Neoplasma 2022; 69(5): 1217–1227

doi:10.4149/neo_2022_220329N352

XIST as a valuable biomarker for prognosis and clinical parameters in diverse tumors: a comprehensive meta- and bioinformatics analysis

Mei-Jing ZHANG[1,#], Zhe YAN[2,#], Jing QIN[3,#], Tian-Hang LUO[2,*], Biao YANG[2,*]

[1]Department of Oncology, Changhai Hospital, Second Military Medical University, Shanghai, China; [2]Department of General Surgery, Changhai Hospital, Second Military Medical University, Shanghai, China; [3]Department of Anesthesiology, Changhai Hospital, The Second Military Medical University, Shanghai, China

**Correspondence: luotianh1@163.com; 191817524@qq.com*
[#]Contributed equally to this work.

Received March 29, 2022 / Accepted July 18, 2022

Long non-coding RNA (lncRNA) X inactivate-specific transcript (XIST) has been found dysregulated in a variety of human tumors and influenced the clinicopathologic characteristics in cancer patients. Therefore, we systematically searched relevant literature that has identified the correlation of lncRNA XIST expression and clinical outcomes of tumor patients and conducted this meta-analysis to elucidate the clinical prognostic value of long noncoding RNA XIST in human tumors. A comprehensive literature search was performed from PubMed, Web of Science, EMBASE, and Cochrane library databases up to August 1, 2019. Pooled hazard ratios (HRs) or odds ratios (ORs) with a 95% confidence interval (95% Cl) were calculated to evaluate the prognosis, as well as the clinicopathological parameters of XIST, respectively. We also further validated this meta-analysis using The Cancer Genome Atlas (TCGA) dataset. The outcome revealed that XIST overexpression in tumor tissue was interacted to a poor overall survival (OS) (HR=0.52, 95% CI: 0.44–0.61, p<0.0001), disease-free survival (DFS) (HR=0.50; 95% CI: 0.36–0.69, p<0.0001), tumor type (digestive system malignancies, HR=0.53; 95% CI: 0.44–0.63, p<0.0001); nondigestive system malignancies, HR=0.48; 95% CI: 0.34–0.67, p<0.0001), lymph node metastasis(LNM) (OR=0.61, 95% CI: 0.37–1.00; p=0.048), differentiation (OR=1.46; 95% CI: 0.94–2.29; p=0.096), distant metastasis (DM) (OR=0.48, 95% CI: 0.31–0.75; p=0.001), tumor size (OR=0.59, 95% CI: 0.38–0.92; p=0.019), and tumor stage (OR=2.36; 95% CI: 1.62–3.43; p<0.001). XIST could have potential value in early diagnosis and result in prediction and provide a novel view for the therapeutic target in clinical application.

Key words: long non-coding RNA; XIST, meta-analysis, bioinformatics analysis, prognostic biomarker

In the past decade, malignant tumor has become a primary cause of morbidity and mortality for human health throughout the world [1]. According to 2019 Cancer Statistics, 1,762,450 new tumor cases and 606,880 tumor deaths were expected to happen in the United States in 2019 [2]. Despite the effective advances in tumor diagnosis and treatment over the past couple of years, the OS of patients remains far from satisfactory. Tumor biomarkers play an important effect in the occurrence and progression of various tumors [3, 4]. However, there is a dearth of effective tumor biomarkers in clinical diagnosis. Consequently, it is an urgent requirement to identify a novel biomarker to improve early diagnosis, more accurate prognosis, and new therapeutic target.

With advancements in sequencing methodologies, a majority of lncRNAs have increasingly received positive attention and turned into a hot topic of research [5]. LncRNA is a new type of noncoding RNA that is identified as more than 200 nucleotides in length and lacks the ability of protein-coding. According to the actual emerging evidence, cancer-related lncRNAs play crucial roles in tumor oncogenes or suppressor genes via regulating gene expression at the epigenetic, transcriptional, and posttranscriptional levels [6]. Up to now, growing evidence has certified that abnormally expressed lncRNAs are correlated with the development and progression of the tumor [7, 8]. Therefore, lncRNAs may serve a role as novel biomarkers and therapeutic strategies for tumors.

XIST, transcribed from the inactive X chromosome, is a kind of lncRNA that is derived from the XIST gene [9]. It was shown in recent studies that lncRNA XIST has been found abnormally expressed in a large of human tumors and influenced clinicopathologic characteristics in cancer patients,

such as non-small cell lung carcinoma (NSCLC) [10], gastric carcinoma [11], pancreatic cancer [12], and so on. However, biological behavior and potential pathogenesis mechanisms of XIST in human tumorigenesis keep enigmatic due to relatively small sample sizes and some results are debatable. Therefore, we systematically searched relevant literature that has identified the correlation between XIST expression and clinical consequences of tumor patients and conducted this meta-analysis to elucidate the clinical prognostic value of long noncoding RNA XIST in human tumors.

Materials and methods

Publication search. Studies in English were systematically searched in four electronic databases including PubMed, Web of Science, EMBASE, and Cochrane library databases by the end of August 1, 2019. The following keywords were searched: ("lncRNA XIST" OR "long non-coding RNA, human" OR "XIST" OR "X-inactive specific transcript") and ("cancer*" OR "tumor*" OR "tumour*" OR "carcinoma*" OR "neoplas*" OR "malignan"). PRISMA registration number is CRD42020151210.

Data inclusion and exclusion criteria. Eligible studies were extracted met the following conditions: a) all studies were published in English; b) studies have basic information such as the first author, year of publication, and so on; c) studies contained related clinicopathological features; d) sufficient datum of HR and 95% CI for OS or DFS were reported. Exclusion criteria met the following conditions: a) studies without meeting the inclusion criteria; b) animal trails, letters, reviews, and case reports; c) unavailable data to extract.

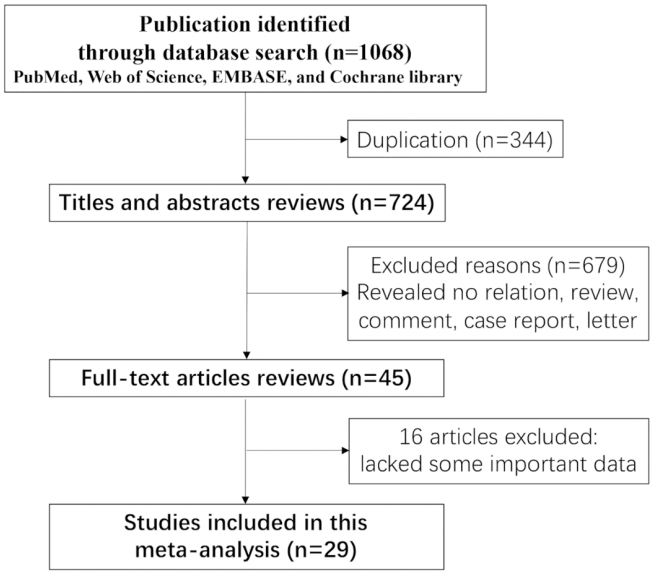

Figure 1. The flow diagram of the process for the literature identification and selection.

