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ORIGINAL ARTICLE

High expression level of long non-coding RNA HOTAIR is associated with poor overall survival in gastric cancer patients: evidence from meta-analysis

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Summary

Purpose: *Although several studies have investigated the association between the development of gastric cancer (GC) and the expression level of long non-coding (lnc) RNA HOTAIR, no clear evidence about whether its expression is associated with the overall survival (OS) of GC patients exists. In this study we tried to explore the association between lncRNA HOTAIR expression levels with OS and other clinical features in GC patients.*

Methods: *Databases including PubMed, EMBASE and the Cochrane Library were used to search eligible studies. The quality of included studies was assessed according to reporting recommendations for tumor marker prognostic studies (REMARK). The association between the expression level of lncRNA HOTAIR and OS was evaluated by calculating the pooled hazard ratio (HR) and 95% confidence interval (95% CI) using the STATA software, version 12.0.*

Results: *A total of 9 studies involving 740 GC and 768 normal gastric tissues were included in this meta-analysis. The average score of quality assessment was 18.89±1.08, (range 16.5-20). The results indicated that high expression levels of lncRNA HOTAIR were associated with poor OS in GC patients (pooled HR: 1.43, 95% CI:1.17-1.76, p=0.000). Subgroup analyses showed that elevated expression of lncRNA HOTAIR was significantly associated with poor OS in Chinese GC patients (HR=1.414, 95%CI: 1.120-1.785, p=0.000), and not treated GC patients (HR=1.464, 95%CI: 1.179-1.817, p=0.001). Subgroup analyses also revealed that some GC patients features (e.g. T3-T4, III/IV stage, differentiation) were associated with an unfavorable outcome.*

Conclusions: *High expression level of lncRNA HOTAIR is associated with a poor OS in GC patients. Thus, lncRNA HOTAIR might be a potentially useful independent prognostic biomarker for GC.*

Key words: *gastric cancer, long non-coding RNA HOTAIR, overall survival*

Introduction

GC is the third leading cause of cancer-related deaths and the fourth most common malignancy in Eastern Asia, especially in China [1,2]. In 2013, GC was diagnosed in 984,000 patients, resulting in the death of about 85% in US [3]. Following liver carcinoma and lung cancer, GC is also the third leading cause of disability-adjusted life years, accounting for 28, 23 and 20%, respectively [4]. Owing to the lack of specific pathology biomakers for early-stage disease, a growing number of GC patients are diagnosed in advanced stages, which may lead to short OS rates [5].

lncRNAs refer to a class of transcribed RNA molecules ranging from 200 to 100 kbp in length

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[6]. LncRNAs are involved in several biological processes such as imprinting [7], embryogenesis [8], transcriptional [9] and epigenetic regulation [10]. HOX transcript antisense intergenic RNA (HOTAIR) is a lncRNA with an approximate length of 2.2 kbp transcribed from the HOXC locus that firstly gained attention for its expression in breast cancer [11]. Later, more evidence has been accumulated about the altered expression of lncRNAs in various diseases including cancer, and the pivotal role played in cancer progression and metastasis, such in the case of liver, gallbladder and lung cancer [12-14]. As a consequence, several studies have investigated the association between development and metastasis of GC and the expression level of HOTAIR, showing a relation with the tumor size, pathological stage, and metastasis in GC patients [15]. However, whether its expression is correlated with OS and clinical features for GC patients remains without a clear conclusion. Therefore, we decided to conduct a meta-analysis involving 9 published studies with a total of 740 GC and 768 normal gastric tissues, with the aim to get an overall understanding about lncRNA HOTAIR and its correlation with OS, along with its clinical characteristics in GC patients.

Methods

Literature search

To identify all publications relevant to the association between lncRNA HOTAIR and OS of GC patients, we performed a comprehensive literature search until January 30, 2016, by using PubMed, EMBASE database and the Cochrane Library. The search terms were as follows: "gastric cancer" OR "stomach neoplasm" OR "stomach cancer" OR "gastric neoplasm" OR "gastric carcinoma" OR "stomach carcinoma" AND "Long Noncoding RNA" OR "Long Noncoding RNA" OR "Long Non Coding RNA" OR "LncRNA". References of interest were tracked. Our research was limited to English-language articles.

