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Review

Prognostic and clinicopathological value of long noncoding RNA XIST in cancer

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ABSTRACT

Background: It has been reported that lncRNA X-inactive specific transcript (XIST) is dysregulated in various cancers. We performed this meta-analysis to clarify its promising functions as a prognosis marker in malignant tumors.

Methods: Eligible studies were recruited by a systematic search in OVID, Embase, Web of Science and PubMed databases. The hazard ratio (HR) and 95% confidence interval (CI) were calculated to explore the relationship between lncRNA XIST expression and patient's survival, which were extracted from the eligible studies. The odds ratio (OR) was calculated to assess the association between lncRNA XIST expression and pathological parameters using stata12.0 software.

Results: Total 10 studies and 878 cancer patients were included in the study. The pooled HR suggested that high lncRNA XIST expression was significantly correlated with poor overall survival (OS) (HR = 2.61, 95% CI = 1.91–3.13, P < 0.0001) and short disease-free survival (DFS) (HR = 2.10, 95% CI = 1.10–3.11, P < 0.0001). It was demonstrated high level of lncRNA XIST was positively correlated with larger tumor size (OR = 1.89, 95% CI 1.34–2.06, P < 0.001), positive distant metastasis (OR = 1.75, 95% CI 1.03–2.96, P = 0.038) and high-grade cancer (OR = 1.64, 95% CI 1.22–2.21, P < 0.001). However, no correlation was observed between expression of lncRNA XIST and age (OR = 0.86, 95% CI 0.62–1.19, P = 0.352), gender (OR = 0.98, 95% CI 0.73–1.33, P = 0.769), lymphatic metastasis (OR = 1.41, 95% CI 0.97–2.04, P = 0.069) and differentiation (OR = 1.16, 95% CI 0.76–1.77, P = 0.497).

Conclusions: This meta-analysis demonstrated that elevated lncRNA XIST expression predicts poor OS, poor DFS, larger tumor size, increased distant metastasis and advanced tumor stage, suggesting that high lncRNA XIST expression may serve as a novel biomarker for poor prognosis and metastasis in cancers.

1. Introduction

lncRNAs refer to a class of non-coding RNA consisting of > 200 nucleotides with no protein-coding potential [1]. Previously, lncRNAs were considered to be the noise of genome transcription with no biological function [2]. However, ever-increasing evidence have revealed that lncRNAs are involved in a wide range of biological processes, such as epigenetic regulation, nuclear import, cell cycle control, imprinting, differentiation, alternative splicing, RNA decay and transcription. Meanwhile, growing subsequent evidence suggest that lncRNAs are frequently dysregulated in a variety of cancers, which play oncogenic or tumor suppressive roles during tumorigenesis [3–5].

The lncRNA XIST (X-inactive specific transcript), a product of the XIST gene, is the master regulator of X inactivation in mammals [6]. lncRNA XIST has been reported to be overexpressed in multiple malignant tumors and be associated with more aggressive phenotypes [7]. Increasing studies revealed that aberrant upregulation of lncRNA XIST directly correlated with advanced tumor stage, worse differentiation and reduced survival durations in many types of solid tumors [8–12]. A crucial role of lncRNA XIST was demonstrated clinically and subclinically. Thus, it is necessary to certificate the potential correlation between lncRNA XIST expression and malignancies by a comprehensive analysis. In this meta-analysis, the association of lncRNA XIST with prognostic and clinicopathological in patients with different types of

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carcinomas was evaluated.

2. Materials and methods

2.1. Search strategies

According to the standard guidelines of meta-analysis [13], a systematic search was independently performed by two authors in the online electronic databases of OVID, Embase, Web of Science and PubMed for relevant articles. The search keywords and their combinations were: "lncRNA OR noncoding RNA OR long intergenic noncoding RNA", "XIST OR X-inactive specific transcript" AND "cancer OR carcinoma OR tumor OR neoplasm". The strategy was correspondingly adjusted in different databases. Only English articles were included in this study.

2.2. Selection and exclusion criteria

The inclusion criteria of this meta-analysis were: (1) research on the association between lnRNA XIST and cancer prognosis; (2) the expression levels of lncRNA XIST in human tumor tissues were measured, and the patients were divided into two groups: high or low lncRNA XIST expression; (3) sufficient data for the computation of ORs or HRs with 95% CIs. The exclusion criteria for our meta-analysis were: (1) duplicate articles, (2) case reports, letters, expert opinions, editorials and reviews, and (3) studies without available data.

2.3. Data extraction

Two investigators extracted and reviewed the data from the original studies independently. A third researcher made a final judgement on any disagreements. The collected data were as follows: first author's name, publication date, country, tumor type, sample size, number of patients with age > 60, male, tumor size > 5 cm, tumor stage, differentiation, LNM and DM in each group, HR and corresponding 95% CI for overall survival (OS) and disease-free survival (DFS). If the survival data were not shown directly in the article, Engauge Digitizer v.4.1 software was used to obtain them from the Kaplan-Meier curve, according to Tierney et al. [14].

