MEDICAL SCIENCE MONITOR

MEDICAL TECHNOLOGY

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 7271-7278
DOI: 10.12659/MSM.910990

Received: 2018.05.06
Accepted: 2018.06.04
Published: 2018.10.11

Value of Diffusion-Weighted Magnetic Resonance Imaging Combined with miR-18a Level in Predicting Radiosensitivity of Cervical Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AC 1 Xinhua Bu*
AD 2 Ji Zhang*
DE 2 Fangzheng Tian
DE 2 Xiulan Wang
DF 3 Linyun Wu
ABFG 2 Weizhong Tian

1 Department of Gynecology and Obstetrics, Taizhou People's Hospital, Taizhou, Jiangsu, P.R. China
2 Department of Radiology, Taizhou People's Hospital, Taizhou, Jiangsu, P.R. China
3 Taizhou Polytechnic College, Taizhou, Jiangsu, P.R. China

* Xinhua Bu and Ji Zhang are co-first authors

Corresponding Author: Weizhong Tian, e-mail: tianweizh1999tz@126.com

Source of support: This study was supported by Jiangsu Provincial Medical Youth Talent (No. QNRC2016509), Taizhou City High-level Talent Research Project (No. 27), and Taizhou City Science and Technology Project (TS024)

Background: Radioresistance during radiotherapy of cervical cancer often leads to treatment failure; therefore, there is an urgent need to develop effective predictive indicators of radiosensitivity for cervical cancer patients.

Material/Methods: Cervical cancer cells were collected from 40 patients who received surgical resections. The relationships between apparent diffusion coefficient (ADC) values of masses before surgery and different micro-RNAs (miRNA) levels (miR-18a, miR-132, and miR-145) of these cells were investigated. Cervical cancer cells were divided into 4 groups according to the ADC values of original tumor tissues and expression level of miR-18a. Then, these cells were exposed with irradiation both *in vitro* and *in vivo*.

Results: Advanced cervical cancer showed lower ADC values in magnetic resonance imaging. miR-18a, miR-132, and miR-145 all were increased in the cervical cancer tissues, while miR-18a showed a more marked negative correlation with ADC values. The results of *in vitro* and *in vivo* assays showed that higher expression of miR-18a in cervical cancer cells leads to more radiosensitivity, especially in cells from cancer tissues with lower ADC values.

Conclusions: The combination of ADC values with expression level of miR-18a may be a new and reliable predictor for radiosensitivity of cervical cancer, helping cervical cancer patients with low ADC values and high expressions of miR-18a to achieve better outcomes in radiotherapy.

MeSH Keywords: MicroRNAs • Radiography, Abdominal • Uterine Cervical Neoplasms

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/910990

2222 1 4 25

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Cervical cancer is one of the most common malignancies in women, and it has a high mortality rate [1]. The most common treatments for cervical cancer are surgery or a combination of chemotherapy and radiotherapy [2]. Radiotherapy is usually recommended for patients who are poor surgical candidates [3]. Unfortunately, radioresistance of cervical cancer cells is the cause of most treatment failures. Predicting the radiosensitivity of cervical cancer patients is of vital importance for achieving better outcomes after comprehensive treatment by reducing the incidence of radiosensitivity [4]. Therefore, developing reliable predictive indicators for cervical cancer patients is urgently needed.

Diffusion-weighted magnetic resonance imaging (DWI), which evaluates the micro-diffusion of water molecules in tissues, has been widely used in the diagnosis of various diseases, especially for cancers [5,6]. DWI can provide functional information before morphological changes and can be quantified as the apparent diffusion coefficient (ADC) [7]. It has been reported that ADC value is a useful index in evaluation of malignancies [8]. Recently, ADC was also shown to be a new predictor for the radiosensitivity of CC patients [9].

MicroRNAs (miRNAs) are endogenous, non-coding, small RNAs that play critical roles in tumor proliferation, progression, and metastasis [10]. Previous studies have revealed that many miRNAs participate in biological responses of cervical cancer, and miR-18a, miR-132, and miR-145 have been reported to modulate the radiosensitivity of cervical cancer cells [11–13]. Therefore, miRNAs can also be regarded as reliable predictors for cervical cancer radiosensitivity. We hypothesized that the radiosensitivity of cervical cancer can be predicted with higher accuracy using the combination of ADC and miRNAs level. To the best of our knowledge, the present study is the first to report on the function-molecular aspect of prediction of cervical cancer.

