European Review for Medical and Pharmacological Sciences 2019; 23: 8422-8428

MiRNA and lung cancer radiosensitivity: a mini-review

T. POWRÓZEK, T. MAŁECKA-MASSALSKA

Department of Human Physiology, Medical University of Lublin, Poland

Abstract. – Radiotherapy (RTH) is still one of the leading treatment options for lung cancer patients. This treatment option is especially significant for patients with diagnosis of locally advanced or advanced tumor. To date, it is difficult to predict RTH outcomes basing only on patients' clinical features. Moreover, there are no established molecular markers, which could improve the prediction of RTH efficacy. Among the most promising markers which could serve as valuable biomarkers of RTH, miRNAs seem to be the most appropriate. According to literature reports, these molecules may be used for the prediction of RTH response, selection of patients who could benefit from RTH, as well as to estimate the risk of toxicity after irradiation. Moreover, thanks to the possibility of its testing in blood samples whenever it is required, miRNAs seem to be a much more attractive predictive marker of response to RTH than other molecular factors. In the present mini-review, we discuss recent findings of experimental studies (cell cultures analysis) and clinical studies concerning the relationship between miRNAs and sensitivity of lung tumors to RTH.

Key Words:
Non-small cell lung cancer, Radiotherapy, MicroRNA, Biomarker.

Introduction

Despite recent advances in early lung cancer (LC) diagnosis and the availability of novel treatment perspectives, the number of patients who could benefit from molecularly targeted therapies or immunotherapy is still low. The above-mentioned limitations are often caused by the lack of characteristic symptoms of the disease at an early stage of its development. Moreover, currently there are only a few known molecular alterations against which molecularly targeted agents can be applied[1-3]. The following concerns, including low social awareness regarding tobacco smoking and its harmful impact on the human body, disregard for screening programs and often insidious and latent tumor development contribute to a high prevalence of LC in the global population. Unfortunately, all of the mentioned concerns contribute to late detection of the disease; hence, LC is still both the most prevalent and fatal human neoplasm[4-7]. Certainly, most of LC cases are detected in either locally advanced or advanced stage of the disease, frequently with the presence of distant metastases. Late disease detection (stage IIIB-IV and inoperable stage IIIA) is always associated with unfavorable prognosis. The 5-year survival rate varies from 14% for IIIA patients to 5% in stage IIIB, and it is only about 1% for metastatic cancer (stage IV)[8,9]. Treatment perspectives for LC include the following: surgery, which is the most appropriate option for radical therapy, molecularly targeted therapies, as well as chemotherapy (CTH) and radiotherapy (RTH), which are still characterized by low effectiveness. The selection of the therapeutic option depends on the disease stage and histological type of tumor. Additionally, the qualification of patients for most appropriate therapy should be complemented by the evaluation of performance status (according to ECOG-WHO or Karnofsky's scale) and the consideration of the risk of the post-treatment side effects. Eventually, molecular testing can be used to consider the qualification of patients for personalized therapy[7,10,11]. Unfortunately, the number of patients who could undergo surgery or molecularly targeted therapy is low, thus CTH and RTH are still leading and most common options of LC treatment.

Lung Cancer Radiotherapy

The main purpose of RTH is the destruction of tumor cells by ionizing radiation, which can result in patient recovery (radical RTH) or alle-

Corresponding Author: Tomasz Powrózek, Ph.D; e-mail: tomaszpowrozek@gmail.com

viation of the disease symptoms associated with local tumor development or metastases (palliative RTH). This treatment option is especially significant for patients with the diagnosis of non-small cell lung cancer (NSCLC). According to literature data[12-14], approximately 60-70% of NSCLC patients require the application of a different type of RTH. Radical RTH is often applied in stage III of NSCLC, and in patients with an early disease stage (I-II) in case of disqualification from surgery (due to non-tumor associated reasons) or because of the patient's decision to resign from surgery[13,14]. However, the outcomes of radical RTH are still unsatisfactory. The 5-year survival rate is achieved by only about 20% of patients in stage I and II of the disease and up to 10% cases in stage III. For early stages of NSCLC, stereotactic body radiotherapy is almost as effective as surgical intervention; however, there is still a lack of randomized trials comparing results achieved with both methods[15]. A review of the available literature reports regarding the effectiveness of standard RTH has demonstrated 2-year survival in up to 70% of treated cases, whereas 5-year survival is achieved in approximately 30% of patients. Those outcomes also suggest that a higher dose of radiation allows achieving better response to RTH. Currently, RTH is the leading treatment option for stage III of NSCLC and it is usually complemented by CTH to improve treatment outcomes. Palliative RTH of the chest is considered to be a therapy regimen used to alleviate disease symptoms in selected patients with good performance status. Moreover, palliative RTH of metastases is used in case of their presence in bones and brain. In patients with endobronchial localization of the tumor, brachytherapy can be considered[16,17].