Ethical approval. All procedures performed in the study were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data extraction and quality assessment. All data were extracted independently by two individuals (Zhang Meijing and Qin Jing) from the included studies. If the datum contained both univariate and multivariate analyses, we choose the latter. Then, the Engauge Digitizer v.4.1 software and Tierney's spreadsheet were utilized to get the HR from Kaplan-Meier survival curves when it was not getting data directly [13]. The quality of eligible studies was assessed in conformity to the Newcastle-Ottawa quality assessment scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) [14]. The total scores were from 0 (lowest) to 9 (highest). If the scores were higher or equal to 6 we considered the studies were high quality. Disagreements were discussed with other independent investigators.

Statistical analysis. Statistical calculation was using Stata SE15.1 (software Corp, College Station, TX, USA). The OR with 95% CI was pooled to estimate the correlation between XIST expression and the clinicopathological features. The HR and 95% CI were merged to estimate the prognostic value of XIST expression on OS. The I 2 statistics and chi-square-based Q test was used to estimate the heterogeneity. If there was no significant heterogeneity (I^2<50% and p>0.05), the fixed-effect model was chosen; otherwise, the random-effect model was adopted to enhance the stability of the meta-analysis. A single study removal analysis was performed to estimate the sensitivity. Publication bias was estimated by Begg's test and Egger's test, respectively. A p-value <0.05 was considered statistically significant.

Bioinformatics analysis. The Kaplan-Meier Plotter online database was used to assess the OS of the core genes. GEPIA [15] was used to determine overall survival related to the core genes which is an online tool that speedily achieves characteristic functionalities based on TCGA and GTEx data. The hazard ratio (HR) with 95% confidence intervals and log-rank p-value were computed and revealed on the plot.

Results

Characteristics of the included studies. The relevant literature search and selection detailed process is shown in Figure 1. A total of 1,068 pieces of literature were retrieved depending on the inclusion and exclusion criteria. After carefully reviewing, 29 of the pieces of literature and 2,710 patients matched to the inclusion criteria were eligible for this meta-analysis.

The detailed information of the 29 studies is presented in Table 1. Among the 29 studies, 28 came from Asians and 1 study came from Ukraine. The 29 studies contained 11 different types of tumor, including 5 studies on colorectal

Table 1. The characteristics of studies included in this meta-analysis.

First author	Year	Country	Tumor type	Reference gene	Sample size	XIST expression						Method	Therapy	Outcome	Expression level	NOS
						Low			High							
						Total	LNM	DM	Total	LNM	DM					
Fang	2016	China	NSCLC	GADPH/U1	53	15	9	-	38	19	-	qRT-PCR	Surgery	PFS	↑	7
Song	2016	China	Nasopharyngeal carcinoma	GADPH/U6	108	32	-	-	76	-	-	qRT-PCR	Surgery	OS	↑	7
Kobayashi	2016	Japan	Cervical squamous cell carcinoma	GADPH	49	25	6	-	24	11	-	qRT-PCR	Chemotherapy	OS	↓	8
Chen	2016	China	Gastric cancer	GADPH	106	52	31	8	54	44	20	qRT-PCR	Surgery	OS	↑	8
Li	2017	China	Osteosarcoma	GADPH	145	70	-	14	75	-	30	qRT-PCR	Surgery	OS	↑	6
Mo	2017	China	Hepatocellular carcinoma	GADPH	88	50	-	-	38	-	-	qRT-PCR	Surgery	DFS	↑	7
Kong	2017	China	Hepatocellular carcinoma	GADPH/U6	52	26	-	-	26	-	-	qRT-PCR	Surgery	OS	↑	7
Xiao	2017	Ukraine	Colorectal cancer	GADPH	120	57	-	-	63	-	-	qRT-PCR	Chemotherapy	OS	↑	7
Du	2017	China	Prostate cancer	GADPH	62	25	-	18	37	-	11	qRT-PCR	Surgery	OS	↓	7
Hu	2017	China	Bladder cancer	GADPH/U6	52	20	2	-	32	14	-	qRT-PCR	Surgery	OS	↑	8
Liang	2017	China	Pancreatic carcinoma	GADPH	73	36	15	17	37	20	19	qRT-PCR	Surgery	OS/DFS	↑	7
Wei	2017	China	Pancreatic carcinoma	RUN6B	64	32	11	11	32	17	18	qRT-PCR	Surgery	OS	↑	7
Zhang	2017	China	Osteosarcoma	GADPH	41	17	-	-	24	-	-	qRT-PCR	Surgery	OS	↓	7
Wu	2017	China	Esophageal squamous cell carcinoma	GADPH	127	63	-	-	64	-	-	qRT-PCR	Surgery	OS/DFS	↑	6
Song	2017	China	Colorectal cancer	GADPH	50	29	-	13	21	-	12	qRT-PCR	Surgery	DFS	↑	7
Ma	2017	China	Gastric cancer	GADPH	98	53	22	-	45	33	-	qRT-PCR	Surgery	OS	↑	7
Du	2017	China	Glioma	GADPH	69	34	-	-	35	-	-	qRT-PCR	Surgery	OS	↑	7
Chen	2017	China	Colorectal cancer	GADPH	115	57	-	-	58	-	-	qRT-PCR	Surgery	OS	↑	8
Ma	2017	China	Hepatocellular carcinoma	GADPH	68	38	-	-	30	-	-	qRT-PCR	Surgery	OS	↓	8
Sun	2018	China	Colorectal cancer	GADPH	120	52	19	21	68	38	42	qRT-PCR	Surgery	OS	↑	7
Zhu	2018	China	Cervical cancer	GADPH	52	33	21	6	19	8	9	qRT-PCR	Surgery	OS	↑	7
Sun	2018	China	Pancreatic carcinoma	GADPH/U6	139	69	-	-	70	-	-	qRT-PCR	Surgery	OS	↑	7
Liu	2018	China	Thyroid cancer	GADPH	77	38	14	-	39	30	-	qRT-PCR	Surgery	OS	↑	7
Yang	2018	China	Osteosarcoma	GADPH	40	19	-	-	21	-	-	qRT-PCR	Surgery	OS	↑	6
Y	2018	China	Esophageal squamous cell carcinoma	GADPH	140	70	43	16	70	48	37	qRT-PCR	Surgery	OS	↑	7
Zhang	2019	China	Colorectal cancer	GADPH	294	138	71	15	156	102	24	qRT-PCR	Surgery	OS	↑	8
Wang	2019	China	Osteosarcoma	GADPH	64	32	-	3	32	-	12	qRT-PCR	Surgery	OS	↑	7
Wang	2019	China	NSCLC	GADPH	96	48	18	36	48	23	44	qRT-PCR	Surgery	OS/DFS	↑	7
Li	2019	China	Esophageal squamous cell carcinoma	GADPH	148	101	66	-	47	11	-	qRT-PCR	Surgery	OS	↑	8

Abbreviations: NSCLC-non-small cell lung carcinoma; LNM-lymph node metastasis; DM-distant metastasis; OS-overall survival; PFS-progression-free survival; NOS-Newcastle-Ottawa Sale

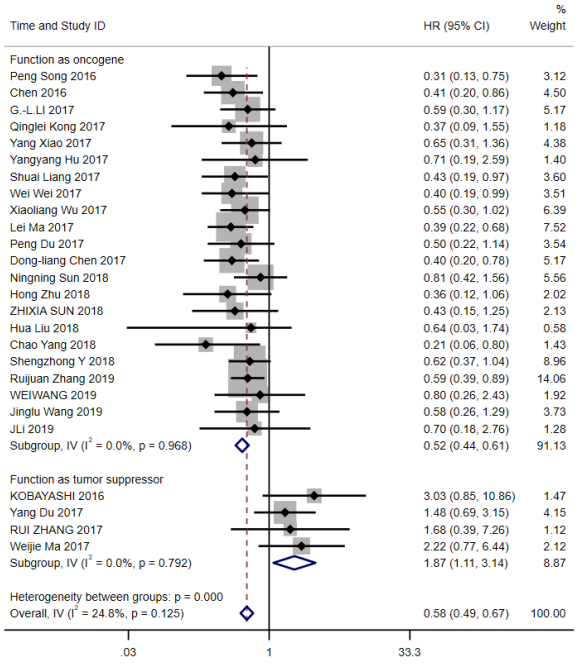

Figure 2. Forest plot for the association between XIST (X inactive-specific transcript) expression levels with OS.

