Systematic Review and Meta-Analysis

Medicine®

OPEN

TUG1, SPRY4-IT1, and HULC as valuable prognostic biomarkers of survival in cancer

A PRISMA-compliant meta-analysis

Yucheng Zhong, MD[a], Zhicong Chen, MD[a,b], Shuyuan Guo, MD[c], Xinhui Liao, MD[a], Haibiao Xie, MD[a], Yien Zheng, MD[c], Bin Cai, MD[c], Peixian Huang, MD[c], Yuhan Liu, MD[a], Qun Zhou, MD[a], Yuchen Liu, PhD[a,*], Weiren Huang, PhD[a,*]

Abstract

Background: Long noncoding RNAs (LncRNAs) are involved in the development and progression of various cancers. Accumulating evidences indicated that expression of lncRNAs was related to the prognosis of tumors.

Methods: Here, 3 well-known lncRNAs associated with cancer were gathered to prove the potential role of lncRNAs as novel predictors of survival in human cancer. This meta-analysis collected all eligible studies about TUG1, SPRY4-IT1, and HULC and explored the relationship between lncRNAs expression and lymph node metastasis (LNM) or overall survival (OS). A comprehensive, computerized literature search was undertaken by using PubMed, EMBASE, Cochrane Library, and Web of Science (up to October 10, 2017). Strength of association between 3 lncRNAs and cancer prognosis was assessed by computing the hazard ratios (HR) with its corresponding 95% confidence interval (CI). According to the inclusion and exclusion criteria, respectively, 10, 9, and 7 studies of 3 lncRNAs were included in this meta-analysis.

Results: In the current meta-analysis, it could be concluded that the expression of these 3 lncRNAs in tumor tissues is not a direct evidence of LNM. In general, there was a significant negative correlation between TUG1 levels and OS time (pooled HR 1.54, 95% CI 1.06–2.24), SPRY4-IT1 levels and OS time (pooled HR 2.12, 95% CI 1.58–2.86) and HULC levels and OS time (pooled HR 2.10, 95% CI 1.18–3.73). It could be revealed from the result that high level expression of these 3 lncRNAs might be correlated with a bad prognosis.

Conclusions: In conclusion, the current meta-analysis demonstrated that TUG1, SPRY4-IT1, and HULC might serve as a moderate predictor of survival in human cancer.

Abbreviations: CI = confidence interval, CRC = colorectal cancer, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, GLA = glioma, HR = hazard ratios, HULC = hepatocellular carcinoma up-regulated long noncoding RNA, LncRNA = long noncoding RNA, LNM = lymph node metastasis, MIBC = muscle-invasive bladder cancer, NOS = Newcastle-Ottawa Scale, NSCLC = nonsmall cell lung cancer, OS = overall survival, OSA = osteosarcoma, RCC = renal cell carcinoma, SE = standard error, SPRY4-IT1 = SPRY4 intronic transcript1, TUG1 = taurine upregulated1.

Keywords: HULC, LncRNA, meta-analysis, prognosis, SPRY4-IT1, TUG1

1. Introduction

Cancer has been a serious public health problem world widely since the beginning of the 20th century, the overall incidence and mortality rate are on the rise.[1] Cancer incidence and mortality have been increasing in China, making cancer the leading cause of death since 2010 and a major public health problem in the

Editor: Daryle Wane.

Y.Z. and Z.C. contributed equally in this study. This work was supported by the National Key Basic Research Program of China (973 Program) (2014CB745201), the Chinese High-Tech (863) Program (2014AA020607), National Natural Science Foundation of China (81402103), International S&T Cooperation program of China (ISTCP) (2014DFA31050), the National Science Foundation Projects of Guangdong Province (2014A030313717), the Shenzhen Municipal Government of China (ZDSYS201504301722174, JCYJ20150330102720130, GJHZ20150316154912494), and Special Support Funds of Shenzhen for Introduced High-Level Medical Team.

The authors declare no conflict of interests.

Supplemental Digital Content is available for this article.

[a] Key Laboratory of Medical Reprogramming Technology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen, [b] Department of Urology, Peking University First Hospital, The Institute of Urology, Peking University, National Urological Cancer Centre, Beijing, [c] Shantou University Medical College, Shantou, China.

[*] Correspondence: Yuchen Liu, and Weiren Huang, Key Laboratory of Medical Reprogramming Technology, Shenzhen Second People's Hospital, the First Affiliated Hospital of Shenzhen University, Shenzhen 518039, China (e-mails: liuyuchenmdcg@163.com, pony8980@163.com).

Medicine (2017) 96:46(e8583)

Received: 21 January 2017 / Received in final form: 12 October 2017 / Accepted: 19 October 2017

http://dx.doi.org/10.1097/MD.0000000000008583

country.[2] As known to us that, in the early stage of tumors without lymph node metastasis (LNM) or distant metastasis, some therapies such as chemotherapy, radiotherapy, and surgery, are effective. However, because of their gradual progression and nonspecific symptoms, most cancers are usually diagnosed in advanced stage.

Furthermore, the prognosis of tumor cannot be fully interpreted by the current cancer staging. The 2 types of commonly used cancer staging methods are as follows. One is Clinical staging: I, II, III, IV, based on a large number of case studies and follow-up results analysis, grouped by the survival rate of patients staging. The other is the TNM staging method. TNM staging determines the local tumor size (T), whether there is regional lymph node metastasis and extent of transfer (N), or distant metastasis (M). TNM stages of tumor lesions are described in detail.

As the development of gene sequencing technology and indepth study of cancer biology, these 2 stage standards have encountered enormous challenges. The more we study the biology of cancer, the more things should be updated, like staging standard and diagnostic methods of cancer. Therefore, early detection of tumors, especially, finding a novel molecular cancer marker is both important and necessary for cancer patients to have timely treatment. Biomarker is indispensable to predict LNM and prognosis by observing the progression of cancers and estimating the prognosis.

Because of the rapid development of second-generation sequencing technology,[3,4] long noncoding RNAs (lncRNAs), defined as noncoding transcripts 200 nucleotides longer in length, have been involved in the development of various human diseases, particularly in cancers.[5–9] LncRNAs also play crucial regulatory roles in different cellular processes, such as gene regulation, posttranslational processing, and tumor genesis.[10]

Meanwhile, it has been shown that many lncRNAs can function as oncogenes or tumor suppressors.[11–15] LncRNA-taurine up-regulated1 (TUG1) was initially detected in a genomic screen for genes upregulated in response to taurine treatment in developing mouse retinal cells.[16] SPRY4 intronic transcript 1 (SPRY4-IT1), which was observed in melanoma, could modulate cell proliferation, cell apoptosis, and invasion.[17] Hepatocellular carcinoma upregulated long noncoding RNA (HULC), located in Chromosome 6p24.3, first found in hepatocellular carcinoma (HCC) patients, has been highly associated with cancers' diagnosis.[18] TUG1, SPRY4-IT1, and HULC were involved in the occurrence and development of various cancers including muscle-invasive bladder cancer (MIBC),[19] esophageal squamous cell carcinoma (ESCC),[20] glioma (GLA),[21] osteosarcoma (OSA),[22] colorectal cancer (CRC),[23] gastric cancer (GC),[16] renal cell carcinoma (RCC),[24] and nonsmall cell lung cancer (NSCLC).[25,26] Their aberrant expressions were closely linked to the clinical pathological characteristics, such as lymph node metastasis, distant metastasis, and overall survival. Therefore, the lncRNA-TUG1, SPRY4-IT1, and HULC may function as potential markers in predicting the prognosis of patients with various kinds of cancer.

