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Original Article

Decreased expression of miR-32 is associated with the clinical outcome of non-small cell lung cancer patients

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Abstract: To investigate the role of miR-32 expression in Chinese non-small cell lung cancer (NSCLC) patients, levels of miR-32 were analyzed using the data from GEO datasets. MiR-32 expression was lower in lung cancer patients than in normal controls. Then we explored the levels of miR-32 in tumor tissues and adjacent non-cancerous tissues of 65 NSCLC patients from the ArrayExpress Microarray database and 149 samples from our biopsies. Our results showed that there were no significantly differences between miR-32 expression and age, gender, lymph node metastasis, tumor differentiation, histology, TNM stage, visceral pleural invasion, vascular invasion, and tumor size. However, miR-32 expression was down-regulated in tumor tissues. Moreover, patients with low miR-32 expression had poorer overall survival and disease free survival, indicating that miR-32 expression might be an independent prognostic marker for NSCLC patients.

Keywords: miR-32 expression, non-small cell lung cancer, clinical factors, prognosis

Introduction

The American Cancer Society estimated that there will be 221,200 new cases of lung and bronchus cancer, and an estimated 158,040 people will die of this disease in the United States in 2015 [1]. The Lung and bronchus cancer remains leading cause of cancer-related death and ranks second in the new cancer cases, though the rates of cancer deaths and new cancer cases gradually decreased over 10 years [2]. The overall 5-year survival rate of lung cancer is only 17.4% [3]. The main cause of death in these patients is that most of them are diagnosed at an advanced stage. Non-small cell lung cancer (NSCLC) accounts for about 80-85% of cases in lung cancer [4]. Thus, there is pressing need for novel biomarkers that can improve early diagnosis and prognosis.

MicroRNAs (miRNAs) are a class of short (about 19-24 nucleotides in length), evolutionary conserved, single-stranded, non-coding RNA molecules that directly bind to the 3'untranslated regions (3' UTRs) of target messenger RNAs (mRNAs), causing either degradation or inhibition of gene translation. MicroRNAs are therefore involved in a wide range of fundamental cellular processes such as growth, mobility, apoptosis, proliferation, differentiation, endocrine homeostasis, tumorgenesis and so on [5]. MiR-32, located on chromosome band Xq26.2, is found to be up-regulated in breast cancer, [6] colorectal cancer, [7] hepatocellular carcinoma, [8] multiple myeloma [9] and so on. Therefore, it acts as a potential oncogene in these tumors. In contrast, miR-32 is down-regulated in oral squamous cell carcinoma, [10] gastric cancer [11] and osteosarcoma, [12] and it acts as a tumor suppressor gene. Therefore, miR-32 may have different functions in different cancers.

In our present study, we focused on the expression levels of miR-32 in tumor tissues and adja-

