Pathol. Oncol. Res. (2015) 21:1259–1264
DOI 10.1007/s12253-015-9960-5

ORIGINAL ARTICLE

Long Noncoding RNA MALAT-1 Can Predict Metastasis and a Poor Prognosis: a Meta-Analysis

Lucheng Zhu [1,2] · **Jihong Liu** [1,2] · **Shenglin MA** [1,2] · **Shirong Zhang** [2]

Received: 25 February 2015 / Accepted: 1 July 2015 / Published online: 10 July 2015

Abstract Elevated expression of MALAT-1 was found in various cancers, and correlated with metastasis and prognostic. This meta-analysis collected all relevant articles and explored correlation of MALAT-1 with lymph node metastasis (LNM), distant metastasis (DM), and overall survival (OS). A quantitative meta-analysis was performed through a systematic search in PubMed, Web of Science, Medline, CNKI, CBM, and the Cochrane Library. The odds ratios (OR) of LNM and DM and hazard ratio (HR) of OS were calculated to assess the association strength. Eight studies with a total of 845 patients were included in the meta-analysis. Six different types of cancer were evaluated, with 2 non-small cell lung cancer (NSCLC), 1 colorectal cancer (CRC), 1 gastric cancer (GC), 2 pancreatic cancer (PC), 1 clear cell renal cell carcinoma (ccRCC), and 1 osteosarcoma (OSA). Compared with low MALAT-1 expression, high MALAT-1 expression correlated with more LNM (OR=2.08, 95 %CI: 1.00-4.32, p=0.05) by a random-effects model (I^2=71 %, p=0.004). A similar result was seen between MALAT-1 expression and DM, the OR was 3.52 (95 %CI: 1.06–11.71, p=0.04) adopting a random-effects model (I^2=59 %, p=0.04). Additionally, our analysis showed a poorer OS in patients with high MALAT-1 expression than those with low MALAT-1 expression (HR=2.12, 95 %CI: 1.60–2.82, p<0.001) adopting a random-effects model (I^2=56 %, p=0.04). MALAT-1 may serve as a molecular marker for cancer metastasis and prognosis.

Keywords MALAT-1 · LncRNA · Metastasis · Prognosis · Survival · Meta-analysis

Introduction

Cancer remains a leading cause of mortality. There are 14.1 million new cancer cases and 8.2 million cancer deaths worldwide [1]. A large amount of tumors develop metastases, especially those with advanced stage. These metastases including lymph node metastases (LNM) and distant metastases (DM) lead to a poor prognosis [2, 3]. In recent years, molecular biomarkers have revolutionized treatment for cancer [4, 5]. However, little is known about the role of long noncoding RNA (lncRNA) in predicting metastases and prognosis of cancer.

LncRNAs (>200 nt in length) are a class of noncoding RNAs that lack protein-coding capacity [6]. LncRNAs were first described as transcriptional "noise" and found to participate in diverse biologic processes including cell development, cell growth, and tumorigenesis [7–9]. Recent studies indicate that lncRNAs are abnormally expressed in malignant tumors and associated with the development of cancer, including tumor growth and metastasis [10–14].

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1) also known as noncoding nuclear-enriched abundant transcript 2 (NEAT-2) is a nuclear lncRNA with a length

Electronic supplementary material The online version of this article (doi:10.1007/s12253-015-9960-5) contains supplementary material, which is available to authorized users.

✉ Shenglin MA
mashenglin@outlook.com

✉ Shirong Zhang
shirley4444@gmail.com

[1] Department of Oncology, Affiliated Hangzhou Hospital of Nanjing Medical University, No.261, huansha Road, shangcheng District, Hangzhou 310006, People's Republic of China

[2] Department of Oncology, Hangzhou First People's Hospital, No.261, huansha Road, shangcheng District, Hangzhou 310006, People's Republic of China

of 8.7 kb, which is expressed from chromosome 11q13 [15]. MALAT-1 was primarily identified as a prognostic factor in patients with stage I lung cancer [15]. Currently, elevated expression of MALAT-1 has been observed in various tumors and MALAT-1 regulates metastasis-associated genes [16–19]. Therefore, MALAT-1 might be feasible as a diagnostic biomarker and prognostic factor. To explore the correlation of MALAT-1 with tumor metastasis and prognosis, we conducted this quantitative meta-analysis.