However, major limitation also has been revealed for the insufficient size of samples and inconsistent results. Therefore, a systematic review and meta-analysis has been carried out to explore the expression of these 3 well-known lncRNAs (TUG1, SPRY4-IT1, and HULC) and lymph node metastasis and the overall survival to prove these 3 lncRNAS might serve as biomarkers in cancer prognosis and diagnosis.

2. Materials and methods

2.1. Meta-analysis

This report is strictly in accordance with the PRISMA guidelines.[27] All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Search strategy

Electronic databases PubMed, EMBASE, Cochrane Library, and Web of Science were systematically performed by using "lncRNA-TUG1 or TUG1 and cancer or tumor or carcinoma," "lncRNA-SPRY4-IT1 or SPRY4-IT1 and cancer or tumor or carcinoma," "lncRNA-HULC or HULC and cancer or tumor or carcinoma" as keywords separately, to identify potentially relevant studies. The latest update of searching was on October 10, 2017.

2.3. Inclusion and exclusion criteria

Inclusion criteria of the studies are as follows: Articles associating with these 3 well-known lncRNAs (TUG1, SPRY4-IT1, and HULC) expression and prognosis of the patients should be investigated. Patients were grouped according to the expression levels of lncRNAs, which were measured in primary tumor tissues. Related clinical pathological characteristics were reported, including lymph node metastasis. Clinical outcomes including overall survival were reported. Eligible articles should contain information on hazard ratios (HR) and corresponding 95% confidence intervals (CI), even if there is no explicit HR in the text, a survival curve should be contained. It is available for the full text. Exclusion criteria are as follows: duplicate publications; nonhuman study or noncomparative or irrelevant; reviews, case reports, letters, editorials, and expert opinions; studies were not grouped according to the expression level of lncRNAs; and studies without available data (explicit HR or a survival curve).

2.4. Risk of bias assessment

The biased risk assessment of each eligible study was based on the basis for assessing the internal validity of the prognostic article[28,29] and the recommendations on the biomarker research report.[30,31]

2.5. Data extraction

According to our criteria, 2 authors (BC and PXH) independently assessed the qualification of the retrieved articles being searched. Any doubt was committed by consensus with YEZ. About data extraction tools, firstly, a standardized Microsoft Excel table has been adopted according to the CHARMS checklist[32]: first author, publication date, country of origin, tumor type, detected sample size, detection method of these 3 well-known lncRNAs (TUG1, SPRY4-IT1, and HULC) expression levels, cut-off values, number of high lncRNAs expression group and low lncRNAs expression group, number of patients with lymph node metastasis, survival analysis, multivariate analysis, follow-up period, HR, and corresponding 95% CIs for overall survival (OS). If only Kaplan–Meier curves were available, data from the graphical survival plots have been extracted and the HRs have been estimated. The process of data extraction was standardized by 3 authors (YCZ, ZCC, and SYG) and 1 author (YCL)

independently intervened to monitor the whole process and achieved consensus in the case of disagreement. All calculations mentioned above were based on the methods illustrated by Parmar et al[33] and Tierney et al[34]

According to the inclusion and exclusion criteria, data were extracted independently by 3 authors (YCZ, ZCC, and SYG). Disagreements were resolved by 2 investigators (YCL, WRH) through discussions. The extracted information for each eligible study included: first author, publication date, country of origin, tumor type, detected sample size, detection method of these 3 well-known lncRNAs (TUG1, SPRY4-IT1, and HULC) expression levels, cut-off values, number of high lncRNAs expression group and low lncRNAs expression group, number of patients with lymph node metastasis, survival analysis, multivariate analysis, follow-up period, HR, and corresponding 95% CIs for OS. If only Kaplan–Meier curves were available, we extracted data from the graphical survival plots and estimated the HRs. All calculations mentioned above were based on the methods illustrated by Parmar et al[33] and Tierney et al.[34]

2.6. Statistical methods

All the statistical analyses were performed with Stata 12.0. The result of the odds ratios was calculated according to the bivariate variables of LNM results. Data of pooled HR were extracted from the qualified studies; the log HR and standard error (SE) were used for combination of the survival results.[34] To evaluate the heterogeneity of the eligible studies, pooled HR were executed by using I^2 statistics in this meta-analysis.[35] Subgroup analysis was performed on the basis of the expression of lncRNAs. For studies evaluating the association between TUG1 expression and prognosis, the subgroup analysis was adopted to discuss the effects of high and low expression of TUG1 in diverse cancers respectively. HULC also uses the above method for subgroup analysis. The random-effects model was employed for the meta-analysis. Sensitivity analyses are important components of meta-analyses to assess the sensitivity of heterogeneity measures to exclusion of studies, and sensible in particular to define a 'desired threshold' in terms of the I^2 or tau-square statistic. The potential publication bias was measured through the Egger test. $P < .05$ were examined to be statistically significant.

3. Results

3.1. Selection of studies

A total of 79 (TUG1), 61 (SPRY4-IT1), and 114 (HULC) published records were retrieved in our preliminary search by looking up the keywords. Moreover, 15, 22, and 36 duplicate references subsequently were excluded. After the title and abstract being screened, 49, 24, and 63 irrelevant references were further excluded. Upon further review of the full articles, a total of 26 publications addressing the relationship between lncRNA and cancer LNM or OS were found to meet all of the inclusion criteria and used for data extraction. Finally, this current meta-analysis was conducted for the remaining 10 (TUG1), 9 (SPRY4-IT1), and 7 (HULC) studies. (Fig. 1)

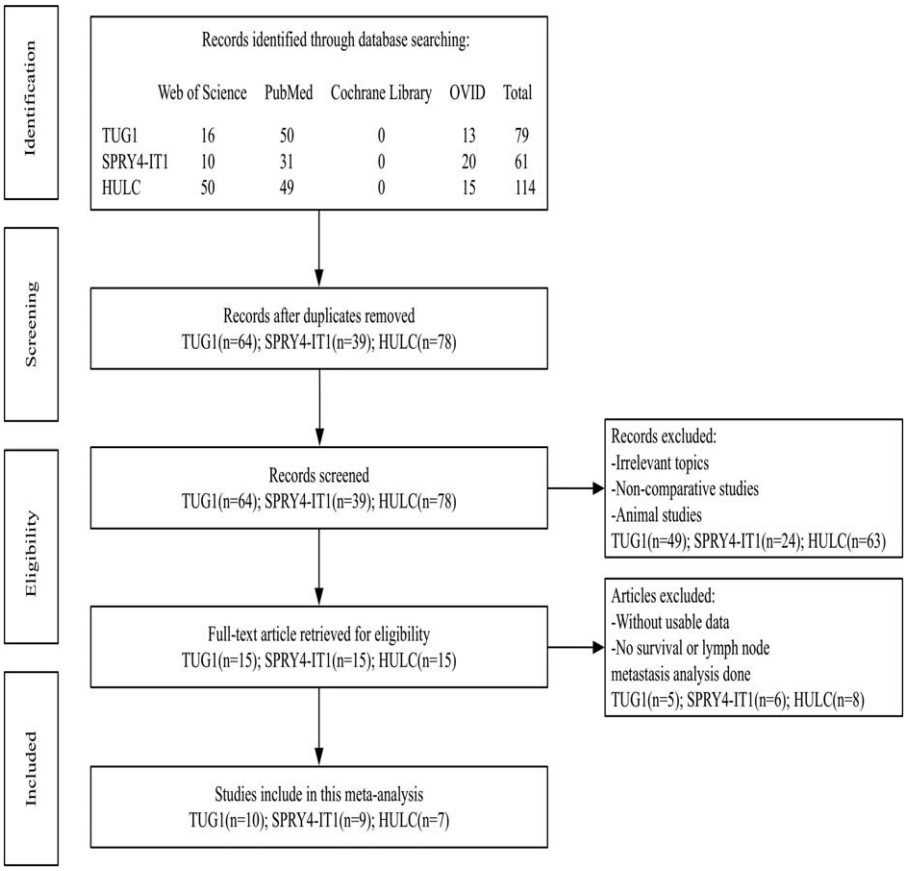

Figure 1. Flowchart presenting the steps of literature search and selection.

