
- [34] Ji Q, Zhang L, Liu X, Zhou L, Wang W, Han Z, Sui H, Tang Y, Wang Y, Liu N, Ren J, Hou F, Li Q. Long noncoding RNA MALAT1 promotes tumor growth and metastasis in colorectal cancer through binding to SFPQ and releasing oncogene PTBP2 from SFPQ/PTBP2 complex. *BJC* 2014; 111: 736-748.
- [35] Tseng JJ, Hsieh YT, Hsu SL, and Chou MM. Metastasis associated lung adenocarcinoma transcript 1 is up-regulated in placenta previa increta/percreta and strongly associated with trophoblast-like cell invasion in vitro. *Mol Hum Reprod* 2009; 15: 725-731.
- [36] Tano K, Mizuno R, Okada T, Rakwal R, Shibato J, Masuo Y, Ijiri K, Akimitsu N. MALAT1 enhances cell motility of lung adenocarcinoma cells by influencing the expression of motility-related genes. *FEBS Lett* 2010; 584: 4575-4580.

Meta-analysis of MALAT1 on prognosis of various tumors

- [37] Chua HL, Bhat-Nakshatri P, Clane SE, Morimiya A, Badve S and Nakshatri H. NF-kappaB represses E-cadherin expression and enhances epithelial to mesenchymal transition of mammary epithelial cells: potential involvement of ZEB-1 and ZEB-2. *Oncogene* 2007; 26: 711-724.
- [38] Ying L, Chen Q, Wang Y, Zhou Z, Huang Y and Qiu F. Upregulated MALAT1 contributes to bladder cancer cell migration by inducing epithelial-to-mesenchymal transition. *Mol Biosyst* 2012; 8: 2289-2294.