Materials and Methods

Publication Search

We searched PubMed, Web of Science, Medline, Embase, and the Cochrane Library from 1966 to Jan 20, 2015. The search strategy used both MeSH terms and free-text words to increase sensitivity. The following search terms were used: "MALAT-1", "MALAT1", "MALAT 1", "Metastasis-associated lung adenocarcinoma transcript 1", "NEAT-2", "NEAT2", "NEAT 2", and "Nuclear enriched abundant transcript 2". The study was approved by the Ethics Committee of Hangzhou First People's Hospital.

Inclusion and Exclusion Criteria

Inclusion criteria are the following: (1) articles investigating the relation of MALAT-1 and cancer patients; (2) the expression levels of MALAT-1 in primary tumor tissues were measured; (3) patients were grouped according to the expression levels of MALAT-1; (4) related clinicopathologic parameters were described. Exclusion criteria are the following: (1) letters, editorials, expert opinions, case reports and reviews. (2) studies without usable data; (3) duplicate publications.

Data Extraction

Two investigators independently extracted data from the eligible studies, and disagreements were resolved by discussion with a third investigator. For each studies, the following information was recorded: the first author, year of publication, country, number of patients, number of high MALAT-1 expression group and low expression group, number of patients with LNM and DM in each group, overall survival (OS), and detection method of MALAT-1.

Quality Control

As all the included studies were non-randomized and retrospective studies. We used the Newcastle-Ottawa Scale (NOS) for assessing the quality. Any discrepancies were resolved by consensus.

Statistical Analysis

We extracted hazard ratios (HRs) according to the following methods raised in previous publication [20]: (1) obtain the HRs directly from the publication; (2) estimate the HRs from O-E statistic and variance; (3) calculate the HRs from data including the number of patients and events at risk in each group, and the log-rank statistic or the p value; (4) retrieve HRs from Kaplan-Meier Curves by extracting several survival rates at specified times from the curves.

Statistical analyses of HRs for OS, and the odds ratios for LNM and DM were calculated by Review Manager Version 5.3 (Revman, the Cochrane Collaboration, Oxford, England). The heterogeneity of the data was evaluated by chi-square Q test and I^2 statistic. For the Q test, a p value less than 0.05 indicated significant heterogeneity; for the I^2 statistics, an I^2 value greater than 50 % was considered significant heterogeneity. Statistical significance was defined as a p value less than 0.05.

Results

Characteristics of Included Studies

As shown in Fig. 1, the electronic search yielded 244 records. After screening titles and abstracts, 34 full-text articles were assessed for eligibility. Finally, after excluding 26 articles, a total of 8 articles were included in the current meta-analysis [21–24, 16, 25, 26, 15]. Among these 8 studies, 5 came from China, 1 from Japan, and 2 from Germany. Six different types of cancer were evaluated in this meta-analysis, with 2 non-small cell lung cancer (NSCLC), 1 colorectal cancer (CRC), 1 gastric cancer (GC), 2 pancreatic cancer (PC), 1 clear cell