Table 1

Characteristics of studies in this meta-analysis.

LncRNA	Study	Year	Country	Cancer type	Total number	Detection method	Cut-off	High expression	Low expression	High with LNM	Low with LNM	Survival analysis	Multivariate analysis	HR statistic	HR (95% CI)	Follow-up months
TUG1	Iliev et al[19]	2016	Czech Republic	MIBC	47	qRT-PCR	Mean	26	21	NA	NA	OS	Yes	Rep	2.54 (1.13–5.74)	30 (median)
	Jiang et al[20]	2016	China	ESCC	218	qRT-PCR	Median	109	109	86	82	OS	Yes	Rep	1.40 (1.01–1.95)	72 (total)
	Ma et al[22]	2016	China	OSE	76	qRT-PCR	ROC	41	35	NA	NA	OS	Yes	Rep	2.78 (1.29–6.00)	60 (total)
	Sun et al[23]	2016	China	CRC	120	qRT-PCR	X-tile algorith	72	48	35	15	OS	Yes	SC	2.18 (0.32–14.9)	36 (mean)
	Zhang et al[16]	2016	China	GC	100	qRT-PCR	Median	50	50	NA	NA	OS	Yes	Rep	1.07 (1.02–1.11)	60 (total)
	Zhang et al[24]	2016	China	RCC	40	qRT-PCR	X-tile algorith	31	9	3	1	NA	NA	NA	NA	NA
	Li et al[21]	2016	China	GLA	120	qRT-PCR	Median	60	60	NA	NA	OS	Yes	SC	0.57 (0.34–0.96)	58 (total)
	Lin et al[25]	2016	China	NSCLC	89	qRT-PCR	X-tile algorith	58	31	NA	NA	OS	Yes	SC	0.73 (0.29–1.86)	80 (total)
	Zhang et al[37]	2016	China	NSCLC	192	qRT-PCR	Mean	96	96	46	60	OS	Yes	Rep	0.39 (0.32–0.74)	60 (total)
	Kuang[38]	2016	China	OC	62	qRT-PCR	Mean	29	33	18	12	NA	NA	NA	NA	NA
SPRY4-IT1	Xie et al[39]	2015	China	GC	61	qRT-PCR	Median	30	31	11	21	OS	Yes	SC	1.21 (0.64–2.32)	36 (median)
	Xie[40]	2014	China	ESCC	92	qRT-PCR	Mean	46	46	29	16	OS	Yes	Rep	2.05 (1.04–4.03)	39 (median)
	Peng et al[41]	2015	China	GC	175	qRT-PCR	ROC	98	77	66	68	OS	Yes	Rep	1.74 (1.32–2.48)	60 (total)
SPRY4-IT1	Zhou[42]	2016	China	GLA	163	qRT-PCR	Median	81	82	NA	NA	OS	Yes	Rep	2.16 (1.46–3.93)	68 (total)
	Zhao[43]	2015	China	UCB	68	qRT-PCR	Mean	38	30	18	1	OS	Yes	Rep	3.72 (2.08–6.72)	60 (total)
	Zhang et al[26]	2014	China	RCC	98	qRT-PCR	Mean	52	46	13	1	OS	Yes	Rep	3.38 (1.82–7.39)	35 (median)
	Sun et al[36]	2014	China	NSCLC	121	qRT-PCR	Median	60	61	NA	NA	OS	Yes	Rep	1.25 (0.95–1.64)	36 (median)
	Cao et al[44]	2016	China	CRC	84	qRT-PCR	Mean	36	48	15	19	OS	Yes	Rep	3.21 (1.55–6.67)	26 (median)
	Cao et al[44]	2016	China	CC	100	qRT-PCR	Mean	46	54	27	9	OS	Yes	Rep	3.87 (1.38–10.83)	53 (median)
HULC	Uzan[45]	2016	Brazil	OSE	33	qRT-PCR	ROC	12	21	4	6	OS	Yes	SC	22.01 (2.26–216.13)	120 (total)
	Sun[46]	2015	China	OSE	78	qRT-PCR	Median	39	39	16	5	OS	Yes	SC	2.28 (1.48–5.43)	60 (total)
	Li et al[21]	2016	China	HCC	38	qRT-PCR	Mean	23	15	8	1	OS	Yes	SC	1.03 (0.30–3.58)	17 (median)
	Jin[47]	2016	China	GC	100	qRT-PCR	ROC	48	52	34	25	OS	Yes	SC	1.32 (0.51–3.41)	40 (total)
	Yang[48]	2015	China	HCC	240	qRT-PCR	Median	NA	NA	NA	NA	OS	Yes	SC	0.89 (0.80–0.98)	120 (total)
	Peng[49]	2014	China	PC	304	qRT-PCR	ROC	212	92	157	23	OS	Yes	Rep	0.36 (0.19–0.71)	60 (total)
	Wang et al[50]	2016	China	CC	244	qRT-PCR	Median	124	120	82	42	OS	Yes	Rep	2.56 (1.32–7.04)	60 (total)

CC = cervical cancer, CRC = colorectal cancer, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, GLA = glioma, HCC = hepatocellular cancer, MIBC = muscle-invasive bladder cancer, NA = not available, NSCLC = nonsmall cell lung cancer, OC = ovarian cancer, OS = overall survival, OSE = osteosarcoma, PC = pancreatic cancer, qRT-PCR = quantitative real-time PCR, RCC = renal cell carcinoma, UCB = urothelial carcinoma of the bladder.

3.2. Characteristics of eligible studies

The eligible studies were published from 2014 to 2017. In the total 26 included studies, 24 were from China and the other 2 were from Czech Republic and Brazil. The types of cancers in the included studies were as follows: muscle-invasive bladder cancer, nonsmall cell lung cancer, glioma, osteosarcoma, colorectal cancer, gastric cancer, renal cell carcinoma, urothelial carcinoma of the bladder, esophageal squamous cell carcinoma, ovarian cancer, and cervical cancer. All the detected samples were tissues or frozen tissues from patients without chemotherapy or radiotherapy before surgery. The expression of TUG1, SPRY4-IT1, and HULC was measured by qRT-PCR and normalized to GAPDH or β-actin. In all the studies, the patients were divided into 2 groups: high and low expression of lncRNAs. All the diagnoses of lymph node metastasis were based on pathology. Among the 26 included studies, not all studies were examined with both OS and LNM. All the studies were of high quality (Table 1)[19–26,36–50] as confirmed by the Newcastle-Ottawa Scale (NOS) in Table 2.[19–26,36–50]

3.3. Meta-analysis

3.3.1. Association between 3 lncRNAs and LNM. Five studies reporting a total of 632 patients with LNM were included on the basis of different TUG1 expression patterns. The random-effects model was expected to be adopted. Analysis showed that the OR of 1.28 with 95% CI 0.67–2.46 ($P=.459$), which meant the expression of TUG1 might not be a direct predictor of LNM (Fig. 2 A).