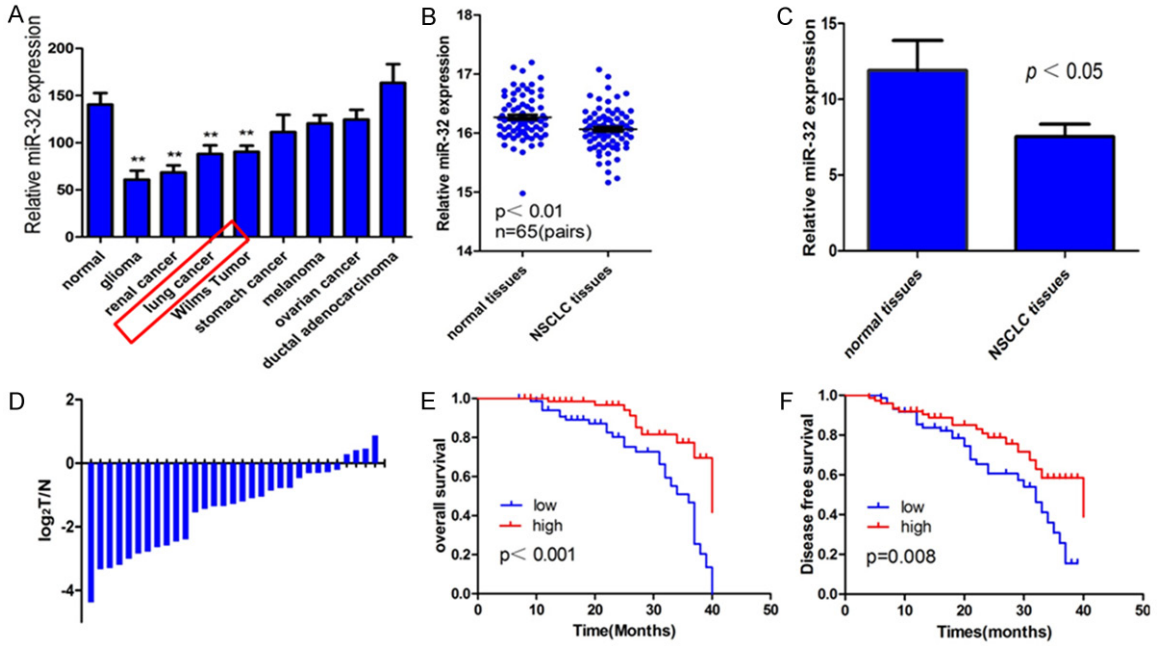

Figure 1. Analysis of miR-32 expressions and clinical significance in NSCLC patients. Relative expression levels of miR-32 in different cancers vs. normal controls from GEO datasets (A), Array Express database (B). (C) Relative expression levels of miR-32 in NSCLC and adjacent normal tissues of 149 patients from our data. (D) Relative expression levels of miR-32 in NSCLC and matched adjacent normal tissues of 31 patients. OS (E) and DFS (F) analysis of miR-32 in NSCLC patients.

cent normal tissues in NSCLC patients. We also studied the relationship between miR-32 expression and clinical characteristics.

Materials and methods

Clinical samples

Fresh tissues were obtained from 149 NSCLC patients when they underwent surgical resection between Jan. 2010 and Sep. 2012 from Shanghai 10th People's Hospital, Tongji University School of Medicine and China-Japan Union Hospital, Jilin University. This study was approved by Ethics Committee of Shanghai 10th People's Hospital, Tongji University School of Medicine (SHSY-IEC-PAP-15-18). All patients provided their written informed consent.

Clinical data of NSCLC patients were collected, including basic information (age, gender), tumor characteristics (distant metastasis, lymph node metastasis, relapse, tumor differentiation, histology, TNM stage, visceral pleural invasion, vascular invasion and tumor size), overall survival (OS), disease free survival (DFS), and chemotherapy.

For analysis, age was divided into two groups (≥ 60 and < 60 years). Tumors were stratified according to size (≥ 5 cm and < 5 cm). The time to tumor relapse or death was confirmed by the patient or relatives, and medical records. OS was the length of time from the date of diagnosis with lung cancer to the time of death, regardless of cause. DFS was defined as the time from the initial date of diagnosis to the time of tumor progression or death due to the disease.

RNA extraction

Total RNA was extracted from tumor and normal tissue with TRIzol reagent (Life Technologies; Grand Island, NY, USA), according to the manufacturer's instructions. RNA concentration was measured in a Nanodrop1000 spectrophotometer (Thermo Fisher Scientific; Waltham, MA, USA), and the quality of all RNA samples was assessed by electrophoresis on 1.5% denaturing agarose gels.

Quantitative RT-PCR

For quantitative real-time PCR (qRT-PCR), cDNA was synthesized from total RNA (10 ng), and quantitative PCR reactions were performed with the Taqman Universal PCR Kit (Life Technologies). U6 small nuclear RNA was used as