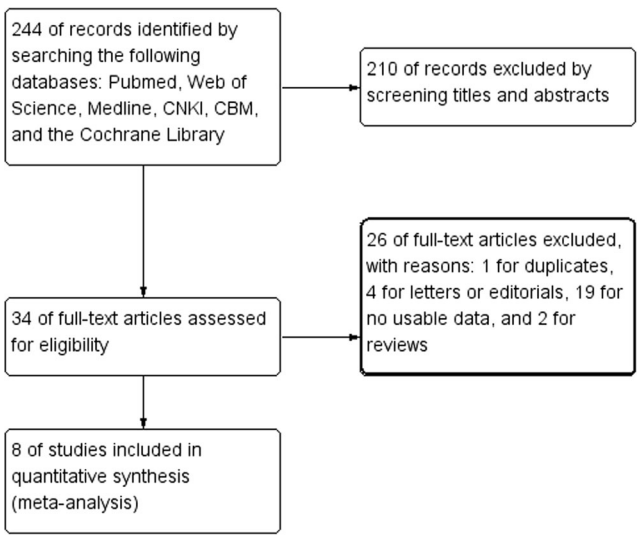

Fig. 1 The flow diagram of this meta-analysis

Table 1 Characteristics of studies in this meta-analysis

Author	Year	Country	Tumor type	Sample size (n)	Malat-1 expression						Method
					High expression	High with LNM	High with DM	Low expression	Low with LNM	High with DM	
Zheng	2014	China	CRC	146	73	42	–	73	49	–	qRT-PCR
Zhang	2014	China	ccRCC	106	46	13	5	60	6	9	qRT-PCR
Pang	2014	China	PC	126	63	46	10	63	22	0	qRT-PCR
Okugawa	2014	Japan	GC	150	88	66	8	62	39	4	qRT-PCR
Liu	2014	China	PC	45	26	15	6	19	8	1	qRT-PCR
Dong	2014	China	OSA	19	14	13	11	5	4	1	qRT-PCR
Schmidt	2012	Germany	NSCLC	222	83	–	–	139	–	–	ISH
Ji	2003	Germany	NSCLC	31	–	–	–	–	–	–	ISH

LNM lymph node metastasis, *DM* distant metastasis, *CRC* colorectal cancer, *ccRCC* clear cell renal cell carcinoma, *PC* pancreatic cancer, GC gastric cancer, *OSA* osteosarcoma, *NSCLC* non-small-cell lung cancer, *qRT-PCR* quantitative real-time PCR, *ISH* in situ hybridization

renal cell carcinoma (ccRCC), and 1 osteosarcoma (OSA). All cancerous specimens were well preserved before RNA extraction. All the diagnoses of LNM and DM were based on pathology.

In these 8 studies, six methods were adopted to category high and low MALAT-1 expression group: (1) the level of MALAT-1 expression measured by qRT-PCR was normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and the cut-off value was MALAT-1/GAPDH ratio of 6.15. (2) the level of MALAT-1 expression measured by qRT-PCR was normalized to GAPDH, and the cut-off value was mean value of MALAT-1 levels. (3) the level of MALAT-1 expression measured by qRT-PCR was normalized to β-actin, and the cut-off value was median value of MALAT-1 levels. (4) the level of MALAT-1 expression measured by qRT-PCR was normalized to GAPDH, and the cut-off value was determined by receiver operating characteristics analyses with the Youden's index of 0.985. (5) the level of MALAT-1 expression measured by qRT-PCR was normalized to GAPDH, and the cut-off value was MALAT-1/GAPDH ratio of 2. (6) the level of MALAT-1 expression measured by in situ hybridization (ISH), high expression group was based on strong signal of ISH. The main characteristics were summarized in Table 1. All the studies were evaluated to be of high quality (Supplementary Table 1, Newcastle-Ottawa Scale (NOS) for assessing the quality).

Association Between MALAT-1 and LNM

Six studies reported the number of patient with LNM based on different MALAT-1 expression levels in a total of 592 patients. The random-effects model was adopted as the significant heterogeneity (I^2=71 %, p=0.004). Analysis showed a pooled OR of 2.08 with 95 %CI 1.00–4.32 (p=0.05) (Fig. 2). Compared with low MALAT-1 expression group, high MALAT-1 expression group had a statistic significant elevated LNM rate. The result showed patients with high MALAT-1 expression in tumor tissues were more susceptibility to develop LNM.