Seven studies reporting a total of 678 patients with LNM were included on the basis of different SPRY4-IT1 expression patterns. The random-effects model was expected to be adopted. Analysis showed the OR of 2.17 with 95% CI (0.65–7.25) ($P=.210$), which revealed that the expression of SPRY4-IT1 might not be an available predictor of LNM (Fig. 2 B).

Six studies reporting a total of 797 patients with LNM were included on the basis of different HULC expression patterns. The random-effects model was adopted. Analysis showed the OR of 4.16 with 95% CI (2.45–7.05), that is the expression of HULC does have a positive influence on LNM. HULC might serve as a direct predictor of LNM. (Fig. 2C)

3.3.2. Association between 3 lncRNAs and OS. Eight of the included studies reported the overall survival (OS) of 962 patients according to TUG1 expression levels. The random-effects model that was used to calculate the pooled HR with corresponding 95% CI because the between-study heterogeneity among the upregulated group for TUG1 expression was confirmed ($P=.011$ for heterogeneity test, $I^2=69.6\%$). However, the significant heterogeneity did not exist across studies in the down-regulated group of 3 studies. The fixed-effects model was used to calculate the pooled HR with corresponding 95% CI for TUG1 expression was confirmed ($P=.342$ for heterogeneity test, $I^2=6.7\%$). According to meta-analysis result, it can be found that the expression of TUG1 might be associated with poor overall survival in different cancers. (Fig. 3A)

All of the included studies reported the OS of 962 patients according to SPRY4-IT1 expression levels. For evaluating the association between SPRY4-IT1 expression and prognosis more reasonably, the random-effect model that was used to calculate the pooled HR with corresponding 95% CI because the between-study heterogeneity among studies SPRY4-IT1 expression was

Table 2

Quality assessment of eligible studies (Newcastle-Ottawa Scale).

	Selection			Comparability			Outcome		
Study	Adequacy of case definition	No. of case	Representativeness of the cases	Ascertainment of exposure	Ascertainment of detection method	Ascertainment of cut-off	Assessment of outcome	Adequate follow up	Total
Iliev et al[19]	1	0	1	1	1	1	0	0	5
Jiang et al[20]	1	1	1	1	1	1	1	1	8
Ma et al[22]	1	1	1	1	1	1	1	1	8
Sun et al[23]	1	1	1	1	1	1	1	1	8
Zhang et al[16]	1	1	1	1	1	1	1	1	8
Zhang et al[24]	1	0	1	1	1	1	1	0	6
Li et al[21]	1	1	1	1	1	1	1	1	8
Lin et al[25]	1	1	1	1	1	1	1	1	8
Zhang et al[37]	1	1	1	1	1	1	1	1	8
Kuang[38]	1	1	1	1	1	1	0	0	6
Xie et al[39]	1	1	1	1	1	1	1	1	8
Xie[40]	1	1	1	1	1	1	1	1	8
Peng[41]	1	1	1	1	1	1	1	1	8
Zhou[42]	1	1	1	1	1	1	1	1	8
Zhao[43]	1	1	1	1	1	1	1	0	7
Zhang et al[26]	1	1	1	1	1	1	1	1	8
Sun et al[36]	1	1	1	1	1	1	1	1	8
Cao et al[44]	1	1	1	1	1	1	1	0	7
Cao et al[44]	1	1	1	1	1	1	1	1	8
Uzan[45]	1	1	1	1	1	1	1	1	8
Sun[46]	1	1	1	1	1	1	1	1	8
Li et al[21]	1	1	1	1	1	1	1	0	7
Jin[47]	1	1	1	1	1	1	1	1	8
Yang[48]	1	1	1	1	1	1	1	1	8
Peng[49]	1	1	1	1	1	1	1	1	8
Wang et al[50]	1	1	1	1	1	1	1	1	8

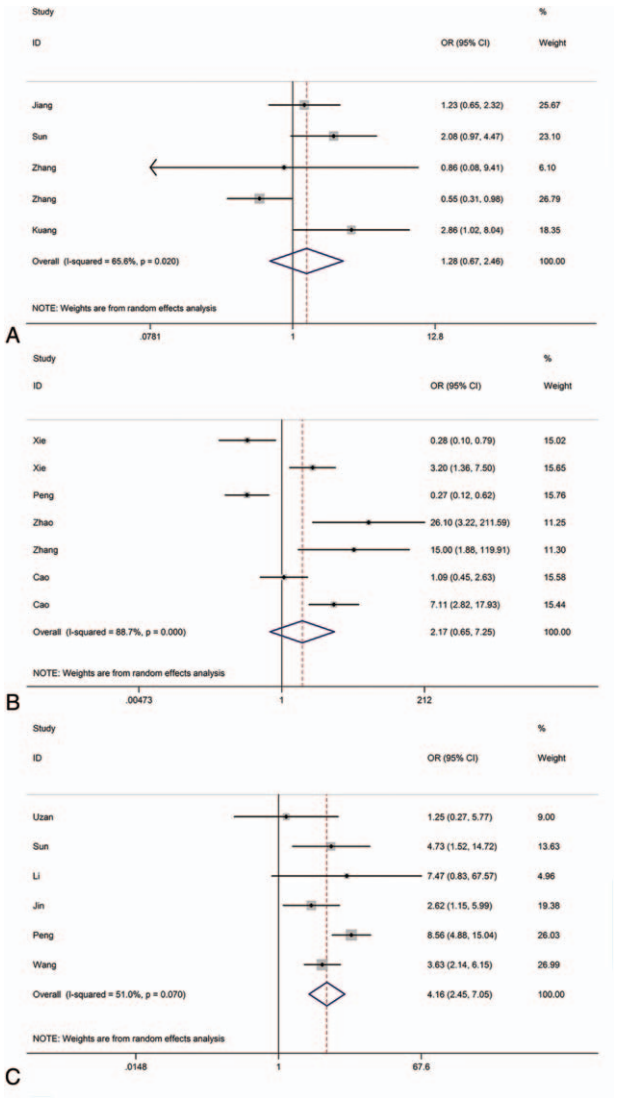

Figure 2. Forest plot of the correlation between the expression level of 3 lncRNAs expression levels and LNM in different cancer patients.

confirmed ($P = .004$ for heterogeneity test, $I^2 = 64.5\%$). According to meta-analysis result, it is known that high expression of SPRY4-IT1 might be associated with poor overall survival in tumors (pooled HR = 2.12, 95% CI 1.58–2.86, $P < .0001$) (Fig. 3 B). In a word, the cancer patients with high expression of SPRY4-IT1 might be correlated with bad prognosis.

Seven included studies reported a total of 1037 patients with OS according to HULC expression levels. The fixed-effects model that was used to calculate the pooled HR with corresponding 95% CI because the between-study heterogeneity among the upregulated group for HULC expression was confirmed ($P = .162$ for heterogeneity test, $I^2 = 38.8\%$). However, the significant heterogeneity did exist across studies in the other group of 2 studies. The random-effects model that was used to calculate the pooled HR with corresponding 95% CI for HULC expression was confirmed ($P = .008$ for heterogeneity test, $I^2 = 85.9\%$). According to meta-analysis result, it can be seen that the expression of HULC might be associated with poor overall survival in various types of carcinomas (Fig. 3C). All the meta-analysis results were summarized in Table 3.