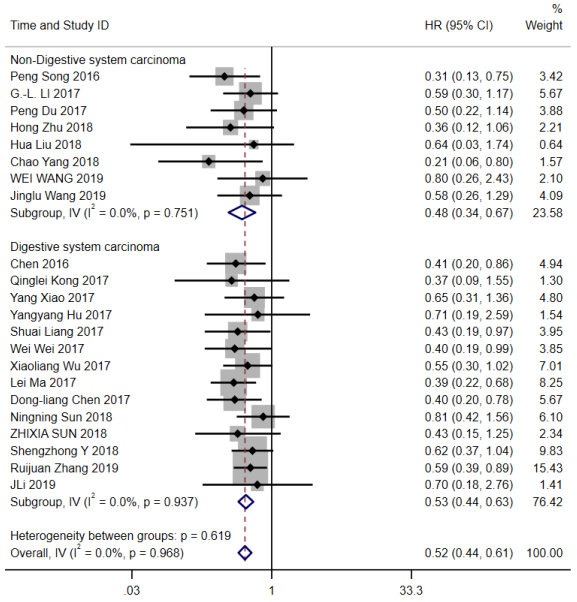

Figure 3. Forest plot for the association between XIST (X inactive-specific transcript) expression levels with tumor types.

cancer [16–20], 1 study on glioma [21], 2 studies on gastric cancer [11, 22], 1 study on thyroid cancer [23], 1 study on nasopharyngeal carcinoma [24], 1 study on prostate cancer [25], 3 studies on osteosarcoma [26–28], 3 studies on hepatocellular carcinoma [29–31], 3 studies on pancreatic cancer [12, 32, 33], 2 studies on cervical squamous cell carcinoma

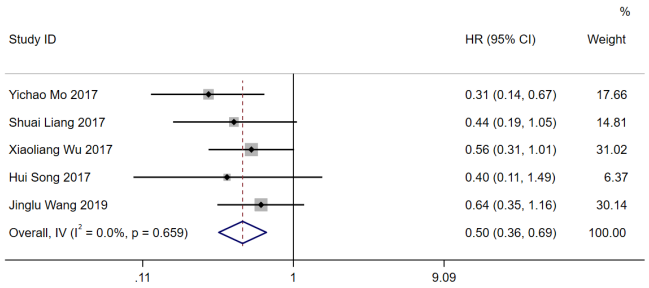

Figure 4. Forest plot for the association between XIST (X inactive-specific transcript) expression levels with DFS.

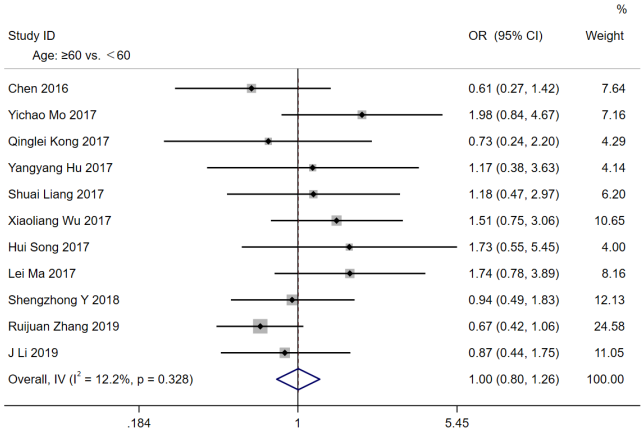

Figure 5. Meta-analysis for the relationship between XIST (X inactive-specific transcript) expression and age.

[34, 35], 2 studies on non-small cell lung cancer [10, 36], 1 study on nasopharyngeal carcinoma [24], 3 studies on esophageal squamous cell carcinoma [37, 38], and 1 study on bladder cancer [39]. 26 studies in total described the OS and 5 studies described the DFS. All patients in the articles were separated into two groups: a high XIST expression group and a low XIST expression group depending on RT-qPCR results. 25 of the 29 studies described that the expression level of XIST was upgraded in tumor tissues and cell lines, and the others found that XIST expression levels were downgraded. The NOS scores of all contained researches were from 6 to 8 [14].

Relationship of XIST expression and OS. The correlation between XIST expression and OS were estimated in 26 studies, and 22 of them act as oncogenes. Therefore, all the information from these 22 studies was gathered and merged for re-analysis. Because there appeared to be no heterogeneity among the studies (I^2=0%; p=0.968), the fixed-effects model was used to assess the merged HR and its 95% CI. The results of the merged HR implied that XIST overexpress was significantly correlated with a worse OS (HR=0.52, 95% CI: 0.44–0.61, p<0.0001; Figure 2).

Then we gathered and re-analyzed the research depending on XIST serving as the cancer inhibitor. There was no statistical heterogeneity between trials (I^2=0%; p=0.792), so the

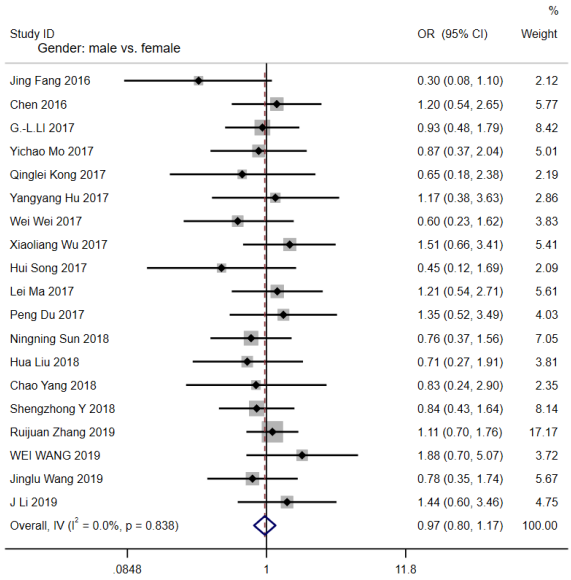

Figure 6. Meta-analysis for the relationship between XIST (X inactive-specific transcript) expression and gender.