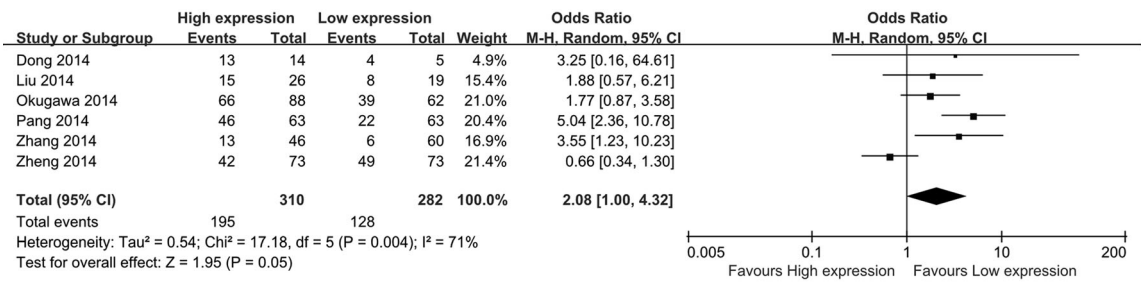

Fig. 2 Forest plot for the association between MALAT-1 expression levels with LNM

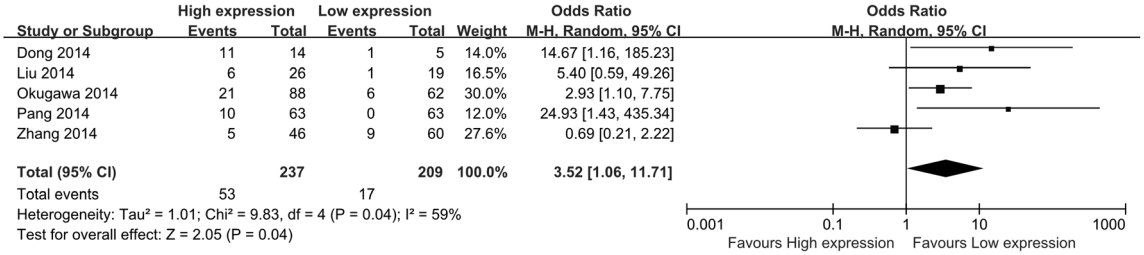

Fig. 3 Forest plot for the association between MALAT-1 expression levels with DM

Association Between MALAT-1 and DM

Five studies reported the number of patient with DM based on different MALAT-1 expression levels in a total of 446 patients. Because the heterogeneity test of among the studies was significant (I^2=59 %, p=0.04), random-effects model was adopted. Analysis showed a pooled *OR*=3.52 (95 %CI: 1.06–11.71, p=0.04) (Fig. 3). High MALAT-1 expression group had a statistic significant elevated DM rate over low expression group, indicating an increased risk of patients with high MALAT-1 expression developing DM.

Association Between MALAT-1 and OS

We analysis pooled HRs of two group. Seven studies with 826 patients were included in this meta-analysis of OS. Due to the significant heterogeneity (I^2=56 %, p=0.04), random-effects model was used. Analysis showed a pooled *HR*=2.12 (95 %CI: 1.60–2.82, p<0.001) (Fig. 4). Compared with low MALAT-1 expression group, high MALAT-1 expression group had a statistic significant reduced OS. High MALAT-1 expression correlated with a worse survival.

Discussion

MALAT-1 is one of the first cancer-related lncRNAs [15], which is abundant in many human cells and highly conserved across mammalian species underscoring its functional importance. Though a large number of studies have focused on relationship between MALAT-1 and tumors and explored mechanism of its biogenesis, interaction partners, and molecular functions, the underlying mechanisms regulating cancer metastasis remain unclear.