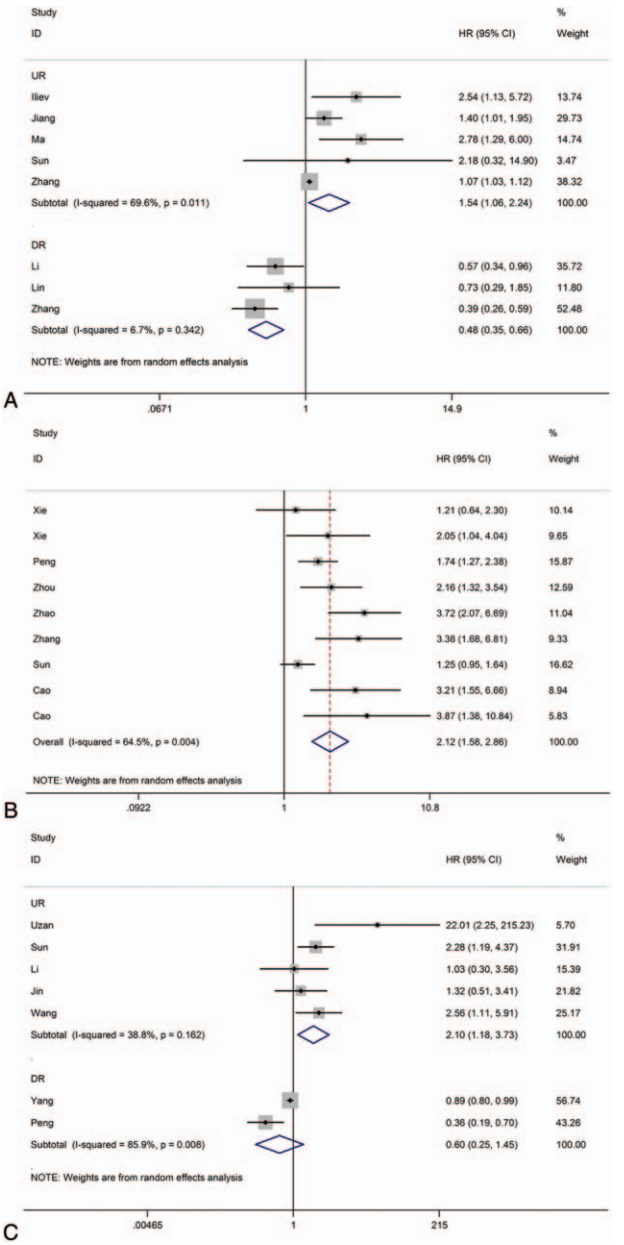

Figure 3. Forest plot of the correlation between 3 lncRNAs expression levels and OS in different cancer patients.

3.4. Publication bias and Sensitivity analysis

Publication bias of the present meta-analysis was evaluated by Egger test. In OS group, according to Egger's test (t = 2.90, $P = .023$), publication bias was shown in group SPRY4-IT1, whereas no significant publication bias was observed by the Egger test in the other 2 groups (Supplement-1, http://links.lww.com/MD/B949). Sensitivity analyses were presented in Supplement-2, http://links.lww.com/MD/B949. Although a single study each time in 3 groups was removed, there was no significant impact on the result patterns.

4. Discussion

The more we learnt about lncRNAs, the more awareness we got that lncRNAs expression might predict poor OS in cancer

Table 3

Results of this meta-analysis.

Outcomes	No. of studies	No. of patients	HR/OR (95% CI)	P	Heterogeneity		Publication bias
					I^2 (%)	Tau-square (%)	P
LNM							
TUG1	5	632	1.28 (0.67–2.46)	0.459	65.6	0.3294	
UR	3	400	1.71 (1.10–2.65)	0.016	10.9	0.02	
DR	2	232	0.57 (0.32–0.99)	0.045	0.0	0	
SPRY4-IT1	7	678	2.17 (0.65–7.25)	0.210	88.7	2.2369	
UR	5	442	4.83 (1.74–13.36)	<0.001	72.9	0.8976	
DR	2	236	0.27 (0.14–0.52)	0.002	0.0	0	
HULC	6	797	4.16 (2.45–7.05)	<0.001	51.0	0.1954	
OS							
TUG1	8	962	1.05 (0.71–1.54)	0.810	83.3	0.2001	.915
UR	5	561	1.54 (1.06–2.24)	0.024	69.6	0.0954	
DR	3	401	0.48 (0.35–0.66)	<0.001	6.7	0.0062	
SPRY4-IT1	9	962	2.12 (1.58–2.86)	<0.001	64.5	0.1193	.023
HULC	7	1037	1.32 (0.74–2.35)	0.347	79.6		.268
UR	5	493	2.10 (1.18–3.73)	0.012	38.8	0.1604	
DR	2	544	0.60 (0.25–1.45)	0.257	85.9	0.3517	

DR = downregulation, LNM = lymph node metastasis, OS = overall survival, UR = upregulation.

patients. However, what methods should be taken to summarize the results of these experiments? In clinic, meta-analysis is a commonly used research tool. Such analysis can summarize all the similar researches and provide a direction in clinical work. However, the concept of combining meta-analysis is not easy; both statistical and biological analyzes are required. It is different from basic research for it is not a simple combination of all outcomes, but understanding and dealing of the intricate results with professional thinking, even sometimes the evidences are conflicting, and it can improve our comprehension of biological systems. This is the first meta-analysis to evaluate the association between 3 well-known lncRNAs levels and clinical prognosis about cancer. The current meta-analysis has been conducted to explore the correction between expression levels of these 3 lncRNAs and overall survival rate for cancer patients. Our results are shown in Table 3, which demonstrated that the expression of TUG1, SPRY4-IT1 and HULC could predict poor survival in diverse types of cancers for patients. Through the above analysis, it can be seen that TUG1, SPRY4-IT1, and HULC were novel predictive factor of poor prognosis in most cancers. Meanwhile, these studies indicated that a signaling pathway can cause extracellular signaling molecules entering into the cell and can directly affect the phenotype of cells, such as cell proliferation, apoptosis and invasion and metabolism. To further study the mechanisms of cancer and targeted therapy and explore the significance of these 3 lncRNAs, a review of TUG1, SPRY4-IT1, and HULC including their potential targets, pathways and related miRNA in this meta-analysis has been systematically made (Table 4).[21,23,25,36–79]

5. Limitations

However, it should be recognized that there are still several limitations in the current meta-analysis. First, given that this report is based only on the results of four databases (PubMed, EMBASE, Cochrane Library, and Web of Science), it is possible that some relevant papers have been missed out. Second, the cut-off definition of lncRNAs expression was different in each study because it was difficult to define a standard cut-off in different types of cancers. Third, some of retrieved articles may not have provided the most accurate estimate of the HR as much as possible, because these data were extracted from Kaplan–Meier curves at most times. However, this approach does not produce a significantly different result from the direct method of HR estimation. Fourth, tau-square, alike I^2, is largely affected by the size of the studies and the number of the included studies. As a result, it may be very misleading in our moderately sized meta-analysis. Until now it is still not a good way to deal with the issue of heterogeneity. Fifth, the samples of the study are limited. Only 26 studies were totally included in the current meta-analysis, which might weaken the reliability of this current meta-analysis' consequences. Sixth, most of the included studies reported that lncRNAs were overexpressed in different types of cancers; low expression of lncRNAs studies was generally less likely to be published. Thus, the results of this meta-analysis should be upheld by future studies.