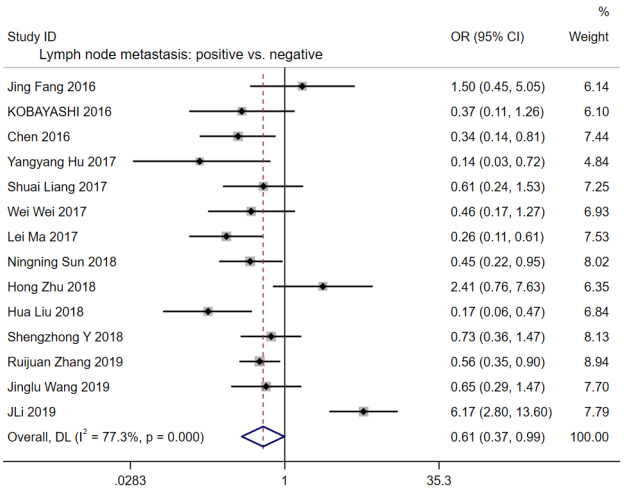

Figure 7. Meta-analysis for the relationship between XIST (X inactive-specific transcript) expression and lymph node metastasis. Note: Weights are from the random-effect model.

fixed-effects model was assessed in the research. The results indicated a conspicuous interrelation of lower expression of XIST and shorter OS (HR=1.87; 95% CI: 1.11–3.14, p=0.019; Figure 2).

Relationship of XIST expression and tumor classification. Among the oncogene, researchers categorized the digestive system malignancies and the non-digestive system malignancies and estimated the correlation between XIST expression levels and OS. There was no statistical heterogeneity between trials (I^2=0%) so the fixed-effects model was assessed in the studies. The results showed that among tumor patients, digestive system malignancies patients (HR=0.53; 95% CI: 0.44–0.63, p<0.0001; Figure 3) showed worse prognosis than non-digestive system malignancies patients (HR=0.48; 95% CI: 0.34–0.67, p<0.0001; Figure 3).

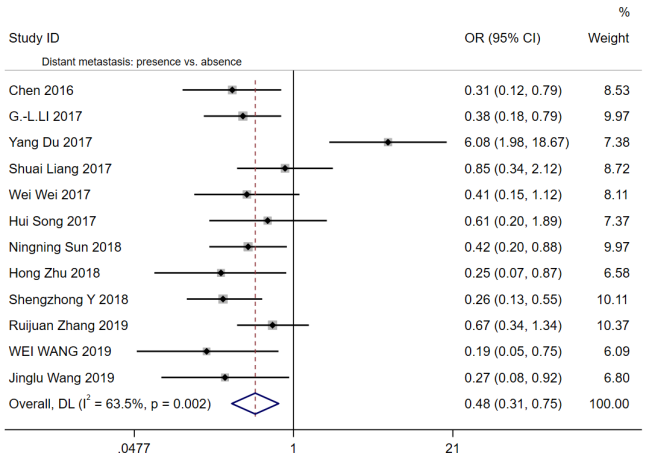

Figure 8. Meta-analysis for the relationship between XIST (X inactive-specific transcript) expression and distant metastasis. Note: Weights are from the random-effect model.

Relationship of XIST expression and DFS. Four studies estimated the correlation between lncRNA XIST expression and DFS. Therefore, all the data was gathered from the 4 studies and merged for reanalysis. There was no statistical heterogeneity (I^2=0%), so the fixed-effects model was assessed in the studies. The results of the pooled HR demonstrated that patients with XIST overexpression were correlated with a worse DFS (HR=0.50; 95% CI: 0.36–0.69, p<0.0001; Figure 4).

Relationship of XIST with clinicopathological characteristics. There are 11 and 19 studies representing tumor patients of age and gender, respectively. There was no statistical heterogeneity between trials (I^2=0%), so the fixed effects model was assessed in the analysis. The pooled results showed that XIST expression did not significant association with age (Figure 5) and gender (Figure 6). There are 14 studies that estimated LNM. A random-effect model was used in the studies due to having significant heterogeneity (I^2=77.3%; p<0.0001). Overall, the expression of lncRNA XIST was correlated with LNM (OR=0.61, 95% CI: 0.37–0.99; p<0.0001; Figure 7). A total of 12 studies assessed DM depending on XIST expression. There was no statistical heterogeneity (I^2=63.5%; p=0.002), so a random-effect model was used in the analysis of the pooled OR. These aggregated results indicated that tumor patients with XIST overexpression were more inclined to DM (OR=0.48, 95% CI: 0.31–0.75; p=0.001; Figure 8). Moreover, we discovered that in patients, XIST overexpression was positively correlated with tumor size (OR=0.59, 95% CI: 0.38–0.92; p=0.001; Figure 9), differentiation (OR=1.46; 95% CI: 0.93–2.34; p=0.006; Figure 10), and clinical stage (OR=2.36; 95% CI: 1.62–3.43; p<0.001; Figure 11). Due to the limitations of the data, more research was needed to draw conclusive conclusions.

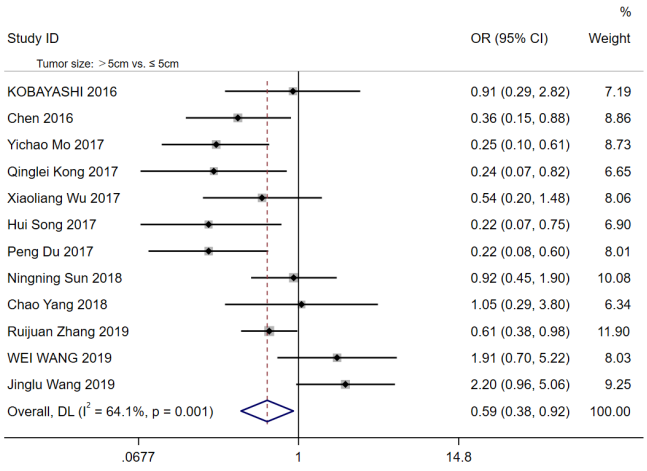

Figure 9. Meta-analysis for the relationship between XIST (X inactive-specific transcript) expression and tumor size. Note: Weights are from the random-effect model.

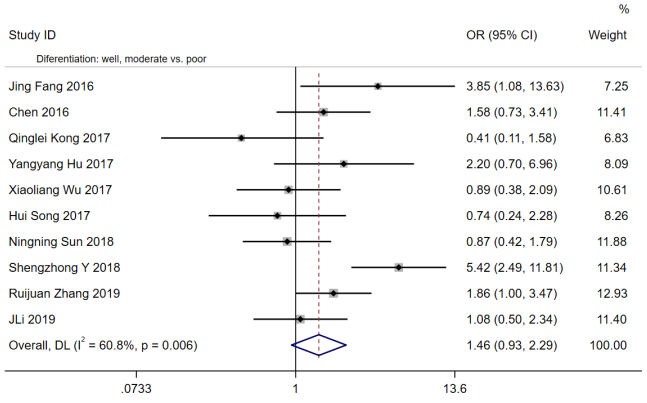

Figure 10. Meta-analysis for the relationship between XIST (X inactive-specific transcript) expression and differentiation. Note: Weights are from the random-effect model.

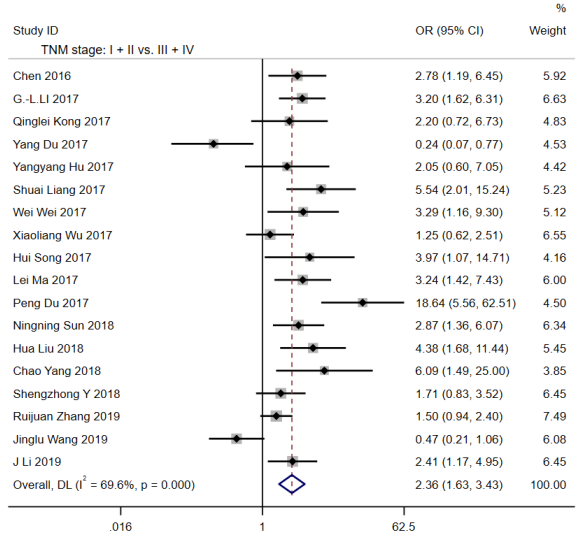

Figure 11. Meta-analysis for the relationship between XIST (X inactive-specific transcript) expression and clinical stage. Note: Weights are from the random-effect model.