MALAT-1 has been thought to influence cellular processes by two ways, namely regulating alternative splicing pre-mRNAs and regulating gene expression [27, 28]. However, *Gutschner* et al. build a MALAT-1 knockout model in lung cancer and found MALAT-1 did not alter alternative splicing but actively regulates gene expression including a set of metastasis-associated genes [29]. Other previous studies [30–36] also showed MALAT-1 could regulate expression of several metastasis-associated genes including melanoma inhibitory activity 2 (*MIA2*, a negative regulator of tumor growth invasion), roundabout 1 (*ROBO1*, an inhibitor of glioma migration and invasion), glypican 6 (*GPC6*, a promoter of breast cancer metastasis), ATP-bind cassette sub family A member 1 (*ABCA1*, an important factor for prostate cancer cell migration and epithelial-to-mesenchymal transition). In addition, *Wu* et al.[37] found knockdown of MALAT-1 reduced the expression of matrix metalloproteinase 9 (MMP-9) and suppressed the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway. MMP-9 had a critical role in degradation of stromal extracellular matrix (ECM) proteins to promote cell invasion and metastasis [38]. Cancer Cell metastasis was often associated with aberrantly activated ERK/MAPK pathway [39, 40]. Besides, Fan et al. [41] found MALAT-1 played important part in TGF-β-induced EMT which was a key step to cancer metastasis. In this meta-analysis, we found high MALAT-1 expression in tumor tissues was significant correlated with LNM and DM, analysis showed a

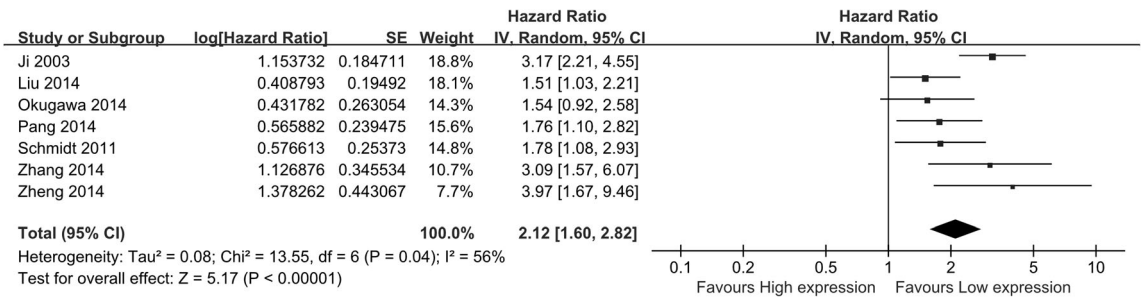

Fig. 4 Meta-analysis of the pooled HRs of OS

pooled OR of 2.08 (95 %CI: 1.00–4.32, p=0.05) and 3.52 (CI 95 %: 1.06–11.71, p=0.04), respectively. In addition, survival analysis confirmed the role of MALAT-1 in metastasis.

Nevertheless, there are several limitations in the study. Different types of cancer included in this study increased the heterogeneity and the inherent molecular differences might influence firmness of the results. All of the included articles article were retrospective studies and most of them had small sample size. Additionally, the cut-off value of MALAT-1 expression differed in these studies. Furthermore, most of included patients were from China, research from other countries might achieve different outcomes. Moreover, number of included studies for each meta-analysis was small in this study, which may generate errors by variation.

Conclusion

This meta-analysis explored the correlation of MALAT-1 expression levels with LNM, DM and OS. The results demonstrated high MALAT-1 expression was significant correlated with LNM (*OR*=2.08, 95 %CI: 1.00–4.32, p=0.05), DM (OR=3.52, 95 %CI: 1.06–11.71, p=0.04), and poor OS (*HR*=2.12, 95 %CI: 1.60–2.82, p<0.001). MALAT-1 can serve as a molecular marker for metastasis and prognosis.

