The prognostic value of HOTAIR for predicting long-term prognosis of patients with gastrointestinal cancers

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Abstract

Background Increased expression of HOX transcription antisense RNA (HOTAIR) has been reported to be associated with unfavorable prognosis in cancer patients. Several studies have evaluated the significance of HOTAIR in the development and progression of gastrointestinal cancers (GICs).

Methods Systematic literature retrieval was performed by searching keywords in several electronic databases, including PubMed, Embase, Web of Science, CNKI, Springer, Google Scholar, and GEO. Relevant articles on association between HOTAIR expression levels and prognosis in patients with GIC were collected and screened with eligible criteria. The RevMan 5.2 software and Stata SE12.0 software was applied.

Results A total of 1297 patients from 15 eligible articles were included in this meta-analysis. The results revealed that increased expression of HOTAIR was significantly associated with shorter overall survival (OS) in GIC patients [hazard ratio (HR) = 1.93, 95% CI: 1.64–2.26], as well as poorer disease-free survival (DFS) [HR=2.79; 95% CI: 1.38–5.63]. Additionally, the pooled odds ratio (OR) indicated that increased HOTAIR was associated with clinicopathological parameters, including lymph node metastasis (OR = 2.48, 95% CI: 1.71–3.61), distant metastasis (OR = 4.34, 95% CI: 2.12–8.91), poor tumor differentiation (OR = 2.90, 95% CI: 1.45–5.80), lymphovascular invasion (OR = 2.86, 95% CI: 1.83–4.46), high depth of tumor invasion (OR = 2.07, 95% CI: 1.36–3.16), and poor clinical stage (OR = 2.72, 95% CI: 1.70–4.35). In survival analysis through the Kaplan–Meier plotter database, enhanced level of HOTAIR was associated with better OS and DFS in gastric cancer patients.

Conclusions High expression level of HOTAIR was related to poor clinical outcome of GIC patients. The HOTAIR could be applied as potential biomarker for assessing the prognosis. Further well-designed studies should be performed to verify the clinical applications of HOTAIR in GIC.

Keywords: colorectal cancer, gastric cancer, HOTAIR, meta-analysis

1. Introduction

Cancer has been the major cause of death in most regions of the world.1 The mechanisms of tumor development and progression has always been a hot research topic worldwide. Although the mechanisms underlying tumorgenesis vary in different cancers, they may share similar genetic regulatory pathways or molecular events.

Gastrointestinal cancers (GICs) have been common malignant tumors in humans, which have become a major health problem. GIC lead to huge economic burden worldwide, especially in Asian countries.2 Gastric cancer (GC) has accounted for up to 7% of the total new cancer cases, contributing to 9% of the total cancer deaths.3,4 Colorectal cancer (CRC) has accounted for up to 10.0% and 9.2% of total new cancer cases in men and women, respectively. It was also responsible for 8.5% of the total cancer deaths worldwide.5,8 GI cancer originated from mucosal epithelial cells, most of which developed into adenocarcinomas. Similar pathways or molecular events would be involved in the development and progression of tumors.

In recent years, long noncoding RNAs (lncRNAs), a class of RNA molecules with a length greater than 200 nt,5,6 have become a research hotspot. LncRNAs have been found to act as...
gene expression regulators and make effects on cancer progression. The IncRNA HOTAIR has been reported to be dysregulated in certain types of cancer and play important roles in invasion or metastasis. Thus, HOTAIR could be applied as a poor prognostic biomarker in various malignant tumors.\(^{[7]-[9]}\)

Numerous studies have shown that HOTAIR was highly expressed in GCs, including GC and CRC.\(^{[10]-[12]}\) The expression level of HOTAIR was higher in GC tissues compared to that of in paired noncancerous tissues or adjacent tissues. In addition, the enhanced expression of HOTAIR was found to be expression in GICs, including GC and CRC.\(^{[10]}\)

The main characteristics were summarized (Table 1).