The indication of RTH application in patients with a limited stage of small-cell lung cancer (SCLC) is high tumor radisosensitivity and frequent disease recurrence in primary localization. Similarly to NSCLC, also in SCLC, RTH is combined with CTH to improve treatment outcomes. RCTH reduces the risk of early death and improves survival rate in SCLC patients compared to CTH used as a single therapy method. Despite that, the most favorable regimen of RCTH for SCLC has not been established yet. Both methods can be applied simultaneously during treatment or sequentially (RTH after CTH)[18,19]. A meta-analysis conducted by Pignon et al[20] demonstrated that RTH added to CTH increased 3-year survival rate in SCLC by about 5% and reduced the risk of early death by 14%. Although RTH and RCTH are beneficial for most LC patients, these methods are characterized by a high risk of post-radiation side-effects and development of severe toxicity[21]. Unfortunately, the RTH outcomes are often difficult to be unequivocally predicted, and the improvement of survival time is rather poorer than expected. However, the attempts are made to improve RTH outcomes and include testing of various radiation doses, different schemes of RTH or RCTH, and combination of various CTH regimens with RTH. Besides there is a lack of molecular predictive factors which could allow selecting patients who would benefit from therapy and in whom RTH could fail.

MiRNAs and Lung Cancer

Among currently tested molecular factors in LC patients, microRNAs (miRNAs) molecules seem to be the most attractive. These small, non-coding RNA molecules belong to epigenetic mechanisms regulating gene expression. However, single miRNA does not encode genetic information, thus it does not carry information about protein structure. These molecules play a crucial role in the regulation of protein synthesis by targeting selected mRNA. MiRNAs, binding to untranslated region located in 3' tail (3'-UTR) of mRNA, modulate its function through the impact on translation process, therefore miRNAs regulate gene expression post-transcriptionally[22,23]. In the case of high miRNAs expression, these molecules effectively bind to specific or partially-specific mRNA sequence leading to a decrease in protein level or even totally inhibit translation. In consequence, however, the gene is either expressed normally or the expression is altered and the accumulation or disintegration of non-functional mRNA is observed in a cell. In healthy cells, there is equilibrium between gene expression and miRNAs synthesis. Therefore, the gene function is precisely controlled and proteins are formed if required for cell cycle. However, protooncogenes are repressed by a still high level of complementary miRNAs, which prevent their transformation into oncogenes. Altered expression of numerous miRNAs is observed in various human diseases, and is especially demonstrated in neoplasms - that appears to be the incorrect equilibrium between mRNA and miRNA level, which leads to the uncontrolled synthesis of proteins, including oncogene proteins. This phenomenon results in the increase or decrease in the level of different miRNAs and, in conse-

quence, unnecessary proteins are formed, while the synthesis of proper proteins is inhibited. Therefore, miRNAs can also be considered as a tumor-suppressor marker and oncogenes[24-27]. All the mentioned alterations affect uncontrolled cell development, proliferation, and migration. Differences in miRNA expression level observed between LC patients and healthy population may be potentially used in daily clinical practice. First of all, miRNAs can be applied as a potential diagnostic marker for early tumor diagnosis, as well as an independent prognostic factor of patient survival[28]. Despite that, miRNAs also manifest their predictive potential through the regulation of protein synthesis. This observation could be useful for estimation of CTH, RTH, and RCTH effectiveness. It is evident that certain proteins regulate the metabolism of chemotherapeutics, such as platinum or other cytostatics, and this process depends on protein expression. A similar protein function can also be observed in the case of cell irradiation. The altered expression of proteins regulating DNA repair mechanism after ionizing radiation affects the RTH efficacy, as well as the intensity of side effects and toxicity. By identifying new miRNAs and understanding their role in the regulation of the function of particular proteins related to RTH response, we will be potentially able to test patients with miRNA signatures to select group of individuals, who will benefit and respond to RTH. Moreover, thanks to the possibility of its detection in blood plasma or serum whenever it is required, miRNAs seem to be a much more attractive predictive marker of response to RTH than other molecular factors.