To verify our hypothesis, cervical cancer cells were collected from 40 patients who received surgical resections. The relationships between ADC values of masses before surgery and miRNAs levels of these cells were investigated. The cervical cancer cells were also used to build a xenografted tumor model to study the different radiosensitivity *in vivo*.

Material and Methods

Patients and samples

We enrolled a total of 40 patients with cervical cancer treated from 1 January 2015 to 1 January 2017 at the Obstetrics and Gynecology Department of Taizhou People's Hospital. These patients with cervical cancer (FIGO stage IB-IIB) received surgeries and 40 paired cervical cancer tissues and adjacent normal tissues were obtained from them. The distance between normal tissue and the cancer mass was 4–5 cm. None of these patients were subjected to preoperative chemotherapy and/or radiotherapy. The patients provided informed consent to participate and the collection of human tissue samples was approved and supervised by the Ethics Committee of Taizhou People's Hospital.

MRI scanning

Routine MRI and DWI scanning were performed before surgery on a clinical MR scanner (Magetom Verio, Siemens, Germany). For routine MRI scanning, sequences of axial sagittal T_2WI, axial T_1WI, and axial T_2WI. For axial DWI scanning, spin echo planar imaging (SE-EPI) sequence was used. The ADC values were measured on ADC maps.

Cell cultures and transfection

The cervical cancer cells isolated from the cancer tissues were cultured with Dulbecco's modified Eagle's medium (DMEM, Gibco, USA) supplemented with 10% fetal bovine serum and penicillin-streptomycin. Low expression of miR-18a was established by gene knockdown through lentivirus vector. miR-18a-siRNA (target sequence: 5'-GGCTTTACAACGGAATGATGA-3') was used for knockdown studies. The siRNA was obtained from GenePharma (Shanghai, China) and transfected with transfection reagent (Lipofectamine 2000, Invitrogen, Carlsbad, USA) according to the manual. At 48 h after transfection, further assays were conducted.

RNA extraction and qRT-PCR

Total RNA from cancer and normal tissues were isolated with Trizol (Invitrogen) according to instructions provided in the user's manual. A NanoDrop-2000 spectrophotometer was used to confirm the quantity and quality of extracted RNA. Then, we used a cDNA synthesis kit (Thermo Scientific, Wilmington, USA) for reverse transcription according to the manufacturer's instructions. The expressions of miR-18a, miR-132, and miR-145 were detected through quantitative reverse transcription polymerase chain reaction (qRT-PCRs) using a PCR Kit (Takara, Dalian, China). The gene expression was measured using the following primers:
miR-18a, 5'-GTTCCTAAGGTTCATCTAGTGCAGATA-3' (forward), 5'-CAGTGCAGGGTCCGAGGTAT-3' (reverse);
miR-132, 5'-CCAGCATAACAGTCTACAGCCA -3' (forward), 5'-TATGGTTGTTCACGACTCCTTCAC-3' (reverse);
miR-145, 5'-CGAGCTCAGTTGGGAAGTTACCTG-3' (forward); 5'-GCTCTAGAGAAGGTA ATAAACATTTGAA-3' (reverse);

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

U6, 5'-CTCGCTTCGGCAGCACATA-3' (forward),
and 5'-CGAATTTGCGTGTCATCCT-3' (reverse).
All the reactions were carried out on a 7500 fast real-time PCR system according to the manufactures' instructions. Each sample was analyzed in triplicate.

Irradiation

Cells and cervical cancer-bearing nude mice were irradiated with ^{60}Co-gamma ray at different doses (dose rate: 1 Gy/min). Mice in each group received local irradiation 2 times every fourth day.