### 2. Results

#### 2.1. Study characteristics

The literature retrieval process was described (Fig. 1). A total of 15 eligible articles (involving 17 studies) were ultimately identified.\(^{[7,10-23]}\) A total of 1297 cancer patients were included in present meta-analysis and the mean sample size of patients was 86.5 (ranged 45–168). The included studies were conducted in several countries. Two tumor types were evaluated, including 4 studies on CRCs and 11 studies on GCs. The cancerous specimens were well preserved for RNA extraction and the diagnoses were made based on pathological examinations. The main characteristics were summarized (Table 1).

#### 2.2. The association between increased HOTAIR expression and overall survival (OS)

Among the 15 eligible articles, the association between OS and HOTAIR expression was reported in 14 articles (including 15 studies involving 1249 cancer patients). The fixed-effects model was applied estimate the pooled hazard ratios (HRs) and corresponding 95% confidence interval (CI). The pooled HRs was expressed as the HRs between high HOTAIR expression group versus low HOTAIR expression group. The result indicated that patients with high level of HOTAIR expression showed a significantly shorter OS, compared to that of with low level of HOTAIR expression (HR = 1.93; 95% CI: 1.64–2.26, \(P = .000\); Fig. 2). Thus, it concluded that increased HOTAIR expression was associated with lower OS. The heterogeneity test revealed a mild heterogeneity (\(I^2 = 31.2\%\), \(P_h = .119\)).

The pooled HRs for OS were also calculated based on different tumor types (Fig. 3). The stratified results were consistent with overall result. Negative correlation was observed between high HOTAIR expression and OS, in patients with both CRC (HR = 2.90; 95% CI: 1.87–4.48; \(P = .000\)) and GC (HR = 1.81; 95% CI: 1.52–2.15; \(P = .000\)) (Table 2).

Additionally, for OS, the calculated pooled HRs was >1 in subgroup meta-analysis stratified by the cut-off value, analysis type, sample size and whether adjuvant therapy was used before surgery, with statistical significance (Table 2).

#### 2.3. The association between increased HOTAIR expression and disease-free survival (DFS)

Among the 15 eligible articles, only 4 studies involving 229 patients provided available data for DFS analysis. The fixed-effects model was applied to analyze the pooled HRs with corresponding 95% CI. The results indicated a significantly positive association between high expression level of HOTAIR and poorer DFS (HR = 2.79; 95% CI: 1.38–5.63; \(P = .004\), Fig. 4). No significant heterogeneity was detected among the 4 studies (\(I^2 = 0\%\); \(P_h = .872\)).

#### 2.4. The association between increased HOTAIR expression and clinicopathological parameters

The pooled odd ratios (ORs) were calculated for exploring the association between increased HOTAIR expression and clinicopathological parameters (Table 3). Increased HOTAIR was significantly related to lymph node metastasis (OR = 2.48, 95% CI: 1.71–3.61; \(P = .000\)), distant metastasis (OR = 4.34, 95% CI: 2.12–8.91; \(P = .000\)), poor tumor differentiation (OR = 2.90, 95% CI: 1.45–5.80; \(P = .003\)), lymphovascular invasion (OR = 2.86, 95% CI: 1.83–4.46; \(P = .000\)), high depth of tumor invasion (OR = 2.07, 95% CI: 1.36–3.16; \(P = .001\)), and poor clinical stage (OR = 2.72, 95% CI: 1.70–4.35; \(P = .017\)).

However, no significant association was observed between the increased HOTAIR expression and the age, sex, tumor size, and Lauren’s classification of GC. Due to the lack of useful data, the association between the increased HOTAIR expression and other clinicopathological parameters could not be analyzed.

#### 2.5. Survival analyses of GC through the Kaplan–Meier plotter database

Survival analysis was performed through the Kaplan–Meier plotter database, with the median expression as the cut-off value.

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**Figure 1.** Flowchart depicting the steps of the literature search and selection process.
The results indicated that advanced expression of HOTAIR were associated with better OS and DFS in all included GC patients (Fig. 5).