MiRNAs and Response to RTH - Cell Line Analysis

Ionizing radiation induces mainly DNA damage response in the cells. However, extensive DNA damage cannot be repaired; thus, it leads to the activation of the programmed death of cells. The massive destruction of tumor cells after radiation is the essence of RTH. Unfortunately, tumor cells already have or may acquire radioprotective (radioresistance) characteristics that enable them to escape from radiation-induced cell death. This fact may be related to altered gene expression encoding proteins involved in the above-mentioned process, as well as altered expression of miRNAs which mediates the translation process[29]. A major mechanism leading to alteration of miRNA expression is the impact of radiation on miRNAs synthesis by affecting Dicer and Drosha mechanisms. In the case of their absence, miRNAs synthesis is decreased. Therefore, in cells characterized by a reduced amount of miRNAs or even its absence, cell survival is decreased and apoptosis induced. Currently, it is believed, that radiation affects the changes in miRNAs expression profile. However, the basis of this mechanism is still unknown. Generally, miRNAs regulate numerous cellular pathways, including DNA damage response to radiation[29-31].

To date several miRNAs were evaluated as potential factors predicting RTH response in LC cell lines. One of the first molecules described in detail, which can be involved in RTH response in LC was miRNA-21. In the study of Wang et al[32] conducted on A549 LC cell line, they investigated the correlation between miRNA-21 and cell response to radiation. MiRNA expression was monitored in the time period from 0 to 8 h after irradiation. The miRNA-21 level significantly increased 4 h after treatment, and authors linked this phenomenon with its ability to modulate cell response to RTH. To confirm these findings, the authors knocked down miRNA-21 by RNAi in A549 cells, and afterwards exposed cells to radiation. Results showed that the survival of A549 cells with knocked-down miRNA-21was significantly lower than in control cells. Moreover, the knock down of miRNA-21 inhibited growth and proliferation of A549 cells. Summarizing, miRNA-21 was estimated as a putative novel marker of response to RTH, because the low expression of miRNA-21 inhibited proliferation of A549 cells and sensitized cells to radiation[32]. Similar conclusions were formulated by Cho et al[33], however, authors additionally investigated another mechanism of miRNA-21 action. The study findings showed, that overexpression of miRNA-21 increased radioresistance of A549 cells and up-regulated EGFR/HER2 signaling pathway, which can be associated with epithelial-mesenchymal transition (cell invasion, migration, and vascularization). In a mice model, combined treatment of anti-miRNA-21 with irradiation progressively decreased tumor burden compared to each treatment alone. Authors believed, that miRNA-21 conferred radioresistance and diverse features of epithelial-mesenchymal transition. MiRNA-21 knock down could be a novel potential strategy for improving the efficacy of RTH via modulation of pro-survival signaling implicated in radiation response and epithelial-mesenchymal transition[33]. Also, Ma et al[34] found a correlation between miRNA-21 expression and response of A549 cell

line to radiation. Interestingly, the authors found another molecular pathway of miRNA action. Silencing of miRNA-21 in radioresistant A549 cells sensitized them to radiation. As a result, the proliferation of tumor cell was inhibited, whereas cell apoptosis was enhanced by inhibition of PI3K/Akt signaling pathway involved in mediation of radiation response by cells mediated by miRNA-21. Several other miRNAs were investigated as markers of response to radiation in cancer cell lines. In the case of A549 cell line, miRNA-451 can also be involved. Overexpression of this molecule can enhance the suppressive effect of radiation on the ability of colony forming by A549 cells and also by activation of PTEN expression. Both mechanisms probably lead to radiosensitization of LC cell line through the enhancement of apoptosis[35]. In another study analyzing the role of miRNA in radiosensitivity of SCLC and NSCLC cell lines, the different molecules including miRNA-21, 1827, 214, 339, 625, 768, 523, 1227 were differentially expressed. Among them, miRNA-214 seems to be the most interesting because of its implication for p38MAPK pathway. A high expression level of miRNA-214 was associated with resistance of NSCLC cell lines to irradiation, and it protected cells against radiation-induced apoptosis. Protection is putatively mediated by p38MAPK, thus in the future, both miRNA-214 and p38MAPK could become interesting treatment targets, and their inhibition could reverse the resistance to irradiation[36]. MiRNAs potentially involved in modulation of LC cells response to radiation are summarized in Table I[35-43].