Publication bias and sensitivity analysis. Begg's funnel plot and Egger's linear regression test were used for assessing the publication bias. No evidence of publication bias was not displayed in obvious asymmetry (Egger's test: p=0.76 and Begg's test: p=0.553; Figure 12 and Figure 13). Furthermore, sensitivity analysis evaluated the stability and reliability of the results. After removing those documents that led to heterogeneity, the overall HR did not change significantly, so the current meta-analysis results were relatively stable (Figure 14).

Bioinformatics analysis. To further gain insight into the clinical relevance of our work and XIST importance, we performed the bioinformatics analysis for the functional impact of the XIST expression on various cancers. Firstly, we estimated the expression of XIST in various cancers via data from GEPIA. As shown in Figure 15, it was found that XIST overexpression was significant in lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), testicular germ cell tumors (TGCT), and thyroid carcinoma (THCA). Then, to validate the results of our meta-analysis, Kaplan-Meier Plotter Database was used to determine the association between the expression of XIST and the OS. Same results as our meta-analysis, it was found that higher expression of XIST was significantly related to worse OS in cervical squamous cell (CESC), kidney renal papillary cell (KIRP), and skin cutaneous melanoma (SKCM) (log-rank p<0.05) (Figure 16).

Discussion

In recent years, the tumor is the primary cause of mortality throughout the world and clinical treatment remains limited. Because of the asymptomatic characteristics of all types of tumors in the early stage, most patients are diagnosed as advanced, missing the best time for surgical resection, which is the only way to cure patients [40]. Despite therapeutic chemotherapy and radiotherapy advances, the 5-year survival of patients with tumors remains unsatisfactory. Consequently, new molecular biomarkers for diagnosing advanced cancer conditions and prognosis are in need. Recently, several studies have evidenced that lncRNAs are abnormally expressed in diverse types of human tumors; moreover, a correlation between lncRNA expression, pathophysiological features, and patient survival has also been indicated, making lncRNAs promising biomarkers for tumor prognosis [41–44]. Because of high sensitivity, specificity, and convenient detection, lncRNAs have focused on their role in cancer pathogenesis and prognosis, providing a novel view into tumor therapeutic strategy. LncRNA XIST is derived from the XIST gene that is only expressed from the formation of the inactive X chromosome in mammals. After more than 20 years of extensive research, much clinical research has demonstrated that aberrant expression of lncRNA XIST not only played a significant role in the proliferation and invasion; but also, in the occurrence and progression of

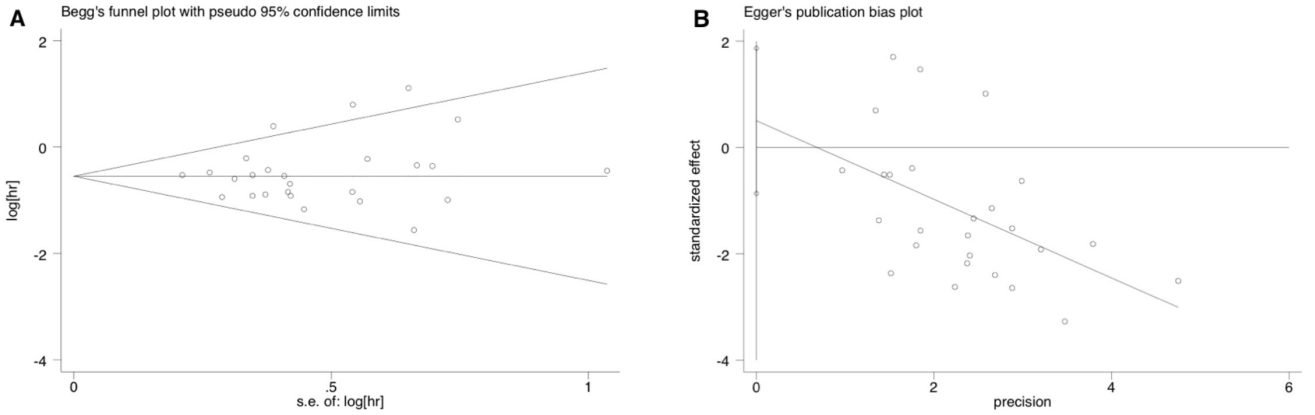

Figure 12. Funnel plot for identifying publication bias for OS. A) Begg's funnel plot analysis for publication bias. B) Egger's funnel plot analysis for publication bias. Each point represents a separate study. Abbreviations: OS-overall survival; HR-hazard ratio; s.e.-standard error.

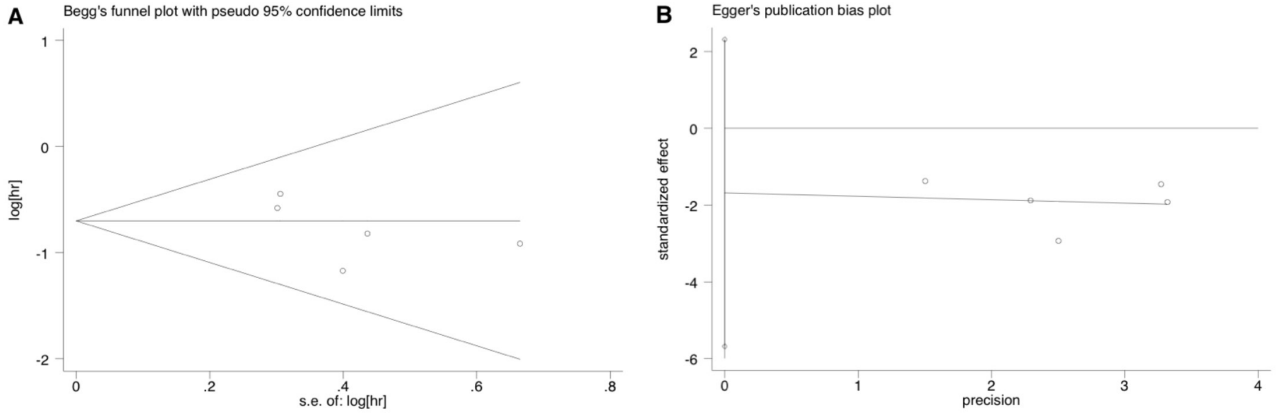

Figure 13. Funnel plot for identifying publication bias for DFS. A) Begg's funnel plot analysis for publication bias. B) Egger's funnel plot analysis for publication bias. Each point represents a separate study. Abbreviations: DFS-disease-free survival; HR-hazard ratio; s.e.-standard error.