Acknowledgments This study was supported by grants from National Natural Science Foundation of China (grant no. 81272611). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Compliance with Ethical Standards

Conflict of Interests All authors declare that there is no conflict of interests.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2014) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. doi:10.1002/ijc.29210
2. Pereira A, Perez-Medina T, Magrina JF, Magtibay PM, Rodriguez-Tapia A, de Leon J, Peregrin I, Ortiz-Quintana L (2014) Correlation between the extent of intraperitoneal disease and nodal metastasis in node-positive ovarian cancer patients. Eur J Surg Oncol 40(8):917–924. doi:10.1016/j.ejso.2014.04.001
3. Lee T, Tanaka H, Ohira M, Okita Y, Yoshii M, Sakurai K, Toyokawa T, Kubo N, Muguruma K, Tanaka S, Ohsawa M, Hirakawa K (2014) Clinical impact of the extent of lymph node micrometastasis in undifferentiated-type early gastric cancer. Oncology 86(4):244–252. doi:10.1159/000358803
4. Treilleux I, Arnedos M, Cropet C, Wang Q, Ferrero JM, Abadie-Lacourtoisie S, Levy C, Legouffe E, Lortholary A, Pujade-Lauraine E, Bourcier AV, Eymard JC, Spaeth D, Bachelot T (2014) Translational studies within the TAMRAD randomized GINECO trial: evidence for mTORC1 activation marker as a predictive factor for everolimus efficacy in advanced breast cancer. Ann Oncol. doi:10.1093/annonc/mdu497
5. Hu A, Huang JJ, Xu WH, Jin XJ, Li JP, Tang YJ, Huang XF, Cui HJ, Sun GB (2014) miR-21 and miR-375 microRNAs as candidate diagnostic biomarkers in squamous cell carcinoma of the larynx: association with patient survival. Am J Transl Res 6(5):604–613
6. Ponting CP, Oliver PL, Reik W (2009) Evolution and functions of long noncoding RNAs. Cell 136(4):629–641. doi:10.1016/j.cell.2009.02.006
7. Kaneko S, Li G, Son J, Xu CF, Margueron R, Neubert TA, Reinberg D (2010) Phosphorylation of the PRC2 component Ezh2 is cell cycle-regulated and up-regulates its binding to ncRNA. Genes Dev 24(23):2615–2620. doi:10.1101/gad.1983810
8. Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, Shi Y, Segal E, Chang HY (2010) Long noncoding RNA as modular scaffold of histone modification complexes. Science 329(5992):689–693. doi:10.1126/science.1192002
9. Wilusz JE, Sunwoo H, Spector DL (2009) Long noncoding RNAs: functional surprises from the RNA world. Genes Dev 23(13):1494–1504. doi:10.1101/gad.1800909
10. Wang X, Song X, Glass CK, Rosenfeld MG (2011) The long arm of long noncoding RNAs: roles as sensors regulating gene transcriptional programs. Cold Spring Harb Perspect Biol 3(1):a003756. doi:10.1101/cshperspect.a003756
11. Ji Q, Zhang L, Liu X, Zhou L, Wang W, Han Z, Sui H, Tang Y, Wang Y, Liu N, Ren J, Hou F, Li Q (2014) Long non-coding RNA MALAT1 promotes tumour growth and metastasis in colorectal cancer through binding to SFPQ and releasing oncogene PTBP2 from SFPQ/PTBP2 complex. Br J Cancer 111(4):736–748. doi:10.1038/bjc.2014.383
12. Shen L, Chen L, Wang Y, Jiang X, Xia H, Zhuang Z (2014) Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. J Neurooncol. doi:10.1007/s11060-014-1613-0
13. Cai B, Wu Z, Liao K, Zhang S (2014) Long noncoding RNA HOTAIR can serve as a common molecular marker for lymph node metastasis: a meta-analysis. Tumour Biol 35(9):8445–8450. doi:10.1007/s13277-014-2311-4
14. Akhbari P, Whitehouse A, Boyne JR (2014) Long noncoding RNAs drive metastatic progression in melanoma (Review). Int J Oncol 45(6):2181–2186. doi:10.3892/ijo.2014.2691
15. Ji P, Diederichs S, Wang W, Boing S, Metzger R, Schneider PM, Tidow N, Brandt B, Buerger H, Bulk E, Thomas M, Berdel WE, Serve H, Muller-Tidow C (2003) MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene 22(39):8031–8041. doi:10.1038/sj.onc.1206928
16. Liu JH, Chen G, Dang YW, Li CJ, Luo DZ (2014) Expression and prognostic significance of lncRNA MALAT1 in pancreatic cancer tissues. Asian Pac J Cancer Prev 15(7):2971–2977
17. Xu C, Yang M, Tian J, Wang X, Li Z (2011) MALAT-1: a long noncoding RNA and its important 3′ end functional motif in colorectal cancer metastasis. Int J Oncol 39(1):169–175. doi:10.3892/ijo.2011.1007
18. Tano K, Akimitsu N (2012) Long non-coding RNAs in cancer progression. Front Genet 3:219. doi:10.3389/fgene.2012.00219
19. Eissmann M, Gutschner T, Hammerle M, Gunther S, Caudron-Herger M, Gross M, Schirmacher P, Rippe K, Braun T, Zornig M, Diederichs S (2012) Loss of the abundant nuclear non-coding RNA MALAT1 is compatible with life and development. RNA Biol 9(8):1076–1087. doi:10.4161/rna.21089
20. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8:16. doi:10.1186/1745-6215-8-16