MiRNA and Response to RTH - Clinical Findings

Promising findings provided by analysis of cell lines encourage researchers to investigate selected miRNAs in LC patients to predict response to RTH. Similarly to other uses of miRNA e.g., tumor diagnostics, it seems the most appropriate to simultaneously analyze a few molecules to improve the accuracy of diagnosis. Thanks to the possibility of non-invasive testing of miRNAs by liquid biopsy at each stage of therapy, those molecules are attractive predictive markers of RTH. However, to date, only a few studies investigated the role of miRNAs circulating in blood as predictors of tumor radiosensitivity (Table II). In the study of Dinh et al[44], the authors investigated the level of miRNA-29a and miRNA-150 expression in plasma samples of NSCLC patients scheduled for RTH. Despite the fact that miRNAs may be involved in response to RTH, the authors also highlighted another interesting phenomenon, suggesting that miRNAs are associated with a high risk of toxicity after irradiation. Expression of both molecules decreased as a result of irradiation, which was related to a decrease in exosomes released to circulation. It was concomitant with an increase of miRNAs in intracellular space, suggesting that exosomal export of miRNAs may be downregulated in NSCLC in response to irradiation. Interestingly, RTH patients with a significant reduction of miRNA-29a level are at a higher risk of severe radiation pneumonitis compared to patients in whom the miRNA level decreased moderately[44]. In another study, Bi et al[45] studied serum miRNAs signature for the prediction of RTH effectiveness in NSCLC patients. The study enrolled 134 individuals with inoperable tumors treated with RTH who were followed-up for at least 18 months. Among 84 studied miRNAs, two molecules: miRNA-885 and miRNA-7 demonstrated the most significant clinical utility regarding response to irradiation and risk of reducing the overall survival (OS) depending on radiation dose. The proposed signature demonstrated diagnostic power, especially for individuals treated with doses of over 70 Gy

Table I. MiRNA potentially involved in radiosensitivity of LC cell lines.

miRNA	Expression level	Pathway/miRNA-target involved in resistance	Reference
miRNA-451	Downexpression	PTEN	35
miRNA-214	Downexpression	p38MAPK	36
miRNA-328-3p	Downexpression	γ-H2AX	37
miRNA-124	Downexpression	TXNRD1	38
miRNA-148b	Downexpression	MLH1	39
miRNA-34a	Downexpression	Myc	40
miRNA-1323	Downexpression	PRKDC	41
miRNA-122	Overexpression	MAPK, PI3K	42
miRNA-21-5p	Downexpression	hMSH2	43

Table II. Recent clinical studies correlating miRNA and effectiveness of RTH in NSCLC patients.

Study	Sample size/ material	Disease stage of NSCLC	Major study findings
Dinh et al[44]	25/plasma	IIA-IIIB	**1.** Five miRNAs (29a, 150, 342, 142, and 125b) decreased in expression in circulation with increasing radiation dose whereas five miRNAs (101, 30d, 320a, 191, and 15b) increased in expression. **2.** Circulating miR-29a and miR-150 improve prediction of unexpected responses to radiation therapy, such as toxicity.
Bi et al[45]	100/serum	Inoperable stages (mostly III)	**1.** Circulating miRNA-885 and miRNA-7 were identified as significant predictors for overall survival of radiotherapy treated NSCLC patients. **2.** Two miRNA-based signature predicts survival and radiation resistance in inoperable NSCLC and may potentially help to select patients who will not benefit from high-dose radiation.
Chen et al[46]	54/plasma	IIIA-IV	**1.** Four miRNAs (98, 302e, 495-3p, 613) demonstrated a higher expression in patients, who benefit from RTH (complete or partial remission) than in non-responders (stable or progressive disease). **2.** Studied miRNAs did not correlate with median PFS or OS in the study group.
Jiang et al[47]	258/serum	IV with brain metastases	**1.** MiRNA-330 is down-expressed in the radiation-sensitive patients than in the radiation-resistant ones. MiRNA-330 allows prediction of radiation sensitivity with a sensitivity of 71.7% and a specificity of 90.1%. **2.** After RTH patients with low miRNA-330 level, demonstrated a lower survival rate and a median survival time compared to patients with high miRNA-330 level.
Sun et al[48]	80/serum	II-III	**1.** Signature of eleven miRNAs (10b, 125b, 125, 134, 155, 200b, 205, 34a, 92a, 145, 22) combined with clinical factors identified a subset of NSCLC patients who derive an overall survival benefit from high-dose RTH (HR=0.22). **2.** In patients with low Dose Response Score measured by miRNAs, high-dose RTH conferred decreased risk of distant metastasis and local progression.