Table 1. Associations between miR-32 expression and clinical characteristics

Factor variable	Number	miR-32 expression (number)		*P* value (Chi-square test)
		Low	High	
Age				
≥ 60	99	50	49	0.863
< 60	50	24	26	
Gender				
Male	92	40	52	0.065
Female	57	34	23	
Lymph node metastasis				
Negative	53	23	30	0.224
Positive	86	47	39	
Unknown	10			
Tumor differentiation				
Poorly	54	25	29	0.661
Moderately	92	48	44	
Well	3	1	2	
Histology				
Adenocarcinoma	88	43	45	0.868
Squamous cell carcinoma	61	31	30	
TNM stage				
I and II	95	46	49	0.729
III and IV	51	27	24	
Unknown	3			
Visceral pleural invasion				
Negative	31	14	17	0.546
Positive	108	56	52	
Unknown	10			
Vascular invasion				
Negative	136	68	68	0.505
Positive	3	2	1	
Unknown	10			
Diameter				
≥ 5 cm	37	20	17	0.702
< 5 cm	99	49	50	
Unknown	13			

internal control. The threshold cycle (Ct) was defined as the fractional cycle number at which the fluorescence passed the fixed threshold. The relative amount of miR-32 to U6 was calculated using the equation $2^{-\Delta\Delta Ct}$.

Online data about miR-32 expression

We analyzed the expression level of miR-32 in 94 normal controls and 448 various cancers included 73 lung cancers from Gene Expression Omnibus datasets (GSE61-741). This project analyzed peripheral blood miRNA profiles and each miRNA had been measured in at least seven replicates which the median of the replica had been computed.

MiR-32 expression was also investigated in 65 pairs of NSCLC and matched normal tissues in the Array Express Microarray database which accession number is E-TABM-22.

Statistical analysis

All analyses were performed using SPSS 18.0 (USA). The expression of miR-32 was presented as the mean ± standard deviation. An independent T-test was used to examine differences between tumor and normal tissues, and a chi-square test was performed to evaluate associations between miR-32 expression and clinical characteristics. OS and DFS curves were calculated using the Kaplan-Meier method and the statistical differences between various groups were compared by the log-rank test. To evaluate independent prognostic factors associated with survival, the univariate and multivariate Cox proportional hazards regression model was used. $P < 0.05$ was considered statistically significant.

Results

MiR-32 expression based on data from online databases

MiR-32 expressions between different cancers and controls were analyzed using GEO datasets (**Figure 1A**). This analysis revealed that there

Table 2. Univariate analysis of overall survival and disease free survival based on patients stratified by clinical characteristics

Factor variable	Overall survival			Disease free survival		
	Months (Mean)	95% CI (Mean)	*P* value (Log-rank test)	Months (Mean)	95% CI (Mean)	*P* value (Log-rank test)
Age						
≥ 60	33.273	31.190-35.356	0.416	29.731	27..222-32.239	0.521
< 60	35.602	33.132-38.072		31.599	27.983-35.216	
Gender						
Male	33.171	31.144-35.198	0.105	27.905	25.276-30.533	0.004
Female	35.892	33.267-38.518		34.235	31.389-27.081	
Lymphnode metastasis						
Negative	34.981	32.471-37.492	0.256	31.451	28.107-34.795	0.129
Positive	32.874	30.585-35.163		28.562	25.806-31.318	
Tumor differentiation						
Poorly	36.528	34.589-38.467	0.145	32.33	29.248-35.412	0.272
Moderately	32.658	30.430-34.887		28.941	26.242-31.640	
TNM stage						
I and II	33.870	31.835-35.905	0.914	30.724	28.065-33.383	0.321
III and IV	34.076	31.357-36.795		28.854	25.705-32.003	
Visceral pleural invasion						
Negative	36.520	33.986-39.053	0.04	33.445	29.584-37.306	0.026
Positive	32.461	30.362-34.560		28.482	25.981-30.984	
Vascular invasion						
Negative	33.545	31.803-35.287	0.692	29.770	27.556-31.983	0.307
Positive	36.000	33.228-38.772		30.000	20.222-39.778	
Chemotherapy						
Negative	32.661	30.250-35.072	0.202	29.571	26.525-32.617	0.682
Positive	34.605	32.246-36.963		30.284	27.224-33.344	
Tumor diameter						
≥ 5 cm	32.594	29.394-35.794	0.15	26.808	22.706-30.911	0.021
< 5 cm	34.013	31.980-36.046		30.839	28.343-33.336	
miR-32 expression						
Low	31.615	29.183-34.047	< 0.001	27.752	25.037-30.466	0.008
High	36.726	34.706-38.746		33.037	30.290-35.784	

was significantly difference of miR-32 levels between lung cancer, glioma, renal cancer, Wilms tumor and normal controls ($P < 0.01$).