2.6. Sensitivity analysis

The sensitivity analysis was performed for the meta-analysis on the association between the HOTAIR expression level and OS. Each study was removed in turn from the pooled analysis. The effects of the removed data set on the overall HR were explored. The results indicated that there was no significant effect after excluding each of the studies, suggesting that the result of the synthetic analysis was robust.

2.7. Publication bias

The potential publication bias was searched for the meta-analysis on association between HOTAIR expression levels and OS. The funnel plot was asymmetric (Fig. 6). Additionally, the statistical evaluation was performed with Begg test ($P_{r|z|} = 0.177$). The results showed no severe publication bias among included studies.

3. Discussion

Cancer has been one major cause of death which was also one of the greatest threats to human health.[24] Poor prognosis including metastasis and recurrence has been malignant biological behavior of tumor attributing to majority of death in cancer patients. The prognosis may be improved after understanding more molecular mechanism underlying the malignant biological behaviors. For example, more biomarkers may be identified to predict the clinical outcome of cancer patients, new therapeutic targets could also be explored to develop appropriate treatment strategies.

Table 1

| First author | Year | Cancer type | Total number | Tumor stage I/II/III/IV | Follow up, mo | Adjuvant therapy before surgery | Criterion of high expression | Detection method | Outcome measures | Multivariate analysis |
|--------------|------|-------------|--------------|------------------------|--------------|-------------------------------|-----------------------------|-----------------|-----------------|---------------------|
| Guo W.      | 2014 | GC          | 102          | 45/57 (I/II–IV)        | Over 60     | No                            | T/N = 2-fold               | qRT-PCR         | OS              | No                  |
| Enido H.    | 2013 | GC          | 68           | 37/27 (I/II–IV)        | Over 60     | No                            | HOTAIR/GAPDH > 1           | qRT-PCR         | OS              | No                  |
| Lee N.K.    | 2014 | GC          | 48           | 21/27 (I/II–III)       | Over 50     | No                            | Median expression          | qRT-PCR         | DFS             | No                  |
| Soboda M.   | 2014 | CRC         | 73           | 51/22 (I/II–IV)        | 12–54       | Part of all                   | T/N = 0.7-fold             | qRT-PCR         | OS              | Yes                 |
| Ma G.       | 2015 | GC          | 71           | 21/50 (I/II–III)       | 60          | Part of all                   | HOTAIR/GAPDH > 1           | qRT-PCR         | OS              | Yes                 |
| Okugawa Y.  | 2014 | GC          | 150          | 48/102 (I/II–IV)       | Median 26   | No                            | In relation to the Youden index | qRT-PCR         | OS              | Yes                 |
| Liu X.H.    | 2014 | GC          | 78           | NR                     | Over 60     | No                            | Median expression          | qRT-PCR         | OS              | No                  |
| Zhao W.     | 2015 | CRC         | 168          | 141/27 (I/II–IV)       | Over 60     | No                            | Median expression          | qRT-PCR         | OS              | Yes                 |
| Kogo R.     | 2011 | CRC         | 100          | NR                     | Mean 36     | No                            | HOTAIR/GAPDH > 0.273       | qRT-PCR         | OS              | Yes                 |
| Liu Y.W.    | 2015 | GC          | 61           | 18/43 (I/II–IV)        | Over 40     | No                            | T/N = 2-fold               | qRT-PCR         | OS, DFS         | No                  |
| Wu Z.H.     | 2014 | CRC         | 120          | 57/63 (I/II–IV)        | Median 55.5 | No                            | T/N = 5-fold               | qRT-PCR         | DFS, OS         | Yes                 |
| Luo Z.F.    | 2016 | CRC         | 80           | 46/34 (I/II–III)       | 70          | No                            | NR                         | qRT-PCR         | OS              | No                  |
| Xu Z.Y.     | 2013 | GC          | 83           | 25/58 (I/II–IV)        | Over 70     | Part of all                   | NR                         | qRT-PCR         | OS              | Yes                 |
| Zhang Z.Z.  | 2015 | GC          | 50           | NR                     | Over 45     | No                            | Median expression          | qRT-PCR         | OS              | No                  |
| Wang F.Q.   | 2017 | GC          | 45           | 8/37 (I/II–III)        | Over 60     | No                            | Median expression          | qRT-PCR         | OS              | No                  |