Despite of the significant progress in early diagnosis, surgical techniques, and chemotherapy, the prognosis of patients with cancer is yet unsatisfactory. There are still many challenges to be dealt with, for example, lack of diagnostic and prognostic markers for cancers, limited efficiency treatment, and molecular targeted therapy. Therefore, more and more novel strategies should focus on the identification of innovative prognostic biomarkers of cancers. In recent years, lncRNAs were found out relating with human cancers and more than thousands of lncRNAs have been found and reported, such as AFAP1-AS1,[80] H19,[81] UCA1,[82]and HOTAIR.[83] More and more reports point out that lncRNAs could act as tumor markers in both diagnosis and predicting the prognosis.[84] Currently, however, there are a few meta-analyses to summarize the study of lncRNAs and molecular markers in prognosis of cancer. There is no doubt that lncRNAs are important regulators in various types of human cancers,[85] thus, the research is promising in the area of tumors.

6. Conclusions

In conclusion, this meta-analysis provides evidences that expressions of 3 lncRNAs (TUG1, SPRY4-IT1, and HULC) are significantly associated with overall survival in cancer patients, which means that these 3 lncRNAs may have great potential to be

Table 4

Summary of 3 lncRNAs with their potential targets, pathways and related microRNAs entered this study.

Potential targets	Pathways	Related microRNAs	Reference
TUG1			
VEGFA	Inhibit cell proliferation, migration and tube formation Reducing spheroid-based angiogenesis ability	miR-299	[42]
HSF2	Increase BTB permeability and then reduce EC tight junction protein	miR-144	[43]
VEGFA	Inhibit cell viability, proliferation, migration and invasion	miR-34a-5p	[44]
PTEN	Polycomb repressive complex 2 (prc2)-mediated transcriptional regulation	NA	[45]
SP1, KLF2	Inhibit cell proliferation, colony formation, tumorigenicity and induces apoptosis in cell line	NA	[46]
PTEN	Inhibit the negative regulation of mir-26a on PTEN	miR-26a	[47]
Bcl-2	Inhibiting Bcl-2-mediated anti-apoptotic pathways	NA	[21]
CELF1	Promote cell proliferation	NA	[25]
EMT-related gene	Increased cell formation, migration, and invasion	NA	[23]
ZEB2	Promote cell invasion and radioresistance	miR-145	[48]
POU2F1	Inhibited cell proliferation and colony formation, and induced G0/G1 cell cycle arrest and apoptosis	miR-9–5p	[49]
P63	Inhibit cell proliferation, migration, and promote apoptosis	NA	[50]
PRC2	Repress cell proliferation	NA	[16]
SPRY4-IT1			
MMP-2, MMP-9	Invasion, migration	NA	[51]
DGAT2, TAG	Cell invasion, proliferation, increases apoptosis, lipin 2-mediated alterations	NA	[52]
Snail1	SPRY4-IT1/Snail1/E-cadherin pathway	NA	[53]
G1	Regulate the epithelial-mesenchymal transition	NA	[54]
ZNF703	Suppressed proliferation and caused apoptosis	NA	[55]
EZH2	Rescued the oncogenic phenotype	NA	[36]
HTR-8, HuR,WNT (WNT3,WNT5B)	Suppress trophoblast cell migration and invasion, prevent the EMT process, Wnt/beta-catenin pathway	NA	[56]
HTR-8	Cell migration, proliferation, and apoptosis	NA	[57]
Ki67,IAP, DPPIV	Cell proliferation, apoptosis, and cell cycle	NA	[58]
Vim, FN, E-Cad, ZO-1, Snail	Induction of epithelial-mesenchymal transition (EMT)	NA	[38]
DNMT1	Regulating epithelial-mesenchymal transition (EMT) process	NA	[38]
MMPs	Cell proliferation, colony formation, and cell migration/invasion	NA	[39]
EMT-related genes	Cells proliferation migration and invasion cell cycle arrestment	NA	[40]
HULC			
ACSL1,PPARA, RXRA	Lipid metabolism, miR-9-mediated RXRA signaling pathway	miR-9	[59]
p18	Cell proliferation	NA	[60]
CUDR, CTNNB1	CUDR-HULC/CUDR-beta-catenin signaling	NA	[61]
IGF2	Posttranscriptional destabilization	NA	[62]
EMT	miR-200a-3p/ZEB1 signaling pathway	miR-200a-3p	[63]
SPHK1	miR-107/E2F1/SPHK1 signaling pathway	miR-107	[64]
Cyclin D1, Bcl-2	Cell proliferation and induce apoptosis	NA	[65]
NKD2	HULC-EZH2- NKD2 signaling pathway	NA	[66]
ESM-1	PI3K/Akt/mTOR signaling pathway	NA	[67]
CREB	PKA pathway	miR-372	[68]
TNF-alpha	HULC-miR-9 pathway	miR-9	[69]
ADAM9	Post-transcriptional regulatory	miR-203	[70]
IL-6, CXCR4	Oxidative stress, cell migration	let-7a/let-7b miR-372/miR-373	[41]

an accurate biomarker to reveal the value of diagnosis and prognosis in diverse cancers. However, there are still many difficulties to overcome, more and more well-designed studies according to the PICOS setting and methodological characteristics (eg, randomization, blinding) with large sample sizes are required to confirm the validity and effectiveness of applying TUG1, SPRY4-IT1, and HULC in the diagnosis and prognosis of cancer patients.

Acknowledgments

The authors are indebted to the donors whose names were not included in the author list, but participated in this program.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
[2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.
[3] Liu MX, Chen X, Chen G, et al. A computational framework to infer human disease-associated long noncoding RNAs. PloS One 2014;9:e84408.
[4] Tang JY, Lee JC, Chang YT, et al. Long noncoding RNAs-related diseases, cancers, and drugs. ScientificWorldJournal 2013;2013:943539.
[5] Cheetham SW, Gruhl F, Mattick JS, et al. Long noncoding RNAs and the genetics of cancer. Br J Cancer 2013;108:2419–25.
[6] Khalil AM, Guttman M, Huarte M, et al. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc Natl Acad Sci U S A 2009;106:11667–72.