Selection criteria

Eligible studies for this meta-analysis met the following criteria: (1) patients were confirmed to have gastric cancer by pathological or histological examination; (2) explored lncRNA expression in GC subjects; (3) evaluation of the association between HOTAIR and OS; (4) sufficient data to estimate the hazard ratio (HR) and its 95% confidence interval (95% CI); (5) publication as a full research article in English.

The exclusion criteria were as follows: (1) studies assessing the molecular structure and function of HOTAIR; (2) review articles, case reports, abstracts, editorials, letters and meta-analyses; (3) articles without sufficient data to analyze after contacting the authors of the study; (4) duplicate publications.

Data extraction

Two reviewers (Ma JC and Zhang YB) independently extracted the relevant data from the selected studies by using a predesigned data form. Any disagreements were solved by discussion. Data retrieved from each publication included: (1) basic characteristics of each study, such as the first author, year of publication, country, sample size, control sources, level of lncRNA expression, cut-off values; (2) OS: if the HRs were reported in the publication, they were directly obtained from the text. Otherwise, we recalculated the HRs from the published data including the number of GC patients at risk or their p value; and (3): if the direct calculation was not possible, we attempted to obtain the HRs from the Kaplan-Meier curves by using the HR digitizer software Engauge 4.0 and the software GetData Graph Digitizer 2.24 to extract and digitize the survival data [16].

Quality assessment

Quality assessment for each eligible study was carried out by the same two reviewers who independently read and scored each publication, according to the reported recommendations for tumor marker prognostic studies (REMARK) [17]. The REMARK checklist was categorized into four main dimensions and 20 items: introduction, materials and methods (patients, specimen characteristics, assay methods, study design, and statistical analysis methods), results (data, analysis and presentation), and discussion. Each item was evaluated as "reported", "unclear", or "not reported" and scored as "1", "0.5", or "0", respectively. Finally, the total score of each study represented the overall result of quality assessment.

Statistics

OS for each GC patient was measured from the date of any treatment (surgery, chemotherapy, or any others) until the date of death resulting from any cause, or the last known follow-up for patients that were still alive. The potential association between the expression level of lncRNA HOTAIR and OS for GC patients was assessed by calculating the pool HR and 95% CI using the software STATA 12.0. Heterogeneity was evaluated with a x^2-based Q-test: if the p value was higher than 0.1 or I^2 was lower than 50%, it demonstrated that all included studies were lacking heterogeneity, and the Mantel-Haenszel method (fixed effect model) was used to merge the studies. Otherwise, the random effect model was adopted. Subgroup analyses were performed for different ethnicity, diagnosis, region, cut-off value and control sources. In addition, potential publication bias was diagnosed and measured by Funnel plots. All p values were two-sided and statistical significance was set at $p \leq 0.05$.

Results

Characteristics of included studies

According to our search strategy, a total of 341 studies were identified. Following the inclusion

and exclusion criteria, 9 case-control studies [18-26] consisting of 740 gastric tumors and 768 non tumor gastric tissues were selected and included in this meta-analysis. Detailed information about the flow chart of the study selection process is reported in Figure 1.

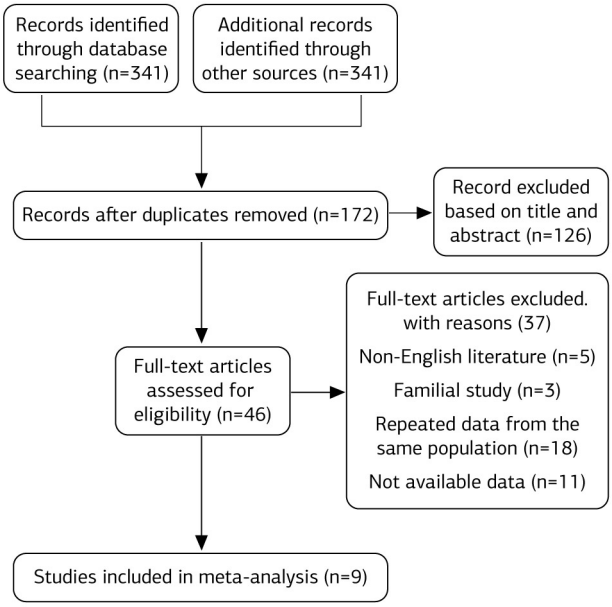

Figure 1. Flow chart of the study selection process.