2.4. Data synthesis and statistical analyses

STATA 12.0 software (Stata, College Station, Texas) was used to perform all statistical analyses in this study. Patients were separated into the high and low lncRNA XIST expression groups according to the original published articles. The heterogeneity among the included studies was judged with the Q-statistic test and the chi-squared test. A "Begg's funnel plot" was used to determine the potential publication bias. A fixed-effects model was used to analyze the pooled results when the included studies did not exhibit significant heterogeneity ($P > 0.1$); otherwise, a random-effects model was employed ($P < 0.1$). A sensitivity analysis was conducted to evaluate the robustness of the overall results. All P-values were determined with a two-tailed test, and $P < 0.05$ was regarded as statistically significant.

3. Results

3.1. Search results and characteristics of the included studies

The initial search of the databases produced 472 studies (Fig. 1). After excluding duplicate articles, 30 potentially eligible studies were selected. After a detailed evaluation, 10 studies were selected for the final meta-analysis with a total of 878 cancer patients (Table 1). Of the 10 studies, 2 are concerned with colorectal cancer (CRC) and 2 with gastric cancer (GC). The remaining 6 studies are regarding esophageal squamous cell carcinoma (ESCC), pancreatic cancer (PC), glioma, nasopharyngeal carcinoma (NPC), non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC), respectively.

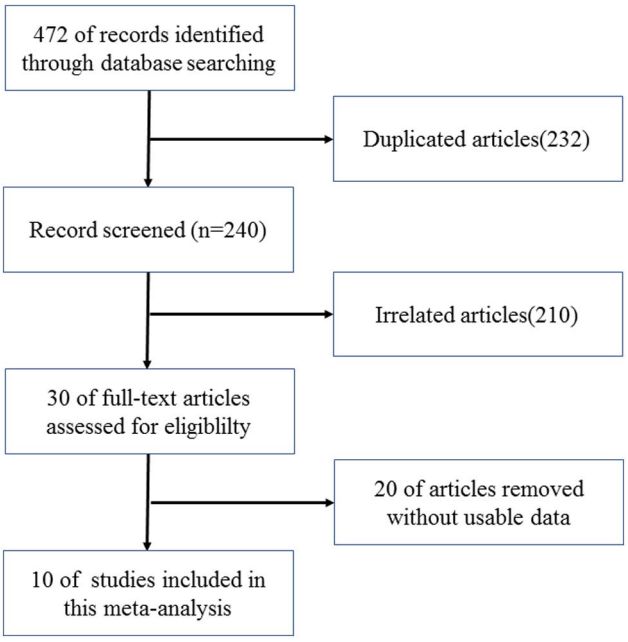

Fig. 1. Workflow of searching strategy and study selection in the meta-analysis.

Not all studies examined both OS and PFS, because most of the studies were retrospective investigated; Eight studies assessed the association between lncRNA XIST and OS, while 3 studies assessed the association between lncRNA XIST and DFS.

3.2. Meta-analysis: lncRNA XIST expression, OS, and DFS in cancer

The relationship between lncRNA XIST expression and overall survival (OS) was evaluated in 8 studies including 740 patients. No significant heterogeneity was observed among the studies ($I^2 = 7.45\%$, $P = 0.189$), so a fixed-effects model was used to pool the results. The pooled HR indicated that XIST expression was negatively associated with OS (HR = 2.61, 95% CI = 1.91–3.13, $P < 0.0001$) (Fig. 2). The association between lncRNA XIST and DFS was investigated in 3 studies, including 265 patients (Fig. 3). We found a negative association with statistically significance between levels of lncRNA XIST and DFS (HR = 2.10, 95% CI = 1.10–3.11, $P < 0.0001$).

3.3. XIST expression and clinicopathological

As shown in Table 2, we performed a meta-analysis to evaluate the relationship between the transcription levels of lncRNA XIST and clinicopathological characteristics of patients with cancer. Age, gender, tumor size, lymph node metastasis, distant metastasis, clinical stage, differentiation data were collected to analyze. Our results demonstrated that the high expression levels of lncRNA XIST were associated with larger tumor size (OR = 1.89, 95% CI 1.34–2.06, $P < 0.001$), positive distant metastasis (OR = 1.75, 95% CI 1.03–2.96, $P = 0.038$) and high-grade cancer (OR = 1.64, 95% CI 1.22–2.21, $P < 0.001$). However, there were no correlation between lncRNA XIST and age (OR = 0.86, 95% CI 0.62–1.19, $P = 0.352$), gender (OR = 0.98, 95% CI 0.73–1.33, $P = 0.769$), lymphatic metastasis (OR = 1.41, 95% CI 0.97–2.04, $P = 0.069$) and differentiation (OR = 1.16, 95% CI 0.76–1.77, $P = 0.497$).