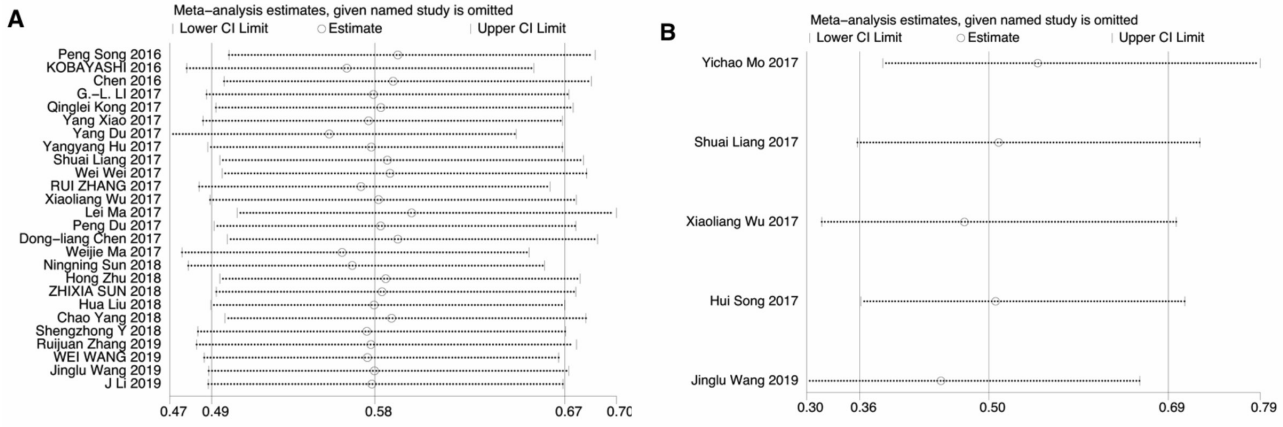

Figure 14. Sensitivity analysis. A) OS; B) DFS. Abbreviations: DFS-disease free survival; OS-overall survival

various tumors [45, 46]. However, due to a lack of systematic research, the mechanism underlying the correlation between lncRNA XIST and tumor consequence is unclear. Given the above consequences, this is a significant meta-analysis to explore the correlation between lncRNA XIST expression and OS in tumor patients.

In this study, we pooled data from a total of 29 retrospective eligible studies with 2,710 tumor patients. Our datum

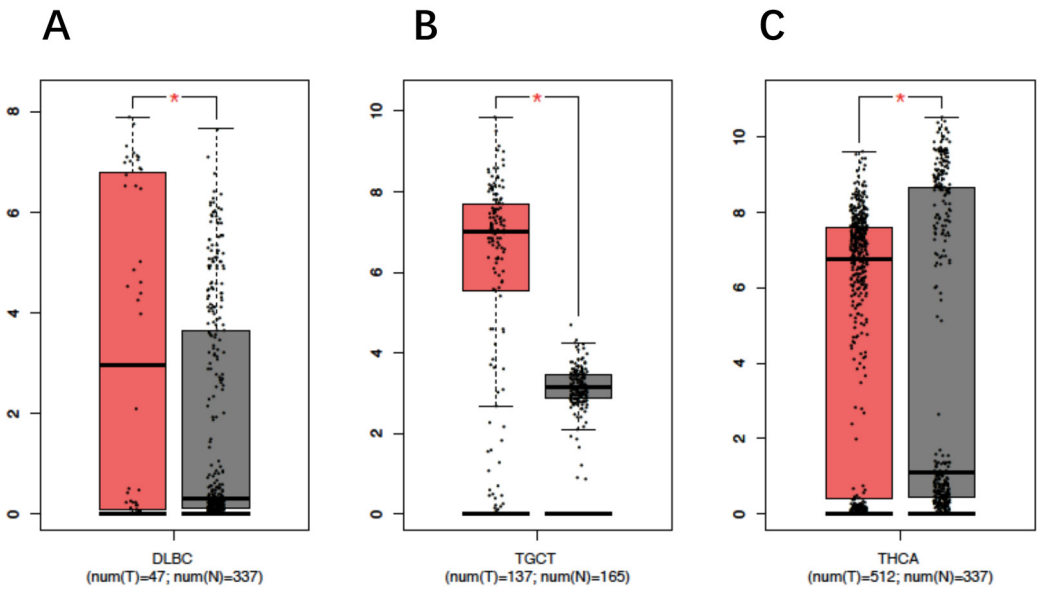

Figure 15. The expression levels of XIST in three kinds of cancer tissues and normal tissues. "*": |Log 2 FC| > 1 and p<0.01. Abbreviations: DLBC-lymphoid neoplasm diffuse large B-cell lymphoma; TGCT-testicular germ cell tumors; THCA-thyroid carcinoma

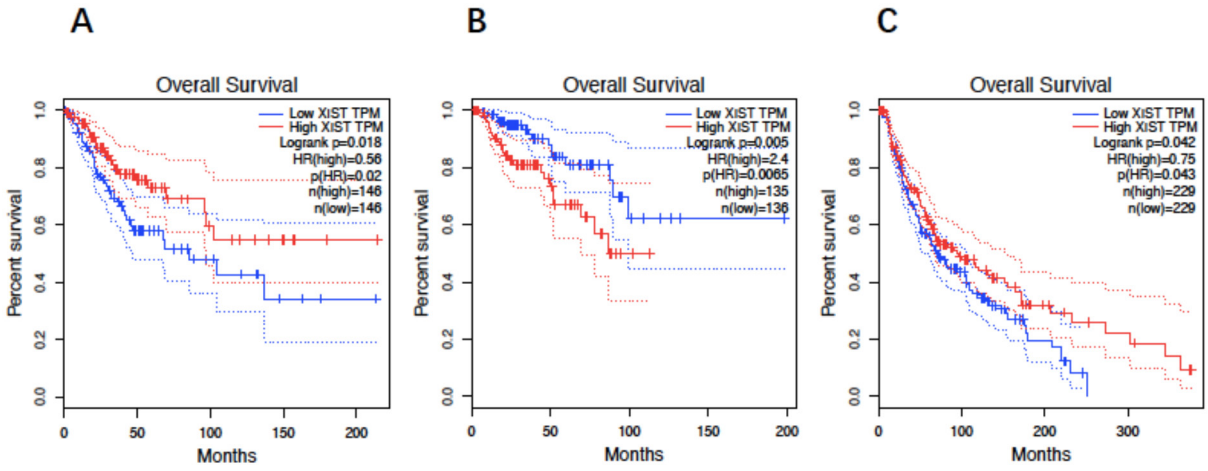

Figure 16. The association between the expression of XIST and the OS. A) The survival curve of patients with CESC. B) The survival curve of patients with KIRP. C) the survival curve of patients with SKCM. Abbreviations: CESC-cervical squamous cell; KIRP-kidney renal papillary cell; SKCM-skin cutaneous melanoma

implied that lncRNA XIST overexpression was interrelated with a poor prognosis. Furthermore, we perceived the remarkable clinical value of XIST in digestive system tumors more than in non-digestive system tumors by subgroup analysis. Also, the high expression of lncRNA XIST was interrelated with poor DFS. The clinicopathological parameters analysis revealed that increased XIST expression was a significant correlation with easier LNM, DM, larger tumor size, poor tumor differentiation, and higher clinical stage. However, no considerable interrelation was perceived between the expression of lncRNA XIST and gender, as well as age. Moreover, we further confirmed the results of our meta-analysis via bioinformatics methods. Same results as our meta-analysis, it was found that higher expression of XIST was significantly related to worse OS in CESC, KIRP, and SKCM.