21. Zheng HT, Shi DB, Wang YW, Li XX, Xu Y, Tripathi P, Gu WL, Cai GX, Cai SJ (2014) High expression of lncRNA MALAT1 suggests a biomarker of poor prognosis in colorectal cancer. Int J Clin Exp Pathol 7(6):3174–3181
22. Zhang HM, Yang FQ, Chen SJ, Che J, Zheng JH (2014) Upregulation of long non-coding RNA MALAT1 correlates with tumor progression and poor prognosis in clear cell renal cell carcinoma. Tumour Biol. doi:10.1007/s13277-014-2925-6
23. Pang EJ, Yang R, Fu XB, Liu YF (2014) Overexpression of long non-coding RNA MALAT1 is correlated with clinical progression and unfavorable prognosis in pancreatic cancer. Tumour Biol. doi:10.1007/s13277-014-2850-8
24. Okugawa Y, Toiyama Y, Hur K, Toden S, Saigusa S, Tanaka K, Inoue Y, Mohri Y, Kusunoki M, Boland CR, Goel A (2014) Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. Carcinogenesis. doi:10.1093/carcin/bgu200
25. Dong Y, Liang G, Yuan B, Yang C, Gao R, Zhou X (2014) MALAT1 promotes the proliferation and metastasis of osteosarcoma cells by activating the PI3K/Akt pathway. Tumour Biol. doi:10.1007/s13277-014-2631-4
26. Schmidt LH, Spieker T, Koschmieder S, Schaffers S, Humberg J, Jungen D, Bulk E, Hascher A, Wittmer D, Marra A, Hillejan L, Wiebe K, Berdel WE, Wiewrodt R, Muller-Tidow C (2011) The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. J Thorac Oncol 6(12):1984–1992. doi:10.1097/JTO.0b013e3182307eac
27. Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, Freier SM, Bennett CF, Sharma A, Bubulya PA, Blencowe BJ, Prasanth SG, Prasanth KV (2010) The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell 39(6):925–938. doi:10.1016/j.molcel.2010.08.011
28. Yang L, Lin C, Liu W, Zhang J, Ohgi KA, Grinstein JD, Dorrestein PC, Rosenfeld MG (2011) ncRNA- and Pc2 methylation-dependent gene relocation between nuclear structures mediates gene activation programs. Cell 147(4):773–788. doi:10.1016/j.cell.2011.08.054
29. Gutschner T, Hammerle M, Eissmann M, Hsu J, Kim Y, Hung G, Revenko A, Arun G, Stentrup M, Gross M, Zornig M, MacLeod AR, Spector DL, Diederichs S (2013) The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res 73(3):1180–1189. doi:10.1158/0008-5472.can-12-2850
30. Hellerbrand C, Amann T, Schlegel J, Wild P, Bataille F, Spruss T, Hartmann A, Bosserhoff AK (2008) The novel gene MIA2 acts as a tumour suppressor in hepatocellular carcinoma. Gut 57(2):243–251. doi:10.1136/gut.2007.129544