and it allowed to distinguish between patients with either high or low risk of early death (OS between groups: 70.7 *vs.* 18.8 months; $p<0.01$)[45]. Based on Chen et al[46] research, 14 miRNAs were selected with putative clinical significance for RTH response. Among selected miRNAs, the following four miRNA-98, 302e, 495, 613 were strongly related to RTH response. Expression of all mentioned molecules was significantly higher in the group of patients who achieved complete or partial remission of the disease compared to the group that achieved stable or progressive disease. However, there was no correlation between either OS or progression-free survival and miRNAs expression[46]. Jiang et al[47] found serum miRNA-330 as a novel predictor of RTH in NSCLC patients. The expression of the above-mentioned molecule was significantly lower in RTH-responders compared to the non-responder group. Moreover, the analysis of miRNA-330 demonstrated high diagnostic accuracy for predicting RTH sensitivity with the sensitivity of 71.7% and specificity of 90.1% (AUC=0.898). However, after RTH, patients with low miRNA expression had shorter OS in contrast to the group with high miRNA level. Most recently, Sun et al[48] combined eleven miRNAs-based signatures with clinical factors of NSCLC patients to generate a dose response score (DRS) for prediction of OS in patients treated with either standard-dose or high-dose of RTH. Subjects qualified to the low DRS group based on the above-mentioned criteria showed

improved OS after therapy with high-dose compared to standard-dose RTH (HR=0.22, $p<0.05$). The study findings revealed miRNA as a useful clinical tool for the identification of patients who could benefit from high-dose RTH without the presence of serious side-effects. Interestingly, patients assigned to low DRS score group were at a lower risk of local or distant metastases development[48].

Although the literature reports concerning the clinical utility of miRNAs as a predictor of RTH are limited, the available data is promising and encourages further research[49]. MiRNAs may be assessed as a predictor of RTH to select responding and non-responding group of patients and also to predict survival after the application of irradiation. Moreover, some papers seem to confirm that miRNAs may also be a valuable predictor of post-radiation toxicity development. However, the obtained results should be treated with caution and need to be confirmed in large clinical trials enrolling a large cohort of patients.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Funding
This study was not funded or financially supported.