The general characteristics of the included publications are presented in Table 1. All of these studies were case-control studies with tissues samples derived from patients presenting with GC. Real-time PCR was performed to measure the expression levels of HOTAIR in cancer tissues and in non-cancer tissues. Regarding the geographical distribution, 5 studies were conducted in China, 2 in Japan, 1 in Iran and 1 in Korea. In 4 studies data were analyzed by using the multivariate and univariate analysis model, while for the others only the univariate analysis was used. The average score of quality assessment was 18.89±1.08, with a range from 16.5 to 20.

Overall survival

The main results of meta-analysis are shown in Figure 2. Among the included studies, 7 reported the HRs for OS. We observed inter-study heterogeneity (I^2=10.8%, p=0.346). Overall, our results showed that high expression levels of lncRNA HOTAIR correlated with poor OS in GC patients (pooled HR:1.43, 95% CI:1.17-1.76, p=0.000).

Subgroup analysis of OS

Studies were grouped according to ethnicity,

Table 1. Characteristics of eligible studies

Study ID	*Ethnicity*	*Cut-off value*	*High HOTAIR (n,%)*	*Control sources*	*Treatment*	*HR*	*Quality assessment*
Endo et al. 2013 [18]	Japanese	HOTAIR/ GAPDH≥1	43(63.24)	Healthy individual	Surgery	Survical curves	18.5
Xu et al. 2013 [19]	Chinese	HOTAIR/ GAPDH≥1	56(67.47)	Healthy individual	Surgery	Survical curves	19.5
Emadi-Andant et al. 2014 [20]	Iran	Mean level	30(50.00)	Adjacent tissue	UC	Not reported HR	18.5
Lee et al. 2014 [21]	Korea	HOTAIR/ GAPDH≥1	28(58.33)	Healthy individual	UC	Reported in text	19
Liu et al. 2014 [22]	Chinese	Mean level	39(50.00)	Healthy individual	NR	Survical curves	20
Okugawa et al. 2014 [23]	Japanese	HOTAIR/ GAPDH≥1	77(51.33)	Adjacent tissue	NR	Reported in text	20
Liu et al. 2015 [24]	Chinese	HOTAIR/ GAPDH≥1	24(39.34)	Adjacent tissue	NR	Survical curves	18.5
Zhang et al. 2015 [25]	Chinese	Mean level	35(70.00)	Healthy individual	NR	Survical curves	16.5
Zhao et al. 2015 [26]	Chinese	Mean level	84(50.00)	Adjacent tissue	NR	Reported in text	19.5

GAPDH: glyceraldehyde phosphate dehydrogenase, UC: unclear, HR: hazard ratio, NR: not reported

treatment, cut-off value, control sources, and methods of analysis according to the reported HR value. Subgroup analysis by ethnicity indicated that high expression of lncRNA HOTAIR was significantly associated with poor OS in Chinese GC patients (HR=1.414, 95% CI: 1.120-1.785, p=0.000), but not in Japanese GC patients (HR=1.449, 95% CI: 0944-2.222, p=0.089) and Korean GC patients (HR=2.209, 95% CI:0.533-9.159, p=0.275). Significant relation was found between high expression levels of HOTAIR and GC patients who did not receive treatments (HR=1.464, 95% CI:1.179-1.817, p=0.001). To further explore the source of heterogeneity in our study, a meta-regression analysis was performed by using covariates including cut-off value, control sources and methods of analysis (Table 2).