We also analyzed miR-32 expression profiles in 65 pairs of primary NSCLC and noncancerous lung tissues from ArrayExpress database. NSCLC tissues had lower miR-32 expression level than the normal tissues ($P < 0.01$, **Figure 1B**).

MiR-32 expression between NSCLC and adjacent normal tissues

The expression level of miR-32 in NSCLC and adjacent normal tissues was detected by qRT-PCR and normalized to U6 small nuclear RNA. **Figure 1C** showed that miR-32 expression was lower in NSCLC tissues than those in adjacent normal tissues. This difference between NSCLC and normal tissues was statistically significant ($P < 0.05$).We also analyzed 31 pairs of normal and matched NSCLC tissues in 149 NSCLC patients. The results showed that 87 percent of tumor tissues had lower level of miR-32 than matched normal tissues ($P < 0.05$) (**Figure 1D**).

Associations between miR-32 expression and clinical characteristics

The median value of miR-32 expression was used as a cutoff to divide the NSCLC patients

Table 3. Univariate and multivariate analysis of overall survival in NSCLC patients

Factor	HR	95% CI (univariate)	*P* value	miR-32 multivariate analysis		
				HR	95% CI (multivariate)	*P* value
Age	1.309	0.665-2.576	0.436			
Gender	0.558	0.265-1.175	0.125			
Lymph-node metastasis	1.061	0.613-1.838	0.832			
Tumor differentiation	1.273	0.710-2.283	0.418			
TNM stage	0.965	0.489-1.903	0.917			
visceral pleural invasion	1.108	0.650-1.890	0.706	2.232	1.014-4.913	0.046
Vascular invasion	0.279	0.058-1.342	0.111			
Chemotherapy	0.596	0.348-1.022	0.060			
Diameter	0.863	0.514-1.450	0.578			
miR-32 expression	0.299	0.147-0.609	0.001			

into two groups: the low miR-32 expression group and the high miR-32 expression group. The relationships between the expression level of miR-32 and clinical features was analyzed. Significant differences were not found between the level of miR-32 and clinical characteristics including age, gender, lymph node metastasis, tumor differentiation, histology, TNM stage, visceral pleural invasion, vascular invasion and tumor diameter (**Table 1**) ($P > 0.05$).

Down-regulation of miR-32 was associated with poor prognostic in NSCLC patients

Next, we evaluated whether miR-32 expression is a prognostic marker for OS and DFS in NSCLC patients using Kaplan-Meier method and log-rank test. As shown in **Figure 1E** and **1F**, patients with low miR-32 expression had poor OS and DFS ($P < 0.01$).

To analyze whether other clinical characteristics might affect OS and DFS, univariate survival analysis, stratified by each of clinical characteristics was performed by Log-rank test (**Table 2**). The results revealed that visceral pleural invasion was significantly associated with OS and DFS ($P < 0.05$). In addition to visceral pleural invasion, gender and tumor size were also related with DFS ($P < 0.05$).

Univariate COX regression analysis revealed that there weren't significant correlations between overall survival and age, gender, lymph-node metastasis, tumor differentiation, TNM stage, visceral pleural invasion, vascular invasion, chemotherapy and diameter. A multivariate COX regression analysis was further carried out to establish if miR-32 expression was a prognostic marker in NSCLC patients (**Table 3**). The result showed that the hazard ratio of visceral pleural invasion was increased and the *P* value was less than 0.05. So down-expression of miR-32 was identified as a predictor of shorter overall survival in NSCLC patients.

Discussion

MiRNAs, a class of small non-coding RNAs, played a key role in non-small cell lung cancer [13]. The status of miRNA in NSCLC was divided into two categories: oncogene and tumor suppressor gene. Among them, miR-1271, miR-141, miR-575, miR-200c and miR-21, reported as oncogenes, could promote NSCLC cell proliferation and growth [14-18]. But some miRNAs, such as let-7, miR-128, miR-181 and miR-34a, had the exactly opposite effects [19-22]. Though functions of some miRNAs were found, miR-32 was rarely studied in NSCLC.