CRC = colorectal cancer, DFS = disease-free survival, GC = gastric cancer, HOTAIR = HOX transcription antisense RNA, NR = not reported, OS = overall survival, qRT-PCR = quantitative real-time-polymerase chain reaction.
GICs are common tumor type worldwide. GC has been the second highest cause of cancer-related mortality, and CRC has been the third most fatal malignancy worldwide.\[24,25\] Surgical resection has been widely applied as the most beneficial therapy for GICs. Despite of the improvement in surgical techniques and adjuvant therapy, the mortality of GICs are still high. The reasons may be the delayed diagnose at an advanced stage, as well as the aggressive and metastatic natures. Lymph node metastasis is the early progression stage of GICs, which directly affects the long-term prognosis of patients.

The genome sequencing projects revealed that, less than 2% of human genome was protein coding genes and more than 90% was transcribed as noncoding RNAs (ncRNA).\[26–28\] These ncRNAs have been classified into 2 groups depending on the nucleotide size: micro-RNAs and lncRNAs. Multiple studies have demonstrated that lncRNAs were involved in various biological processes, via chromosome remodeling, transcription, and posttranscriptional processing.\[29–32\] Of which, HOTAIR has been one of the most studied lncRNAs, which was identified from a custom tilling array of the HOXC locus. The enhanced expression of HOTAIR has been associated with invasiveness,

### Table 2

Pooled HR for HOTAIR expression according to subgroup analysis.

| Categories                              | Studies (n) | Number of patients | HR (95% CI) for OS | P       | Heterogeneity |
|-----------------------------------------|-------------|--------------------|--------------------|---------|---------------|
| [1] OS                                   | 15          | 1249               | 1.93 (1.64–2.26)   | .000    | 31.2 .119     |
| [2] Cancer type                         |             |                    |                    |         |               |
| (1) Gastric cancer                      | 11          | 876                | 1.81 (1.52–2.15)   | .000    | 16.4 .288     |
| (2) Colon cancer                        | 4           | 373                | 2.90 (1.87–4.48)   | .000    | 33.3 .213     |
| [3] Cutoff value                        |             |                    |                    |         |               |
| Median                                  | 4           | 341                | 1.83 (1.22–2.75)   | .003    | 53.2 .093     |
| T/N=2-fold                              | 2           | 163                | 2.25 (1.55–3.26)   | .000    | 0 .640        |
| Others                                  | 9           | 745                | 2.06 (1.59–2.67)   | .000    | 32.2 .161     |
| [4] Analysis type                       |             |                    |                    |         |               |
| Multivariate                            | 7           | 765                | 1.91 (1.52–2.41)   | .000    | 43.4 .102     |
| Survival curves                         | 8           | 484                | 1.94 (1.55–2.43)   | .000    | 28.2 .203     |
| [5] Adjuvant therapy before surgery     |             |                    |                    |         |               |
| No                                      | 12          | 1022               | 1.88 (1.59–2.24)   | .000    | 41.9 .063     |
| Part of all                             | 3           | 227                | 2.27 (1.43–3.62)   | .001    | 0 .644        |
| [6] Sample size                         |             |                    |                    |         |               |
| ≥100                                    | 5           | 640                | 2.16 (1.44–3.24)   | .000    | 56.5 .056     |
| <100                                    | 10          | 609                | 1.99 (1.55–2.56)   | .000    | 18.0 .277     |

CI = confidence interval, HR = hazard ratio, OS = overall survival.