The mechanisms underlying the correlation between high XIST expression and poor outcome of tumor patients is uncertain. Evidence of this study suggests that XIST may act as an oncogene in several malignant tumors. Long non-coding RNA XIST regulates gastric cancer progression by acting as a molecular sponge of miR-101 to modulate EZH2 expression or regulate the miR-497/MACC1 axis individually. Moreover, in non-small cell lung cancer lncRNA

XIST inhibits cell proliferation via regulating the miR-744/RING1 axis or repressing KLF2 expression. Meanwhile, long noncoding RNA XIST promotes malignancies via regulating miR-101/EZH2 in esophageal squamous cell carcinoma. Long non-coding RNA XIST exerts oncogenic functions via miR-34a-5p or miR-140/miR-124/iASPP or miR133a/EGFR axis in pancreatic cancer. However, there are different study outcomes in cervical squamous cell carcinoma, osteosarcoma, and hepatocellular carcinoma. One revealed that XIST expression was significantly downgraded, while the other revealed that XIST was upgraded in tumor tissues and cell lines [26, 31, 34]. The abnormal phenomena symbolize those inconsistent outcomes that can increase our understanding of the underlying molecular mechanisms of lncRNA XIST and require rigorous experimental design and repetitive experiments in the future.

In spite of it all, the present study was limited in several aspects that should be further emphasized: 1) among all included studies, most studies came from Asians. Therefore, the results of our data are not adequately the prognosis of global representative; 2) several HRs in some studies could not be calculated directly from the primary data, which the inaccuracy might add the potential bias; 3) potential biases might exist because of studies with positive results were more likely to be published. Thus, our results might overvalue the predictive significance of lncRNA XIST in the prognosis of human tumors to some extent.

In summary, the current analysis had a large number of studies, and the number of samples exceeded 2,000, achieving specific stable results. Our results clarify the significance of lncRNA XIST as a potential clinical indicator of poor prognosis and adverse pathological features in tumor patients. These outcomes also could have potential value in early diagnosis and result in prediction, and provide a novel view for the therapeutic target in clinical treatment. Considering the localization of this analysis, further comprehensive, large-scale, and good-quality clinical research should be required to clarify the accuracy of the prognostic value of lncRNA XIST in tumor patients and to improve more reliable clinical applications.

References

[1] TORRE LA, SIEGEL RL, WARD EM, JEMAL A. Global Cancer Incidence and Mortality Rates and Trends--An Update. Cancer Epidemiol Biomarkers Prev 2016; 25: 16–27. https://doi.org/10.1158/1055-9965.EPI-15-0578

[2] SIEGEL RL, MILLER KD, JEMAL A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7–34. https://doi.org/10.3322/caac.21551

[3] XIE J, CHEN L, SUN Q, LI H, WEI W et al. An immune subtype-related prognostic signature of hepatocellular carcinoma based on single-cell sequencing analysis. Aging (Albany NY) 2022; 14: 3276–3292. https://doi.org/10.18632/aging.204012

[4] YANG B, ZHANG M, LUO T. Identification of Potential Core Genes Associated With the Progression of Stomach Adenocarcinoma Using Bioinformatic Analysis. Front Genet 2020; 11: 517362. https://doi.org/10.3389/fgene.2020.517362

[5] BATISTA PJ, CHANG HY. Long noncoding RNAs: cellular address codes in development and disease. Cell 2013; 152: 1298–1307. https://doi.org/10.1016/j.cell.2013.02.012

[6] TANG Y, ZHOU T, YU X, XUE Z, SHEN N. The role of long non-coding RNAs in rheumatic diseases. Nat Rev Rheumatol 2017; 13: 657–669. https://doi.org/10.1038/nrrheum.2017.162

[7] WANG KC, CHANG HY. Molecular mechanisms of long noncoding RNAs. Mol Cell 2011; 43: 904–914. https://doi.org/10.1016/j.molcel.2011.08.018

[8] BHAN A, SOLEIMANI M, MANDAL SS. Long Noncoding RNA and Cancer: A New Paradigm. Cancer Res 2017; 77: 3965–3981. https://doi.org/10.1158/0008-5472.CAN-16-2634

[9] BROWN CJ, BALLABIO A, RUPERT JL, LAFRENIERE RG, GROMPE M et al. A gene from the region of the human X inactivation centre is expressed exclusively from the inactive X chromosome. Nature 1991; 349: 38–44. https://doi.org/10.1038/349038a0

[10] WANG J, CAI H, DAI Z, WANG G. Down-regulation of lncRNA XIST inhibits cell proliferation via regulating miR-744/RING1 axis in non-small cell lung cancer. Clin Sci (Lond) 2019; 133: 1567–1579. https://doi.org/10.1042/CS20190519

[11] CHEN DL, JU HQ, LU YX, CHEN LZ, ZENG ZL et al. Long non-coding RNA XIST regulates gastric cancer progression by acting as a molecular sponge of miR-101 to modulate EZH2 expression. J Exp Clin Cancer Res 2016; 35: 142. https://doi.org/10.1186/s13046-016-0420-1

[12] LIANG S, GONG X, ZHANG G, HUANG G, LU Y et al. The lncRNA XIST interacts with miR-140/miR-124/iASPP axis to promote pancreatic carcinoma growth. Oncotarget 2017; 8: 113701–113718. https://doi.org/10.18632/oncotarget.22555

[13] 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. https://doi.org/10.1186/1745-6215-8-16

[14] LO CK, MERTZ D, LOEB M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol 2014; 14: 45. https://doi.org/10.1186/1471-2288-14-45

[15] TANG Z, LI C, KANG B, GAO G, LI C et al. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. Nucleic Acids Res 2017; 45: W98–W102. https://doi.org/10.1093/nar/gkx247

[16] XIAO Y, YURIEVICH UA, YOSYPOVYCH SV. Long noncoding RNA XIST is a prognostic factor in colorectal cancer and inhibits 5-fluorouracil-induced cell cytotoxicity through promoting thymidylate synthase expression. Oncotarget 2017; 8: 83171–83182. https://doi.org/10.18632/oncotarget.20487