[7] Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 2010;464:1071–6.
[8] Yang Z, Zhou L, Wu LM, et al. Overexpression of long non-coding RNA HOTAIR predicts tumor recurrence in hepatocellular carcinoma patients following liver transplantation. Ann Surg Oncol 2011;18: 1243–50.
[9] Li D, Feng J, Wu T, et al. Long intergenic noncoding RNA HOTAIR is overexpressed and regulates PTEN methylation in laryngeal squamous cell carcinoma. Am J Pathol 2013;182:64–70.
[10] Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. Cell 2009;136:629–41.
[11] Han L, Zhang EB, Yin DD, et al. Low expression of long noncoding RNA PANDAR predicts a poor prognosis of non-small cell lung cancer and affects cell apoptosis by regulating Bcl-2. Cell Death Dis 2015;6: e1665.
[12] Hu Y, Pan J, Wang Y, et al. Long noncoding RNA linc-UBC1 is negative prognostic factor and exhibits tumor pro-oncogenic activity in gastric cancer. Int J Clin Exp Pathol 2015;8:594–600.
[13] Li T, Xie J, Shen C, et al. Amplification of long noncoding RNA ZFAS1 promotes metastasis in hepatocellular carcinoma. Cancer Res 2015;75: 3181–91.
[14] Liu B, Sun L, Liu Q, et al. A cytoplasmic NF-kappaB interacting long noncoding RNA blocks IkappaB phosphorylation and suppresses breast cancer metastasis. Cancer Cell 2015;27:370–81.
[15] Saito T, Kurashige J, Nambara S, et al. A long non-coding RNA activated by transforming growth factor-beta is an independent prognostic marker of gastric cancer. Ann Surg Oncol 2015;22(Suppl 3):S915–22.
[16] Zhang E, He X, Yin D, et al. Increased expression of long noncoding RNA TUG1 predicts a poor prognosis of gastric cancer and regulates cell proliferation by epigenetically silencing of p57. Cell Death Dis 2016;7: e2109.
[17] Khaitan D, Dinger ME, Mazar J, et al. The melanoma-upregulated long noncoding RNA SPRY4-IT1 modulates apoptosis and invasion. Cancer Res 2011;71:3852–62.
[18] Panzitt K, Tschernatsch MM, Guelly C, et al. Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as noncoding RNA. Gastroenterology 2007;132:330–42.
[19] Iliev R, Kleinova R, Juracek J, et al. Overexpression of long non-coding RNA TUG1 predicts poor prognosis and promotes cancer cell proliferation and migration in high-grade muscle-invasive bladder cancer. Tumor Biol 2016;37:13385–90.
[20] Jiang L, Wang W, Li G, et al. High TUG1 expression is associated with chemotherapy resistance and poor prognosis in esophageal squamous cell carcinoma. Cancer Chemother Pharmacol 2016;78:333–9.
[21] Li J, Zhang M, An G, et al. LncRNA TUG1 acts as a tumor suppressor in human glioma by promoting cell apoptosis. Exp Biol Med (Maywood, NJ) 2016;241:644–9.
[22] Ma B, Li M, Zhang L, et al. Upregulation of long non-coding RNA TUG1 correlates with poor prognosis and disease status in osteosarcoma. Tumor Biol 2016;37:4445–55.
[23] Sun J, Ding C, Yang Z, et al. The long non-coding RNA TUG1 indicates a poor prognosis for colorectal cancer and promotes metastasis by affecting epithelial-mesenchymal transition. J Transl Med 2016;14:42.
[24] Zhang M, Lu W, Huang Y, et al. Downregulation of the long noncoding RNA TUG1 inhibits the proliferation, migration, invasion and promotes apoptosis of renal cell carcinoma. J Mol Histol 2016;47:421–8.
[25] Lin PC, Huang HD, Chang CC, et al. Long noncoding RNA TUG1 is downregulated in non-small cell lung cancer and can regulate CELF1 on binding to PRC2. BMC Cancer 2016;16:583.
[26] Zhang EB, Yin DD, Sun M, et al. P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression. Cell Death Dis 2014;5:e1243.
[27] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
[28] Altman DG. Systematic reviews of evaluations of prognostic variables. BMJ 2001;323:224–8.
[29] Bouwmeester W, Zuithoff NP, Mallett S, et al. Reporting and methods in clinical prediction research: a systematic review. PLoS Med 2012;9:1–2.
[30] McShane LM, Altman DG, Sauerbrei W, et al. REporting recommendations for tumour MARKer prognostic studies (REMARK). Br J Cancer 2005;93:387–91.
[31] Henry NL, Hayes DF. Cancer biomarkers. Mol Oncol 2012;6:140–6.
[32] Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med 2014;11:e1001744.
[33] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815–34.
[34] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
[35] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[36] Sun M, Liu XH, Lu KH, et al. EZH2-mediated epigenetic suppression of long noncoding RNA SPRY4-IT1 promotes NSCLC cell proliferation and metastasis by affecting the epithelial-mesenchymal transition. Cell Death Dis 2014;5:e1298.
[37] Zhang CY, Li RK, Qi Y, et al. Upregulation of long noncoding RNA SPRY4-IT1 promotes metastasis of esophageal squamous cell carcinoma via induction of epithelial-mesenchymal transition. Cell Biol Toxicol 2016;32:391–401.
[38] Kuang D, Zhang X, Hua S, et al. Long non-coding RNA TUG1 regulates ovarian cancer proliferation and metastasis via affecting epithelial-mesenchymal transition. Exp Mol Pathol 2016;101:267–73.
[39] Xie M, Nie FQ, Sun M, et al. Decreased long noncoding RNA SPRY4-IT1 contributing to gastric cancer cell metastasis partly via affecting epithelial-mesenchymal transition. J Transl Med 2015;13:250.
[40] Xie HW, Wu QQ, Zhu B, et al. Long noncoding RNA SPRY4-IT1 is upregulated in esophageal squamous cell carcinoma and associated with poor prognosis. Tumour Biol 2014;35:7743–54.
[41] Peng W, Wu G, Fan H, et al. Long noncoding RNA SPRY4-IT1 predicts poor patient prognosis and promotes tumorigenesis in gastric cancer. Tumor Biol 2015;36:6751–8.
[42] Zhou Y, Wang DL, Pang Q. Long noncoding RNA SPRY4-IT1 is a prognostic factor for poor overall survival and has an oncogenic role in glioma. Eur Rev Med Pharmacol Sci 2016;20:3035–9.
[43] Uzan VR, Lengert A, Boldrini E, et al. High expression of HULC is associated with poor prognosis in osteosarcoma patients. PLoS One 2016;11:e0156774.
[44] Cao D, Ding Q, Yu W, et al. Long noncoding RNA SPRY4-IT1 promotes malignant development of colorectal cancer by targeting epithelial-mesenchymal transition. Onco Targets Ther 2016;9:5417–25.
[45] Sun XH, Yang LB, Geng XL, et al. Increased expression of lncRNA HULC indicates a poor prognosis and promotes cell metastasis in osteosarcoma. Int J Clin Exp Pathol 2015;8:2994–3000.
[46] Jin C, Shi W, Wang F, et al. Long non-coding RNA HULC as a novel serum biomarker for diagnosis and prognosis prediction of gastric cancer. Oncotarget 2016;7:51763–72.
[47] Yang X, Xie X, Xiao YF, et al. The emergence of long non-coding RNAs in the tumorigenesis of hepatocellular carcinoma. Cancer Lett 2015; 360:119–24.
[48] Peng W, Gao W, Feng J. Long noncoding RNA HULC is a novel biomarker of poor prognosis in patients with pancreatic cancer. Med Oncol 2014;31:346.
[49] Zhao XL, Zhao ZH, Xu WC, et al. Increased expression of SPRY4-IT1 predicts poor prognosis and promotes tumor growth and metastasis in bladder cancer. Int J Clin Exp Pathol 2015;8:1954–60.
[50] Wang WT, Ye H, Wei PP, et al. LncRNAs H19 and HULC, activated by oxidative stress, promote cell migration and invasion in cholangiocarcinoma through a ceRNA manner. J Hematol Oncol 2016;9:117.
[51] Cai H, Liu X, Zheng J, et al. Long non-coding RNA taurine upregulated 1 enhances tumor-induced angiogenesis through inhibiting microRNA-299 in human glioblastoma. Oncogene 2017;36:318–31.
[52] Cai H, Xue Y, Wang P, et al. The long noncoding RNA TUG1 regulates blood-tumor barrier permeability by targeting miR-144. Oncotarget 2015;6:19759–79.
[53] Dong R, Liu GB, Liu BH, et al. Targeting long non-coding RNA-TUG1 inhibits tumor growth and angiogenesis in hepatoblastoma. Cell Death Dis 2016;7:e2278.
[54] Du Z, Sun T, Hacisuleyman E, et al. Integrative analyses reveal a long noncoding RNA-mediated sponge regulatory network in prostate cancer. Nat Commun 2016;7:10982.
[55] Huang MD, Chen WM, Qi FZ, et al. Long non-coding RNA TUG1 is up-regulated in hepatocellular carcinoma and promotes cell growth and apoptosis by epigenetically silencing of KLF2. Mol Cancer 2015;14:165.
[56] Li J, An G, Zhang M, et al. Long non-coding RNA TUG1 acts as a miR-26a sponge in human glioma cells. Biochem Biophys Res Commun 2016;477:743–8.