### Table 3

Meta-analysis results of the associations between increased HOTAIR expression and clinicopathological parameters.

| Clinicopathological parameter                       | Studies (n) | Number of patients | OR (95% CI) | P       | Heterogeneity |
|-----------------------------------------------------|-------------|--------------------|-------------|---------|---------------|
| Age (≥65 vs <65)                                    | 6           | 592                | 0.97 (0.70–1.35) | .858    | 0.0 .437     |
| Sex (male vs female)                                | 11          | 913                | 1.02 (0.76–1.37) | .902    | 0.0 .930     |
| Tumor size (≥5 vs <5)                               | 4           | 472                | 0.95 (0.65–1.38) | .772    | 0.0 .882     |
| Tumor differentiation (poorly/others vs well/moderately) | 5           | 517                | 2.90 (1.45–5.80) | .003    | 52.4 .078     |
| Lymph node metastasis (yes vs no)                   | 8           | 640                | 2.48 (1.71–3.61) | .000    | 0.0 .865     |
| Lymphovascular invasion (yes vs no)                 | 6           | 562                | 2.96 (1.83–4.46) | .000    | 4.1 .390     |
| Lauren’s classification (intestinal vs diffuse)      | 6           | 479                | 0.85 (0.58–1.25) | .409    | 8.6 .361     |
| Depth of tumor invasion (T3/T4 vs T1/T2)            | 6           | 478                | 2.07 (1.36–3.16) | .001    | 0.0 .652     |
| Distant metastasis (yes vs no)                      | 4           | 443                | 4.34 (2.12–8.91) | .000    | 49.6 .114     |
| TNM stage (II–IV vs I–II)                           | 5           | 368                | 2.72 (1.70–4.35) | .017    | 53.5 .057     |

CI = confidence interval, OR = odds ratio, TNM = tumor-node-metastasis.
metastatic progression and poor prognosis in various cancers.\[7,10,33,34\] HOTAIR has been involved in cancer invasion and metastasis through its roles in chromatin remodeling. Various target genes, including the HOXD cluster could be silenced by HOTAIR. Its roles may be played by targeting polycomb repressive complex 2 (PRC2) and lysine-specific demethylase 1 (LSD1) complexes to chromatin for coupled histone methylation and demethylation processes.\[35\] Numerous studies have also revealed that HOTAIR played a key role in carcinogenesis, which may be considered as a promising diagnostic marker and potential therapeutic target in human cancers.\[36–38\] Kogo et al.\[7\] reported that the relative expression of HOTAIR in tumors was an independent prognostic indicator for OS, and the relative risk of death was 5.6 times higher in CRC patients with higher HOTAIR level.

The mechanism on the association between HOTAIR and cancer prognosis has been investigated. SiRNA-mediated knockdown of HOTAIR was reported to induce gene expression changes, thus inhibiting epithelial-to-mesenchymal transition (EMT) and further in vitro migration and invasion.\[14\] Emadi-Andani et al.\[39\] suggested that HOTAIR expression was correlated with perineural invasion, distant metastasis and TNM staging in GC. A study by Zhang et al.\[22\] found that poly-r(C)-binding protein-1 (PCBP1) and HOTAIR played inverse roles in GC pathogenesis and metastatic progression. The function of PCBP1 as a robust tumorigenic and metastatic inhibitor has been confirmed in other studies.\[22\] A possible mechanism may be that a ribonucleoprotein (mRNP) complex, comprising PCBP1, silenced translation of mRNAs that were involved in mediating EMT and metastatic progression at the transcript-selective translational regulatory level.\[40\] In addition, high expression of HOTAIR was positively correlated with the upregulation of ICAM1 and some members of MMPs family, including MMP1, MMP3, and MMP9.\[21\] In an in vitro study,
be one of a set of biomarkers for the prognosis prediction for patients with GICs. The accuracy of prediction could be improved with a combination of biomarkers compared to single or a few ones. Secondly, since HOTAIR could be applied for predicting prognosis, including the OS and DFS, it could provide information for physician to choose treatment strategy and monitoring interval. Thirdly, HOTAIR could be applied to indicate some clinicopathologic characteristics, including lymph node metastasis, distant metastasis, poor tumor differentiation, lymphovascular invasion, high depth of tumor invasion, and poor clinical stage. Thus, the disease progression of patients should be regularly monitored for managing the recurrence of cancer. Fourthly, HOTAIR expression could be a therapeutic target for GICs. Since enhanced HOTAIR expression in GIC was associated with advanced clinicopathological features and poor prognosis independently, which suggested that HOTAIR could be a potential therapeutic target for GICs. However, there were also some limitations in present meta-analysis. First, the sample size of included patients was relatively small, thus larger scale and better designed studies would be necessary to confirm the results obtained in this meta-analysis. Secondly, partial HRs could not be directly obtained from the study, which was acquired by calculation or extraction from the survival curve. Since the varied clinical outcomes in different tumors, there was always a certain heterogeneity in the pooled analysis. Thirdly, postoperative treatments were different in different studies, thus making a great impact on OS or DFS. Fourthly, most patients included in this meta-analysis were Asian, and patients of other races should be included in future studies. Fifthly, since negative results have been rarely published, the results of this study may overestimate the role of HOTAIR in judging cancer prognosis to some extent. Although no significant publication bias was observed based on the trim and fill method and the sensitivity analysis also showed the results were robust, potential publication bias may still exist. Finally, the cut-off definition for high HOTAIR expression was not consistent, which was one of the sources of heterogeneity. Therefore, large-size, multicenter, and high-quality studies with a unified criterion should be performed for validating the prognosis predicting value of HOTAIR expression in clinical applications.