[17] SONG H, HE P, SHAO T, LI Y, LI J et al. Long non-coding RNA XIST functions as an oncogene in human colorectal cancer by targeting miR-132-3p. J BUON 2017; 22: 696–703.
[18] CHEN DL, CHEN LZ, LU YX, ZHANG DS, ZENG ZL et al. Long noncoding RNA XIST expedites metastasis and modulates epithelial-mesenchymal transition in colorectal cancer. Cell Death Dis 2017; 8: e3011. https://doi.org/10.1038/cddis.2017.421
[19] SUN N, ZHANG G, LIU Y. Long non-coding RNA XIST sponges miR-34a to promotes colon cancer progression via Wnt/beta-catenin signaling pathway. Gene 2018; 665: 141–148. https://doi.org/10.1016/j.gene.2018.04.014
[20] ZHANG R, WANG Z, YU Q, SHEN J, HE W et al. Atractylenolide II reverses the influence of lncRNA XIST/miR-30a-5p/ROR1 axis on chemo-resistance of colorectal cancer cells. J Cell Mol Med 2019; 2: 3151–3165. https://doi.org/10.1111/jcmm.14148
[21] DU P, ZHAO H, PENG R, LIU Q, YUAN J et al. LncRNA-XIST interacts with miR-29c to modulate the chemoresistance of glioma cell to TMZ through DNA mismatch repair pathway. Biosci Rep 2017; 37. https://doi.org/10.1042/BSR20170696
[22] MA L, ZHOU Y, LUO X, GAO H, DENG X et al. Long non-coding RNA XIST promotes cell growth and invasion through regulating miR-497/MACC1 axis in gastric cancer. Oncotarget 2017; 8: 4125–4135. https://doi.org/10.18632/oncotarget.13670
[23] LIU H, DENG H, ZHAO Y, LI C, LIANG Y. LncRNA XIST/miR-34a axis modulates the cell proliferation and tumor growth of thyroid cancer through MET-PI3K-AKT signaling. J Exp Clin Cancer Res 2018; 37: 279. https://doi.org/10.1186/s13046-018-0950-9
[24] SONG P, YE LF, ZHANG C, PENG T, ZHOU XH. Long non-coding RNA XIST exerts oncogenic functions in human nasopharyngeal carcinoma by targeting miR-34a-5p. Gene 2016; 592: 8–14. https://doi.org/10.1016/j.gene.2016.07.055
[25] DU Y, WENG XD, WANG L, LIU XH, ZHU HC et al. LncRNA XIST acts as a tumor suppressor in prostate cancer through sponging miR-23a to modulate RKIP expression. Oncotarget 2017; 8: 94358–94370. https://doi.org/10.18632/oncotarget.21719
[26] ZHANG R, XIA T. Long non-coding RNA XIST regulates PDCD4 expression by interacting with miR-21-5p and inhibits osteosarcoma cell growth and metastasis. Int J Oncol 2017; 51: 1460–1470. https://doi.org/10.3892/ijo.2017.4127
[27] YANG C, WU K, WANG S, WEI G. Long non-coding RNA XIST promotes osteosarcoma progression by targeting YAP via miR-195-5p. J Cell Biochem 2018; 119: 5646–5656. https://doi.org/10.1002/jcb.26743
[28] Wang W, Shen H, Cao G, Huang J. Long non-coding RNA XIST predicts poor prognosis and promotes malignant phenotypes in osteosarcoma. Oncol Lett 2019; 17: 256–262. https://doi.org/10.3892/ol.2018.9596
[29] MO Y, LU Y, WANG P, HUANG S, HE L et al. Long non-coding RNA XIST promotes cell growth by regulating miR-139-5p/PDK1/AKT axis in hepatocellular carcinoma. Tumour Biol 2017; 39: 1010428317690999. https://doi.org/10.1177/1010428317690999
[30] KONG Q, ZHANG S, LIANG C, ZHANG Y, KONG Q et al. LncRNA XIST functions as a molecular sponge of miR-194-5p to regulate MAPK1 expression in hepatocellular carcinoma cell. J Cell Biochem 2018; 119: 4458–4468. https://doi.org/10.1002/jcb.26540
[31] MA W, WANG H, JING W, ZHOU F, CHANG L et al. Downregulation of long non-coding RNAs JPX and XIST is associated with the prognosis of hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 2017; 41: 163–170. https://doi.org/10.1016/j.clinre.2016.09.002
[32] WEI W, LIU Y, LU Y, YANG B, TANG L. LncRNA XIST Promotes Pancreatic Cancer Proliferation Through miR-133a/EGFR. J Cell Biochem 2017; 118: 3349–3358. https://doi.org/10.1002/jcb.25988
[33] SUN Z, ZHANG B, CUI T. Long non-coding RNA XIST exerts oncogenic functions in pancreatic cancer via miR-34a-5p. Oncol Rep 2018; 39: 1591–1600. https://doi.org/10.3892/or.2018.6245
[34] KOBAYASHI R, MIYAGAWA R, YAMASHITA H, MORIKAWA T, OKUMA K et al. Increased expression of long non-coding RNA XIST predicts favorable prognosis of cervical squamous cell carcinoma subsequent to definitive chemoradiation therapy. Oncol Lett 2016; 12: 3066–3074. https://doi.org/10.3892/ol.2016.5054
[35] ZHU H, ZHENG T, YU J, ZHOU L, WANG L. LncRNA XIST accelerates cervical cancer progression via upregulating Fus through competitively binding with miR-200a. Biomed Pharmacother 2018; 105: 789–797. https://doi.org/10.1016/j.biopha.2018.05.053
[36] FANG J, SUN CC, GONG C. Long noncoding RNA XIST acts as an oncogene in non-small cell lung cancer by epigenetically repressing KLF2 expression. Biochem Biophys Res Commun 2016; 478: 811–817. https://doi.org/10.1016/j.bbrc.2016.08.030
[37] WU X, DINGLIN X, WANG X, LUO W, SHEN Q et al. Long noncoding RNA XIST promotes malignancies of esophageal squamous cell carcinoma via regulation of miR-101/EZH2. Oncotarget 2017; 8: 76015–76028. https://doi.org/10.18632/oncotarget.18638
[38] LI J, HE D. Long noncoding RNA Xist predicts the presence of lymph node metastases in human oesophageal squamous cell carcinoma. Br J Biomed Sci 2019; 76: 147–149. https://doi.org/10.1080/09674845.2019.1594489
[39] HU Y, DENG C, ZHANG H, ZHANG J, PENG B et al. Long non-coding RNA XIST promotes cell growth and metastasis through regulating miR-139-5p mediated Wnt/beta-catenin signaling pathway in bladder cancer. Oncotarget 2017; 8: 94554–94568. https://doi.org/10.18632/oncotarget.21791
[40] BRAY F, FERLAY J, SOERJOMATARAM I, SIEGEL RL, TORRE LA et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424. https://doi.org/10.3322/caac.21492
[41] YARMISHYN AA, KUROCHKIN IV. Long noncoding RNAs: a potential novel class of cancer biomarkers. Front Genet 2015; 6: 145. https://doi.org/10.3389/fgene.2015.00145

[42] YANG B, LUO T, ZHANG M, LU Z, XUE X et al. The novel long noncoding RNA RP11-357H14.17 acts as an oncogene by promoting cell proliferation and invasion in diffuse-type gastric cancer. Onco Targets Ther 2017; 10: 2635–2643. https://doi.org/10.2147/OTT.S134121

[43] LUO T, ZHAO J, LU Z, BI J, PANG T et al. Characterization of long non-coding RNAs and MEF2C-AS1 identified as a novel biomarker in diffuse gastric cancer. Transl Oncol 2018; 11: 1080–1089. https://doi.org/10.1016/j.tranon.2018.06.007

[44] QIU Y, LI H, ZHANG Q, QIAO X, WU J. Ferroptosis-Related Long Noncoding RNAs as Prognostic Marker for Colon Adenocarcinoma. Appl Bionics Biomech 2022; 2022: 5220368. https://doi.org/10.1155/2022/5220368

[45] DA ROCHA ST, HEARD E. Novel players in X inactivation: insights into Xist-mediated gene silencing and chromosome conformation. Nat Struct Mol Biol 2017; 24: 197–204. https://doi.org/10.1038/nsmb.3370

[46] XIE J, LI H, CHEN L, CAO Y, HU Y et al. A Novel Pyroptosis-Related lncRNA Signature for Predicting the Prognosis of Skin Cutaneous Melanoma. Int J Gen Med 2021; 14: 6517–6527. https://doi.org/10.2147/IJGM.S335396