MiR-32, located on chromosome band Xq26.2, was reported to express differentially in different cancers. MiR-32 expression was markedly increased in breast cancer tissues and cells. Furthermore, the over-expression of miR-32 promoted the cell proliferation, colon formation and anchorage-independent growth of breast cancer cells [6]. The first research about the level of miR-32 expression in colorectal cancer revealed that miR-32 levels were significantly higher in colorectal tissues than in non-cancerous tissues. And high miR-32 expression levels tended to have poor overall survival, indicating that high miR-32 might be a marker of poor prognosis for patients [7]. Studies evaluating

the associations between prostate tumors, multiple myeloma, hepatocellular carcinoma and miR-32 levels showed that miR-32 expression was also strongly up-regulated in tumor tissues [8, 9, 23]. In the above tumors, the levels of miR-32 expression were increased. But in oral squamous cell carcinoma and osteosarcoma, its expressions in tumor tissues were lower than the normal tissues [10, 12]. In oral squamous cell carcinoma, low-level expression of miR-32 was an independent unfavorable prognostic factor. It might suppress oral squamous cell carcinoma through targeting the downstream gene EZH2 which was a tumor-promoting gene. Level of miR-32 was also significantly down-regulated in osteoscarcoma tissues compared with the adjacent normal tissues. To sum up, miR-32 played different roles in different cancers.

In NSCLC, some researchers reported that miR-32 functioned as a tumor suppressor [24, 25]. Though their study evaluated the relationships between miR-32 expression and clinical features, the clinical features were incomplete. Our study included more comprehensive clinical factors and was the first study to report the association between miR-32 expression and disease free survival in NSCLC patients.

In the present study, we compared levels of miR-32 expression of health people with that of different cancer patients based on GEO datasets. We found that miR-32 expression was significantly down-regulated in lung cancer, glioma, renal cancer and Wilms tumor ($P < 0.01$). Then we analyzed miR-32 expression between tumor tissues and matched adjacent non-tumor tissues from 65 NSCLC patients from Array Express database. MiR-32 expression was markedly decreased in tumor tissues, demonstrating that miR-32 might play a role in NSCLC. Hereafter, levels of miR-32 expression of tumor and adjacent normal tissues of 149 NSCLC patients was calculated. The result was the same as the previous research. Furthermore, we also explored 31 paired tumor tissues and matched adjacent normal tissues from the 149 NSCLC patients, finding that 87% (27/31) patients had lower miR-32 expression in tumor tissues.

Relationships between miR-32 expression and clinical factors were examined. There weren't any significantly differences between age, gender, lymph node metastasis, tumor differentiation, histology, TNM stage, visceral pleural invasion, vascular invasion, tumor size and miR-32 expression ($P > 0.05$). The relations between OS, DFS and miR-32 expression were analyzed by Kaplan-Meier survival analysis to explore the potential prognostic value of miR-32. Patients with low miR-32 expression had poorer OS and DFS, suggesting that miR-32 expression might be an independent prognostic marker for NSCLC patients. Univariate COX analysis showed that visceral pleural invasion had no influence on overall survival ($P > 0.05$), but multivariate COX analysis about miR-32 expression and clinical factors revealed that the hazard ratios of visceral pleural invasion increased and the p value of visceral pleural invasion was less than 0.05. Therefore, miR-32 could be used as an independent prognostic marker for NSCLC to remind the doctor and the patient that the patient might have higher risk of death.

We also analyzed which clinical features might play a role in overall survival and disease free survival. Univariate analysis showed that visceral pleural invasion was both remarkably associated with OS and DFS. In addition, gender and tumor size also had effects on DFS. Patients who had visceral pleural invasion tended to have poor OS and DFS, indicating that visceral pleural invasion might be a prognostic marker for NSCLC as shown in other studies [27, 28]. Tumor size was strongly associated with DFS ($P < 0.05$). The disease-free survival time of patients whose tumor diameter was ≥ 5 cm was shorter than that of patients whose tumor diameter was < 5 cm. Male had poorer DFS than female. So the male and the patients whose tumor size was greater or equal to 5 cm should pay more attention on their health status.