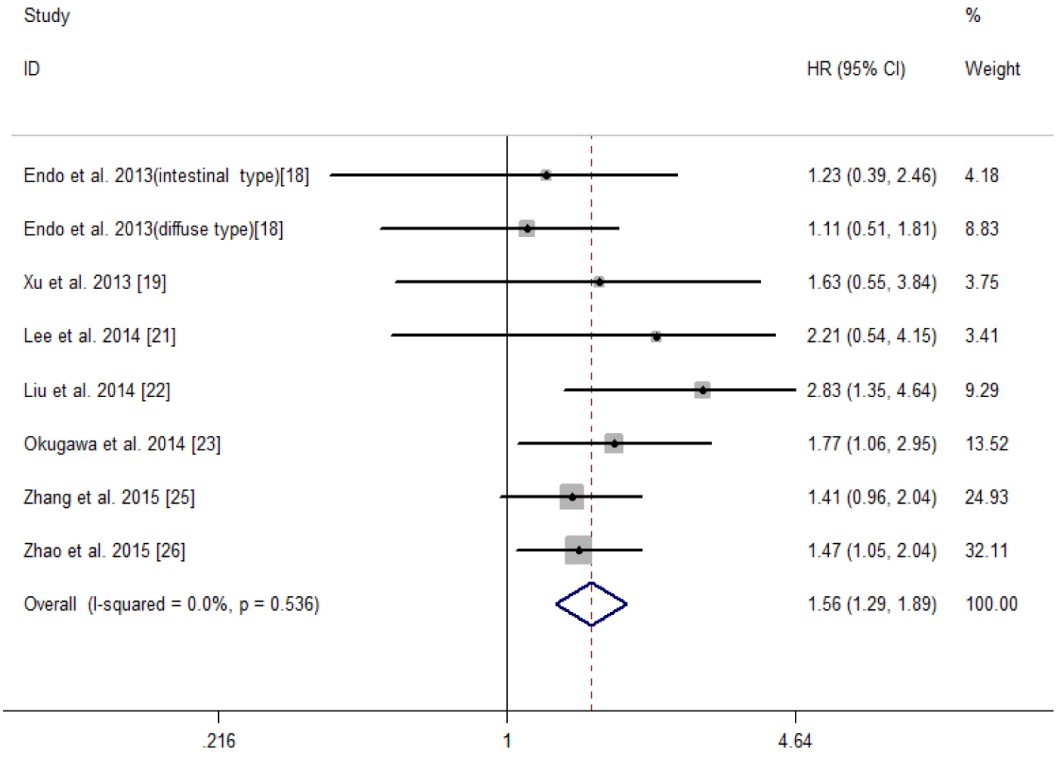

Figure 2. Forest plots of included studies evaluating the association between the expression of HOTAIR and overall survival for gastric cancer patients.

Table 2. Subgroup analysis of association between HOTAIR and OS for gastric cancer patients

Subgroups		*No. of studies*	*Meta-analysis*		
			HR	*95%CI*	*p value*
Ethnicity	Chinese	4	1.414	1.120, 1.785	0.000
	Japanese	3	1.449	0.944, 2.222	0.089
	Korean	1	2.209	0.533, 9.159	0.275
Treatment	Surgery	3	1.109	0.589, 2.090	0.748
	No treatment	4	1.464	1.179, 1.817	0.001
	UC	1	2.209	0.533, 9.159	0.275
Cut-off value	HOTAIR/GAPDH≥1	5	1.516	1.033, 2.224	0.033
	Mean level	3	1.404	1.106, 1.783	0.005
Control sources	Healthy individual	6	1.321	0.987, 1.764	0.061
	Adjacent tissue	2	1.553	1.170, 2.061	0.002
Methods of analysis	Multivariate	5	1.516	1.033, 2.224	0.033
	Univariate	3	1.404	1.106, 1.783	0.005
Methods of HR value reporting	Reported in survical curves	5	1.291	0.959, 1.736	0.092
	Reported in text	3	1.574	1.192, 2.077	0.001

UC: unclear, HR: hazard ratio

Table 3. Association between high expression of LncRNA HOTAIR and clinical features for GC patients