References

1) Reck M, Rabe KF. Precision diagnosis and treatment for advanced non-small-cell lung cancer. N Engl J Med 2017; 377: 849-861.
2) Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res 2016; 5: 288-300.
3) Bironzo P, Di Maio M. A review of guidelines for lung cancer. J Thorac Dis 2018; 10 (Suppl 13): S1556-S1563.
4) Ridge CA, McErlean AM, Ginsberg MS. Epidemiology of lung cancer. Semin Intervent Radiol 2013; 30: 93-98.
5) Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer. Chest 2013; 143 (5 Suppl): e1S-e29S.
6) Dela Cruz CS, Tanoue LT, Matthay RT. Lung cancer: epidemiology, etiology and prevention. Clin Chest Med 2011; 32: 605-644.
7) Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008; 83: 584-594.
8) Knight SB, Crosbie PA, Balata H, Chudziak J, Hussel T, Dive C. Progress and prospects of early detection in lung cancer. Open Biol 2017; 7: 170070.
9) Yang P. Epidemiology of lung cancer prognosis: quantity and quality of life. Methods Mol Biol 2009; 471: 469-486.
10) Gadgeel SM, Ramalingam SS, Kalemkerian GP. Treatment of lung cancer. Radiol Clin North Am 2012; 50: 961-974.
11) de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. Transl Lung Cancer Res 2018; 7: 220-233.
12) Delaney G, Barton M, Jacob S, Jalaludin B. A model for decision making for the use of radiotherapy in lung cancer. Lancet Oncol 2003; 4: 120-128.
13) Parashar B, Arora S, Wernicke AG. Radiation therapy for early stage lung cancer. Semin Intervent Radiol 2013; 30: 185-190.
14) Baker S, Dahele M, Lagerwaard FJ, Senan S. A critical review of recent developments in radiotherapy for non-small cell lung cancer. Radiat Oncol 2016; 11: 115.
15) Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. Radiother Oncol 2010; 94: 1-11.
16) McCloskey P, Balduyck B, Van Schil PE, Faivre-Finn C, O'Brien M. Radical treatment of non-small cell lung cancer during the last 5 years. Eur J Cancer 2013; 49: 1555-1564.
17) Glatzer M, Elicin O, Ramella S, Nestle U, Putora PM. Radio(chemo)therapy in locally advanced nonsmall cell lung cancer. Eur Resp Rev 2016; 25: 65-70.
18) Kepka L, Sprawka A, Casas F, Abdel-Wahab S, Agarwal JP, Jeremic B. Radiochemotherapy in small-cell lung cancer. Expert Rev Anticancer Ther 2009; 9: 1379-1387.
19) Jeremic B, Casas F, Wang L, Perin B. Radiochemotherapy in extensive disease small cell lung cancer ED-SCLC. Front Radiat Ther Oncol 2010; 42: 180-186.
20) Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, Brodin O, Joss RA, Kies MS, Lebeau B. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992; 327: 1618-1624.
21) López Rodríguez M, Cerezo Padellano L. Toxicity associated to radiotherapy treatment in lung cancer patients. Clin Transl Oncol 2007; 9: 506-512.
22) Mott JL, Mohr AM. Overview of microRNA biology. Semin Liver Dis 2015; 35: 3-11.
23) Wahid F, Shehzad A, Khan T, Kim YY. MicroRNAs: synthesis, mechanism, function, and recent clinical trials. Biochim Biophys Acta 2010; 1803: 1231-1243.
24) MacFarlane LA, Murphy PR. MicroRNA: biogenesis, function and role in cancer. Curr Genomics 2010; 11: 537-561.

25) He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 2004; 5: 522-531.

26) Peng Y, Croce CM. The role of MicroRNAs in human cancer. Signal Trans Target Ther 2016; 15004.

27) Jansson MD, Lund AH. MicroRNA and cancer. Mol Oncol 2012; 6: 590-610.

28) Schoof CR, da Silva Botelho EL, Izzotti A, dos Reis Vasques L. MicroRNAs in cancer treatment and prognosis. Am J Cancer Res 2012; 2: 414-433.

29) Czochor JR, Glazer PM. MicroRNAs in cancer cell response to ionizing radiation. Antioxid Redox Signal 2014; 21: 293-312.

30) Iorio MV, Croce CM. Causes and consequences of microRNA dysregulation. Cancer J 2012; 18: 215-222.

31) Kumar M, Lu Z, Takwi AA, Chen W, Callander NS, Ramos KS, Young KH, Li Y. Negative regulation of the tumor suppressor p53 gene by microRNAs. Oncogene 2011; 30: 843-853.

32) Wang XC, Wang W, Zhang ZB, Zhao J, Tan XG, Luo JC. Overexpression of miRNA-21 promotes radiation-resistance of non-small cell lung cancer. Radiat Oncol 2013; 8: 146.

33) Cho BJ, Kim HH, Lee DJ, Choi EJ, Hwang YH, Chun SH, Kim IA. MicroRNA-21 inhibitor potentiates anti-tumor effect of radiation therapy in vitro and in vivo. Tumor Microenviron Ther 2014; 2: 1-13.

34) Ma Y, Xia H, Liu Y, Li M. Silencing miR-21 sensitizes non-small cell lung cancer A549 cells to ionizing radiation through inhibition of PI3K/Akt. BioMed Res Int 2014; 014:617868. doi: 10.1155/2014/617868.