In summary, our result demonstrates that miR-32 expression was significantly lower in NSCLC tissues than in normal tissues. The relationships between miR-32 expression and clinical factors including age, gender, lymph node metastasis, tumor differentiation, histology, TNM stage, visceral pleural invasion, vascular invasion and tumor size were not found. Patients with low miR-32 expression tended to be poorer OS and DFS, indicating that miR-32 expression might be an independent prognostic marker for NSCLC patients.

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Disclosure of conflict of interest

None.

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References

[1] Siegel R L, Miller K D, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5-29.

[2] Cheng I, Le GM, Noone AM, Gali K, Patel M, Haile RW, Wakelee HA, Gomez SL. Lung Cancer Incidence Trends by Histology Type among Asian American, Native Hawaiian, and Pacific Islander Populations in the United States, 1990-2010. Cancer Epidemiol Biomarkers Prev 2014; 23: 2250-2265.

[3] Han Y, Jia C, Cong X, Yu F, Cai H, Fang S, Cai L, Yang H, Sun Y, Li D, Liu J, Xie R, Yuan X, Zhong X, Li M, Wei Q, Lv Z, Fu D, Ma Y. Increased Expression of TGFβR2 Is Associated with the Clinical Outcome of Non-Small Cell Lung Cancer Patients Treated with Chemotherapy. PLoS One 2015; 10: e0134682.

[4] Feng B, Zhang K, Wang R, Chen L. Non-small-cell lung cancer and miRNAs: novel biomarkers and promising tools for treatment. Clin Sci (Lond) 2015; 128: 619-634.

[5] Bartel DP. MicroRNAs: Target Recognition and Regulatory Functions. Cell 2009; 136: 215-233.

[6] Xia H, Long J, Zhang R, Yang X, Ma Z. MiR-32 contributed to cell proliferation of human breast cancer cells by suppressing of PHLPP2 expression. Biomed Pharmacother 2015; 75: 105-10.

[7] Wu W, Yang P, Feng X, Wang H, Qiu Y, Tian T, He Y, Yu C, Yang J, Ye S, Zhou Y. The relationship between and clinical significance of MicroRNA-32 and phosphatase and tensin homologue expression in colorectal cancer. Genes Chromosomes Cancer 2013; 52: 1133-1140.

[8] Yan S, Chen M, Li G, Wang YQ, Fan JG. MiR-32 induces cell proliferation, migration, and invasion in hepatocellular carcinoma by targeting PTEN. Tumour Biol 2015; 36: 4747-4755.

[9] Pichiorri F, Suh SS, Ladetto M, Kuehl M, Palumbo T, Drandi D, Taccioli C, Zanesi N, Alder H, Hagan JP, Munker R, Volinia S, Boccadoro M, Garzon R, Palumbo A, Aqeilan RI, Croce CM. MicroRNAs regulate critical genes associated with multiple myeloma pathogenesis. Proc Natl Acad Sci U S A 2008; 105: 12885-12890.

[10] Xiao J. MiR-32 Functions as a Tumor Suppressor and Directly Targets EZH2 in Human Oral Squamous Cell Carcinoma. Med Sci Monit 2014; 20: 2527-2535.

[11] Zhang J, Kuai X, Song M, Chen X, Yu Z, Zhang H, Mao Z. microRNA-32 inhibits the proliferation and invasion of the SGC-7901 gastric cancer cell line in vitro. Oncol Lett 2013; 7: 270-274.

[12] Xu J, Zhang W, Wan R, Yang YQ. MicroRNA-32 inhibits osteosarcoma cell proliferation and invasion by targeting Sox9. Tumor Biol 2014; 35: 9847-9853.

[13] Zhang Y, Yang Q, Wang S. MicroRNAs: a new key in lung cancer. Cancer Chemother Pharmacol 2014; 74: 1105-1111.

[14] Wang Y, Xu L, Jiang L. miR-1271 promotes non-small-cell lung cancer cell proliferation and invasion via targeting HOXA5. Biochem Biophys Res Commun 2015; 458: 714-719.