[57] Tan J, Qiu K, Li M, et al. Double-negative feedback loop between long non-coding RNA TUG1 and miR-145 promotes epithelial to mesenchymal transition and radioresistance in human bladder cancer cells. FEBS Lett 2015;58920:3175–81.
[58] Xie CH, Cao YM, Huang Y, et al. Long non-coding RNA TUG1 contributes to tumorigenesis of human osteosarcoma by sponging miR-9-5p and regulating POU2F1 expression. Tumor Biol 2016;37:15031–41.
[59] Zhai HY, Sui MH, Yu X, et al. Overexpression of long non-coding RNA TUG1 promotes colon cancer progression. Med Sci Monit 2016;22: 3281–7.
[60] Chai S, An W, Guo L, et al. Effect of long non-coding RNA SPRY4-IT1 on invasion and migration of A549 cells. Zhongguo Fei Ai Za Zhi 2015;18:487–92.
[61] Mazar J, Zhao W, Khalil AM, et al. The functional characterization of long noncoding RNA SPRY4-IT1 in human melanoma cells. Oncotarget 2014;5:8959–69.
[62] Ru N, Liang J, Zhang F, et al. SPRY4 intronic transcript 1 promotes epithelial-mesenchymal transition through association with Snail1 in osteosarcoma. DNA Cell Biol 2016;35:290–5.
[63] Shen F, Cai WS, Feng Z, et al. Long non-coding RNA SPRY4-IT1 pormotes colorectal cancer metastasis by regulate epithelial-mesenchymal transition. Oncotarget 2017;8:14479–86.
[64] Shi Y, Li J, Liu Y, et al. The long noncoding RNA SPRY4-IT1 increases the proliferation of human breast cancer cells by upregulating ZNF703 expression. Mol Cancer 2015;14:51.
[65] Zuo Q, Huang S, Zou Y, et al. The Lnc RNA SPRY4-IT1 modulates trophoblast cell invasion and migration by affecting the epithelial-mesenchymal transition. Sci Rep 2016;6:37183.
[66] Zou Y, Jiang Z, Yu X, et al. Upregulation of long noncoding RNA SPRY4-IT1 modulates proliferation, migration, apoptosis, and network formation in trophoblast cells HTR-8SV/neo. PloS One 2013;8:e79598.
[67] Zhao W, Mazar J, Lee B, et al. The long noncoding RNA SPRIGHTLY regulates cell proliferation in primary human melanocytes. J Invest Dermatol 2016;136:819–28.
[68] Cui M, Xiao Z, Wang Y, et al. Long noncoding RNA HULC modulates abnormal lipid metabolism in hepatoma cells through an miR-9-mediated RXRA signaling pathway. Cancer Res 2015;75:846–57.
[69] Du Y, Kong G, You X, et al. Elevation of highly up-regulated in liver cancer (HULC) by hepatitis B virus X protein promotes hepatoma cell proliferation via down-regulating p18. J Biol Chem 2012;287:26302–11.
[70] Gui X, Li H, Li T, et al. Long noncoding RNA CUDR regulates HULC and beta-catenin to govern human liver stem cell malignant differentiation. Mol Ther 2015;23:1843–53.
[71] Hammerle M, Gutschner T, Uckelmann H, et al. Posttranscriptional destabilization of the liver-specific long noncoding RNA HULC by the IGF2 mRNA-binding protein 1 (IGF2BP1). Hepatology (Baltimore, MD) 2013;58:1703–12.
[72] Li SP, Xu HX, Yu Y, et al. LncRNA HULC enhances epithelial-mesenchymal transition to promote tumorigenesis and metastasis of hepatocellular carcinoma via the miR-200a-3p/ZEB1 signaling pathway. Oncotarget 2016;7:42431–46.
[73] Lu Z, Xiao Z, Liu F, et al. Long non-coding RNA HULC promotes tumor angiogenesis in liver cancer by up-regulating sphingosine kinase 1 (SPHK1). Oncotarget 2016;7:241–54.
[74] Peng W, Wu J, Feng J. Long noncoding RNA HULC predicts poor clinical outcome and represents pro-oncogenic activity in diffuse large B-cell lymphoma. Biomed Pharmacother 2016;79:188–93.
[75] Yang XJ, Huang CQ, Peng CW, et al. Long noncoding RNA HULC promotes colorectal carcinoma progression through epigenetically repressing NKD2 expression. Gene 2016;592:172–8.
[76] Zhu Y, Zhang X, Qi L, et al. HULC long noncoding RNA silencing suppresses angiogenesis by regulating ESM-1 via the PI3K/Akt/mTOR signaling pathway in human gliomas. Oncotarget 2016;7:14429–40.
[77] Wang J, Liu X, Wu H, et al. CREB up-regulates long non-coding RNA, HULC expression through interaction with microRNA-372 in liver cancer. Nucleic Acids Res 2010;38:5366–83.
[78] Ma Y, Huang D, Yang F, et al. Long noncoding RNA highly upregulated in liver cancer regulates the tumor necrosis factor-alpha-induced apoptosis in human vascular endothelial cells. DNA Cell Biol 2016; 35:296–300.
[79] Wan D, Shen S, Fu S, et al. miR-203 suppresses the proliferation and metastasis of hepatocellular carcinoma by targeting oncogene ADAM9 and oncogenic long non-coding RNA HULC. Anticancer Agents Med Chem 2016;16:414–23.
[80] Chen RP, Huang ZL, Liu LX, et al. Involvement of endoplasmic reticulum stress and p53 in lncRNA MEG3-induced human hepatoma HepG2 cell apoptosis. Oncol Rep 2016;36:1649–57.
[81] Chen T, Yang P, He ZY. Long noncoding RNA H19 can predict a poor prognosis and lymph node metastasis: a meta-analysis in human cancer. Minerva Med 2016;107:251–8.
[82] Hong HH, Hou LK, Pan X, et al. Long non-coding RNA UCA1 is a predictive biomarker of cancer. Oncotarget 2016;7:44442–7.
[83] Ma G, Wang Q, Lv C, et al. The prognostic significance of HOTAIR for predicting clinical outcome in patients with digestive system tumors. J Cancer Res Clin Oncol 2015;141:2139–45.
[84] Serghiou S, Kyriakopoulou A, Ioannidis JP. Long noncoding RNAs as novel predictors of survival in human cancer: a systematic review and meta-analysis. Mol Cancer 2016;15:50.
[85] Cai H, Liu X, Zheng J, et al. Long non-coding RNA taurine upregulated 1 enhances tumor-induced angiogenesis through inhibiting microRNA-299 in human glioblastoma. Oncogene 2016;36:318–31.