Clinical features		*No. of studies*	*Heterogenity test*		*Meta-analysis*		
			I^2 %	*p value*	*OR*	*95%CI*	*p value*
Gender	Male vs Female	8	66	0.004	1.95	1.18, 3.22	0.009
Size of tumor (cm)	≥5 vs <5	3	0	0.84	1.06	0.68, 1.67	0.79
Depth of tumor invasion	T3-T4 vs T1-T2	5	68	0.01	4.55	3.10, 6.68	<0.0001
Lymph node metastasis	Present vs absent	7	94	<0.0001	1.31	0.99, 1.72	0.06
Stage	III/IIII vs I/II	6	69	0.007	1.56	1.07, 2.28	0.02
Lauren's classification	Diffuse vs intestinal	5	18	0.31	1.01	0.70, 1.41	0.98
Grade of differentiation	Well and moderate vs poor differentiation	3	94	<0.0001	4.04	2.48, 6.60	<0.0001
CEA value (ng/ml)	≥5 vs <5	2	79	0.03	0.8	0.37, 1.73	0.58
CA19.9 value (U/L)	≥37 vs <37	2	0	0.5	2.15	0.79, 5.84	0.13

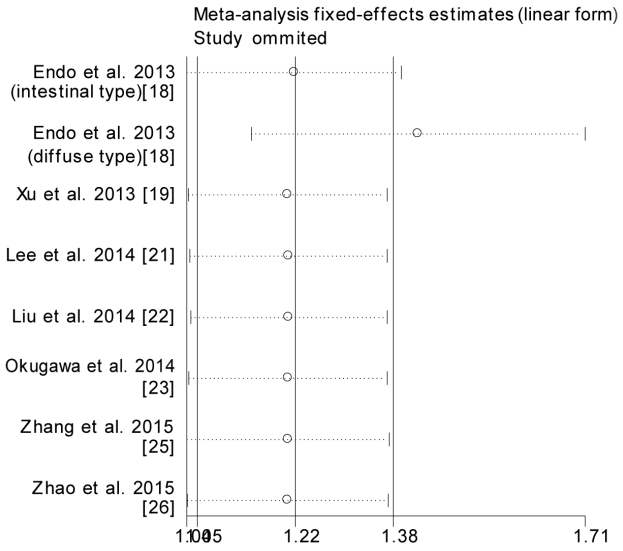

Figure 3. Sensitivity analysis for OS.

Association between high expression levels of lncRNA HOTAIR and clinical features in GC patients

The performed meta-analysis showed that male (random effect model, OR=1.95, 95% CI: 1.18-3.22, p=0.009), T3-T4 (random effect model, OR=4.55, 95% CI: 3.10-6.68), III/IV (random effect model, OR=1.56, 95%CI: 1.07-2.28, p=0.02), and good and moderate differentiation (random effect model, OR=4.04, 95% CI: 2.48-6.60, p<0.0001) were clinical features significantly associated with high expression levels of lncRNA HOTAIR (Table 3).

Sensitivity analysis and publication bias

Sensitivity analysis for OS is displayed in Figure 3. The results of obtained pattern were not significantly impacted by deleting any of the included studies. Due to the limited number of included studies (<10), publication bias was not applicable in this meta-analysis.

Discussion

GC is one of the most lethal malignancies and the fifth most frequently diagnosed cancer worldwide [27]. The high mortality rate and the overall poor survival for this pathology indicate the importance of the primary disease prevention, early diagnosis and long-term patient follow-up [28]. It is thus crucial to identify predictive and prognostic biomarkers for GC, which can improve the clinical diagnosis and treatment. The main aim of our study was to investigate the association between the expression level of lncRNA HOTAIR and the OS of GC patients, along with their clinical characteristics.

HOTAIR is a 2158 nucleotide lncRNA residing in the HOXC locus on chromosome 12q 13.13 [29]. HOTAIR forms a complex with the polycomb-repressive complex 2, which is composed by SUZ12, EZH2 and EED, and binds to a lysine of the trimethylate histone H3, thereby inhibiting the expression of HOXD gene [30]. Several studies have demonstrated that primary cancer tissues exhibited a higher expression of HOTAIR compared to the adjacent non-cancer tissues. *In vitro*, knocking down the HOTAIR with targeted siRNAs could decrease the invasion and migration of tumor cells. Otherwise, if the expression of HOTAIR was

enhanced, the migration of tumor cells would be promoted [31].