[15] Zhang X, Li P, Rong M, He R, Hou X, Xie Y, Chen G. MicroRNA-141 Is a Biomarker for Progression of Squamous Cell Carcinoma and Adenocarcinoma of the Lung: Clinical Analysis of 125 Patients. Tohoku J Exp Med 2015; 235: 161-169.

[16] Wang H, Yan C, Shi X, Zheng J, Deng L, Yang L, Yu F, Yang Y, Shao Y. MicroRNA-575 targets BLID to promote growth and invasion of non-small cell lung cancer cells. FEBS Lett 2015; 589: 805-811.

[17] Kim MK, Jung SB, Kim J, Roh MS, Lee JH, Lee EH, Lee HW. Expression of microRNA miR-126 and miR-200c is associated with prognosis in patients with non-small cell lung cancer. Virchows Arch 2014; 465: 463-471.

[18] Yang Y, Meng H, Peng Q, Yang X, Gan R, Zhao L, Chen Z, Lu J, Meng QH. Downregulation of microRNA-21 expression restrains non-small cell lung cancer cell proliferation and migration through upregulation of programmed cell death 4. Cancer Gene Ther 2014; 22: 23-29.

[19] Xia X. Clinical significance and the correlation of expression between Let-7 and K-ras in non-small cell lung cancer. Oncol Lett 2010; 1: 1045-1047.

[20] Hu J, Cheng Y, Li Y, Jin Z, Pan Y, Liu G, Fu S, Zhang Y, Feng K, Feng Y. microRNA-128 plays a critical role in human non-small cell lung can-

cer tumourigenesis, angiogenesis and lymphangiogenesis by directly targeting vascular endothelial growth factor-C. Eur J Cancer 2014; 50: 2336-2350.
[21] Huang P, Ye B, Yang Y, Shi J, Zhao H. MicroRNA-181 functions as a tumor suppressor in non-small cell lung cancer (NSCLC) by targeting Bcl-2. Tumor Biol 2015; 36: 3381-3387.
[22] Shi Y, Liu C, Liu X, Tang DG, Wang J. The microRNA miR-34a Inhibits Non-Small Cell Lung Cancer (NSCLC) Growth and the CD44hi Stem-Like NSCLC Cells. PLoS One 2014; 9: e90022.
[23] Ambs S, Prueitt R L, Yi M, Hudson RS, Howe TM, Petrocca F, Wallace TA, Liu CG, Volinia S, Calin GA, Yfantis HG, Stephens RM, Croce CM. Genomic Profiling of MicroRNA and Messenger RNA Reveals Deregulated MicroRNA Expression in Prostate Cancer. Cancer Res 2008; 68: 6162-6170.
[24] Bai Y, Wang YL, Yao WJ, Guo L, Xi HF, Li SY, Zhao BS. Expression of miR-32 in human non-small cell lung cancer and its correlation with tumor progression and patient survival. Int J Clin Exp Pathol; 2015; 8: 824-829.
[25] Zhu D, Chen H, Yang X, Chen W, Wang L, Xu J, Yu L. miR-32 functions as a tumor suppressor and directly targets SOX9 in human non-small cell lung cancer. Onco Targets Ther 2015; 8: 1773-83.
[26] Adachi H, Tsuboi M, Nishii T, Yamamoto T, Nagashima T, Ando K, Ishikawa Y, Woo T, Watanabe K, Kumakiri Y, Maehara T, Morohoshi T, Nakayama H, Masuda M. Influence of visceral pleural invasion on survival in completely resected non-small-cell lung cancer. Eur J Cardiothorac Surg 2015; 48: 691-7.
[27] Park I, Chung KY, Kim KD, Kim DJ. Prognostic factors for disease-free survival in pT2N0 non-small cell lung cancer. Asian Cardiovasc Thorac Ann 2006; 14: 139-144.
[28] Cao X, Chen YZ, Luo RZ, Zhang L, Zhang SL, Zeng J, Jiang YC, Han YJ, Wen ZS. Tyrosine-protein phosphatase non-receptor type 12 expression is a good prognostic factor in resectable non-small cell lung cancer. Oncotarget 2015; 6: 11704-11713.