35) Tian F, Han Y, Yan X, Zhong D, Yang G, Lei J, Li X, Wang X. Upregulation of microrna-451 increases the sensitivity of A549 cells to radiotherapy through enhancement of apoptosis. Thorac Cancer 2016; 7: 226-231.

36) Salim H, Akbar NS, Zong D, Vaculova AH, Lewensohn R, Moshfegh A, Viktorsson K, Zhivotovsky B. MiRNA-214 modulates radiotherapy response of non-small cell lung cancer cells through regulation of p38MAPK, apoptosis and senescence. Br J Cancer 2012; 107: 1361-1373.

37) Ma W, Ma C, Zhou N, Li X, Zhang Y. Up- regulation of miR-328-3p sensitizes non-small cell lung cancer to radiotherapy. Sci Rep 2016; 6: 31651.

38) Hao C, Xu X, Ma J, Xia J, Dai B, Liu L, Ma Y. MicroRNA-124 regulates the radiosensitivity of non-small cell lung cancer cells by targeting TXNRD1. Oncol Lett 2017; 13: 2071-2078.

39) Zhai G, Li G, Xu B, Jia T, Sun Y, Zheng J, Li J. MiRNA-148b regulates radioresistance in non-small lung cancer cells via regulation of MutL homologue 1. Biosci Rep 2016; 36. pii: e00354.

40) He X, Yang A, McDonald DG, Riemer EC, Vanek KN, Schulte BA, Wang GY. MiR-34a modulates ionizing radiation-induced senescence in lung cancer cells. Oncotarget 2017; 8: 69797-69807.

41) Li Y, Han W, Ni TT, Lu L, Huang M, Zhang Y, Cao H, Zhang HQ, Luo W, Li H. Knockdown of microRNA-1323 restores sensitivity to radiation by suppression of PRKDC activity in radiation-resistant lung cancer cells. Oncol Rep 2015; 33: 2821-2828.

42) Ma D, Jia H, Qin M, Dai W, Wang T, Liang E, Dong G, Wang Z, Zhang Z, Feng F. MiR-122 induces radiosensitization in non-small cell lung cancer cell line. Int J Mol Sci 2015; 16: 22137-22150.

43) Song Y, Zuo Y, Qian XL, Chen ZP, Wang SK, Song L, Peng LP. Inhibition of microRNA-21-5p promotes the radiation sensitivity of non-small cell lung cancer through HMSH2. Cell Physiol Biochem 2017; 43: 1258-1272.

44) Dinh TK, Fendler W, Chałubińska-Fendler J, Acharya SS, O'Leary C, Deraska PV, D'Andrea AD, Chowdhury D, Kozono D. Circulating miR-29a and miR-150 correlate with delivered dose during thoracic radiation therapy for non-small cell lung cancer. Radiat Oncol 2016; 11: 61.

45) Bi N, Schipper MJ, Stanton P, Wang W, Kong FM. Serum miRNA signature to identify a patient's resistance to high-dose radiation therapy for unresectable non-small cell lung cancer. J Clin Oncol 2013; 31 suppl: 7580.

46) Chen X, Xu Y, Liao X, Liao R, Zhang L, Niu K, Li T, Li D, Chen Z, Duan Y, Sun J. Plasma miRNAs in predicting radiosensitivity in non-small cell lung cancer. Tumour Biol 2016; 37: 11927-11936.

47) Jiang LP, Zhu ZT, Zhang Y, He CY. Downregulation of microRNA-330 correlates with the radiation sensitivity and prognosis of patients with brain metastasis from lung cancer. Cell Physiol Biochem 2017; 42: 2220-2229.

48) Sun Y, Hawkins PG, Bi N, Dess RT, Tewari M, Hearn JWD, Hayman JA, Kalemkerian GP, Lawrence TS, Ten Haken RK, Matuszak MM, Kong FM, Jolly S, Schipper MJ. Serum microRNA signature predicts response to high-dose radiation therapy in locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2018; 100: 107-114.

49) Amin NP, Mohindra P, Jabbour SK. Serum microRNA guiding personalized radiation therapy in non-small cell lung cancer. J Thorac Dis 2018 (Suppl 33); 10: S4108-S4112.