31. Xu Y, Li WL, Fu L, Gu F, Ma YJ (2010) Slit2/Robo1 signaling in glioma migration and invasion. Neurosci Bull 26(6):474–478
32. Legg JA, Herbert JM, Clissold P, Bicknell R (2008) Slits and Roundabouts in cancer, tumour angiogenesis and endothelial cell migration. Angiogenesis 11(1):13–21. doi:10.1007/s10456-008-9100-x
33. Yiu GK, Kaunisto A, Chin YR, Toker A (2011) NFAT promotes carcinoma invasive migration through glypican-6. Biochem J 440(1):157–166. doi:10.1042/bj20110530
34. Sekine Y, Demosky SJ, Stonik JA, Furuya Y, Koike H, Suzuki K, Remaley AT (2010) High-density lipoprotein induces proliferation and migration of human prostate androgen-independent cancer cells by an ABCA1-dependent mechanism. Mol Cancer Res 8(9):1284–1294. doi:10.1158/1541-7786.mcr-10-0008
35. Toh B, Wang X, Keeble J, Sim WJ, Khoo K, Wong WC, Kato M, Prevost-Blondel A, Thiery JP, Abastado JP (2011) Mesenchymal transition and dissemination of cancer cells is driven by myeloid-derived suppressor cells infiltrating the primary tumor. PLoS Biol 9(9):e1001162. doi:10.1371/journal.pbio.1001162
36. Gutschner T, Hammerle M, Diederichs S (2013) MALAT1—a paradigm for long noncoding RNA function in cancer. J Mol Med (Berl) 91(7):791–801. doi:10.1007/s00109-013-1028-y
37. Wu XS, Wang XA, Wu WG, Hu YP, Li ML, Ding Q, Weng H, Shu YJ, Liu TY, Jiang L, Cao Y, Bao RF, Mu JS, Tan ZJ, Tao F, Liu YB (2014) MALAT1 promotes the proliferation and metastasis of gallbladder cancer cells by activating the ERK/MAPK pathway. Cancer Biol Ther 15(6):806–814. doi:10.4161/cbt.28584
38. Li N, Wang HX, Zhang J, Ye YP, He GY (2012) KISS-1 inhibits the proliferation and invasion of gastric carcinoma cells. World J Gastroenterol 18(15):1827–1833. doi:10.3748/wjg.v18.i15.1827
39. Hong SK, Yoon S, Moelling C, Arthan D, Park JI (2009) Noncatalytic function of ERK1/2 can promote Raf/MEK/ERK-mediated growth arrest signaling. J Biol Chem 284(48):33006–33018. doi:10.1074/jbc.M109.012591
40. Xander P, Brito RR, Perez EC, Pozzibon JM, de Souza CF, Pellegrino R, Bernardo V, Jasiulionis MG, Mariano M, Lopes JD (2013) Crosstalk between B16 melanoma cells and B-1 lymphocytes induces global changes in tumor cell gene expression. Immunobiology 218(10):1293–1303. doi:10.1016/j.imbio.2013.04.017
41. Fan Y, Shen B, Tan M, Mu X, Qin Y, Zhang F, Liu Y (2014) TGF-beta-induced upregulation of malat1 promotes bladder cancer metastasis by associating with suz12. Clin Cancer Res 20(6):1531–1541. doi:10.1158/1078-0432.ccr-13-1455