However, the potential mechanism of how lncRNA HOTAIR promotes cancer cell migration and invasion still remains unclear. It has been reported that high expression level of lncRNA HOTAIR was strongly associated with lymph node metastasis in hepatocellular carcinoma patients. The knock down of HOTAIR reduced the level of VEGF (vascular endothelial growth factor) and MMP-9 (matrix metalloproteinase 9), which play critical roles in tumor cell metastasis [32]. Moreover, overexpression of HOTAIR can promote downregulation of HOXA5 protein that is related to the invasion and migration of the NSCLC cells [33]. An extensive study on tumor cells with high invasive capacity (e.g. CEN2, S18, and 5-8F) showed that in these cell lines the expression level of HOTAIR was higher than in cell lines with low invasive capacity, such as CEN1, S26 and 6-10B [34].

The present meta-analysis involved 9 studies and revealed that a high expression level of lncRNA HOTAIR is associated with a poor OS in GC patients. Wang et al. previously revealed that there was a significant association between high expression of HOTAIR and poor OS in patients presenting with digestive system tumor (HR=2.578, 95% CI: 2.054-3.259, p<0.001) [35]. Another meta-analysis showed that pool HR elevating the expression of HOTAIR in digestive system tumors tissues was 2.36 (95% CI: 1.88-2.97) compared to patients with a lower expression of HOTAIR [36]. Moreover, Li et al. suggested that elevated HOTAIR expression levels were associated with poor OS (HR=1.99, 95% CI:1.02-3.90) in 4 estrogen-dependent cancer types [37]. Zhang et al. [38] and Serghiou et al. [39] also found a poor OS in cancer patients, with results similar to the above-mentioned studies. The present study demonstrated that the high expression of lncRNA HOTAIR is significantly associated with poor OS in GC patients (pool HR:1.43, 95% CI:1.17-1.76, p=0.000), thus suggesting that GC patients highly expressing HOTAIR may live a shorter life. Through subgroup analysis, we identified that some parameters in GC patients such as male gender, T3-T4, III/IV stage, and well and moderate differentiation are associated with an unfavorable outcome. Several studies have shown that N status, depth of invasion and vessel invasion were also associated with a poor OS for cancer patients [40,41].

Additionally, our subgroup analysis showed that cut-off values, control sources and methods of analysis did not significantly change the pool HR results for OS. Of course, the quality of included studies might affect the results of the meta-analysis. In our study, we assessed their quality by using the REMARK parameters and scale, developed for tumor prognostic markers studies. Furthermore, both the meta-analysis and subgroup analysis have not indicated that the quality score of included studies influenced the heterogeneity between high and low expression levels of HOTAIR in GC patients. However, due to the limited number of the included studies (<10), publication bias was not evaluable in this meta-analysis. Although we pushed off the prognostic significance of lncRNA HOTAIR for GC patients, further research is needed to elucidate its mechanism of action in GC. Moreover, larger case-control studies are needed to confirm HOTAIR as a clinical prognostic indicator.

It should be finally emphasized that there were some limitations in our meta-analysis: (1) most of HRs were not obtained directly from the original papers, meaning that survival curves have been reconstructed to extract or calculate the HRs by ourselves; (2) because it was difficult to reach a consensus value, the cut-off value which was used to judge high expression of HOTAIR was reported in various types in different studies; (3) the language of included studies was English, other types of languages were excluded; (4) we did not evaluate the role of lncRNA HOTAIR in different biological subtypes of GC, so large-center studies are needed to strengthen our conclusions.

Conclusions

High expression level of the lnc RNA HOTAIR was significantly associated with poor OS in GC patients. Thus, lncRNA HOTAIR might represent a potentially powerful independent prognostic marker for GC.

Acknowledgements

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Conflict of interests

The authors declare no confict of interests.

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