4. Materials and methods

4.1. Literature retrieval

Systematic literature search and retrieval was conducted in multiple databases, including PubMed, Embase, Web of Science, CNKI, Springer, Google Scholar, Wanfang, and GEO. The keywords for the search were as follows: “HOTAIR,” “HOX transcription antisense RNA,” “gastric cancer,” “colorectal cancer,” “prognosis,” “clinicopathology,” and “survival analysis.” The relevant articles were retrieved, with the deadline of September 18, 2017. In addition, the reference list was manually reviewed for including other relevant articles.

4.2. Inclusion and exclusion criteria

The inclusion criteria for the articles were as follows: the roles of HOTAIR in the development of GICs was investigated; associations of HOTAIR expression with prognosis or clinicopathological features were described; the expression level of HOTAIR in primary cancerous tissue was determined; and patients were divided into high and low expression groups.
according to the expression level of HOTAIR. The exclusion criteria for the articles were as follows: duplicate publications; studies without valuable data or data acquired from animal experiments; reviews, letters, case reports, and expert opinions; the expression level of HOTAIR was detected in serum.

4.3. Date extraction and quality assessment

The data and information from all eligible studies were independently extracted by 2 investigators (YZ and L-JW) through cross-check. Following data and information were collected from each study: author, publication year, cancer type, total number of patients, tumor stage, follow-up period, outcome measures, the criteria for high HOTAIR expression, determination method, HR, and corresponding 95% CI. In addition, the data of clinicopathological parameters were also extracted from the eligible studies. For studies providing the results of both univariate and multivariate analysis, only the latter was selected because of increased precision for interpreting confounding factors. If a study reported only Kaplan–Meier curves, the survival data were extracted with Engauge Digitizer version 4.1. If there was disagreement, a consensus was reached by a third investigator (W-FL). The quality of all the included studies was evaluated with Newcastle-Ottawa Scale (NOS). The NOS scores ranged from 0 to 9, and the study with a NOS score ≥6 was considered high quality. The quality of all studies included in this meta-analysis varied from 5 to 9, with a mean value of 6.8.

4.4. Statistical methods

This meta-analysis was performed with the RevMan5.2 software and Stata SE12.0 software. The heterogeneity among studies was determined by the Chi-square-based Q test and I² statistics. A P-value less than .05 for the Q test and I² value above 50% were considered significantly heterogeneous. The fixed effects model was applied for studies without obvious heterogeneity (Pₐ > .05, I² < 50%); otherwise, the random effects model was adopted (Pₐ ≤ .05, I² ≥ 50%). Potential publication bias was assessed with a funnel plot. The sensitivity analysis was performed to assess the stability of the results. A P-value less than .05 was considered statistically significant.

Author contributions

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