Cell viability assays

The cervical cancer cells obtained from the CC patients were divided into 4 groups according to the ADC value of tumor tissues and expression of miR-18a: (1) cells with higher ADC value (higher than the median) and higher expression of miR-18a (higher than the median); (2) cells with higher ADC value and lower expression of miR-18a (lower than the median); (3) cells with lower ADC value and higher expression of miR-18a (higher than the median); and (4) cells with lower ADC value and lower expression of miR-18a. Then, the cells were seeded in 96-well plates (1×10^4 cells/well). After 24-h incubation, the cells were irradiated at different doses from 0 Gy to 8 Gy. Then, after another 24-h incubation, cell viability was determined using standard MTT assays. The absorbances at 490 nm were measured under a multi-plate reader (Biotech, USA).

Cancer irradiation *in vivo*

Nude mice (female, 4 weeks old) were purchased from Beijing Huafukang Animal Center (Beijing, China) and housed under specific pathogen-free (SPF) conditions. All the animal operations were approved by the Institutional Animal Care and Use Committee of the Taizhou People's Hospital. These mice were randomly divided into 5 groups (3 mice in each group). The subcutaneous xenograft cervical cancer model was established by the subcutaneous injection of different cancer cells (cells with higher ADC value and higher expression of miR-18a; cells with higher ADC value and lower expression of miR-18a; cells with lower ADC value and higher expression of miR-18a; and cells with lower ADC value and lower expression of miR-18a). Briefly, 1×10^7 cervical cancer cells dispersed in 100 µL of phosphate-buffered saline (PBS) were subcutaneously injected into the left back of the nude mice. Two weeks later, the tumor sizes reached about 6~8 mm in diameter. Then, these cancer-bearing mice were irradiated with ^{60}Co-gamma ray at a 6-Gy dose. Tumor-bearing mice without irradiation were regarded as controls. The tumors were monitored with calipers every other day, and tumor volumes were calculated as length×(width)^2/2. At 11 days after irradiation, the mice were sacrificed by cervical dislocation and xenograft tumors were excised for photography.

Statistical analysis

Data are shown as the mean ±S.D. We used the *t* test, chi-square test, and Pearson's correlation coefficient for statistical analysis. P<0.05 was considered significant. Origin 8.5 software was used for the statistical analysis and plotting.

Results

Advanced cervical cancer showed lower ADC values

The ADC values of cervical cancer masses were measured. Figure 1 shows a typical MR image of cervical cancer. An ill-defined mass with heterogenous MR intensity can be found in the cervix. The mass shows high intensity in the DW image with low ADC value for $(0.73\pm0.14)\times10^{-3}$ mm^2/s. Then, the relationships between ADC values and clinicopathological characteristics were evaluated (Table 1). The median ADC value of tumor masses was used as the cutoff. We found that cervical cancers with more advanced stages, larger tumor size, and poorer differentiation showed lower ADC values.

ADC values are correlated with miRNA expressions

According to previous reports, several miRNAs participate in the radiosensitivity modulation of cervical cancers. In the present study, we measured the expression levels of miR-18a, miRNA-132, and miRNA-145 in tumor tissues and in normal tissues ajacent to the tumor mass. As shown in Figure 2A, the expressions of these miRNAs all were enhanced when compared with the normal control tissue. Moreover, correlation analysis showed that miR-18a (r=–0.835, p<0.001) and miR-132 (r=–0.414, p=0.008) expressions were significantly inversely correlated with ADC values in cervical cancer tissues (Figure 2B, 2C), but the miR-145 (r=–0.059, p=0.716) expression did not show a significant correlation with ADC values in cervical cancer tissues (Figure 2D). miR-18a showed a more marked negative correlation with ADC values when compared with miR-132.

Higher expression of miR-18a in cervical cancer cells leads to more radiosensitivity

To investigate the radiosensitivity of cervical cancer cells, cells were divided into 4 groups according to the ADC values of original tumor tissues and expression level of miR-18a. Then, these cells were exposed to various doses of radiation. As shown in Figure 3A, the viability of cervical cancer cells with high expression of miR-18a and low ADC values were obviously decreased in a radiation dose-dependent manner, which shows a good radiosensitivity, but the cervical cancer cells in the other 3 groups exhibited unsatisfied radiosensitivity, with

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

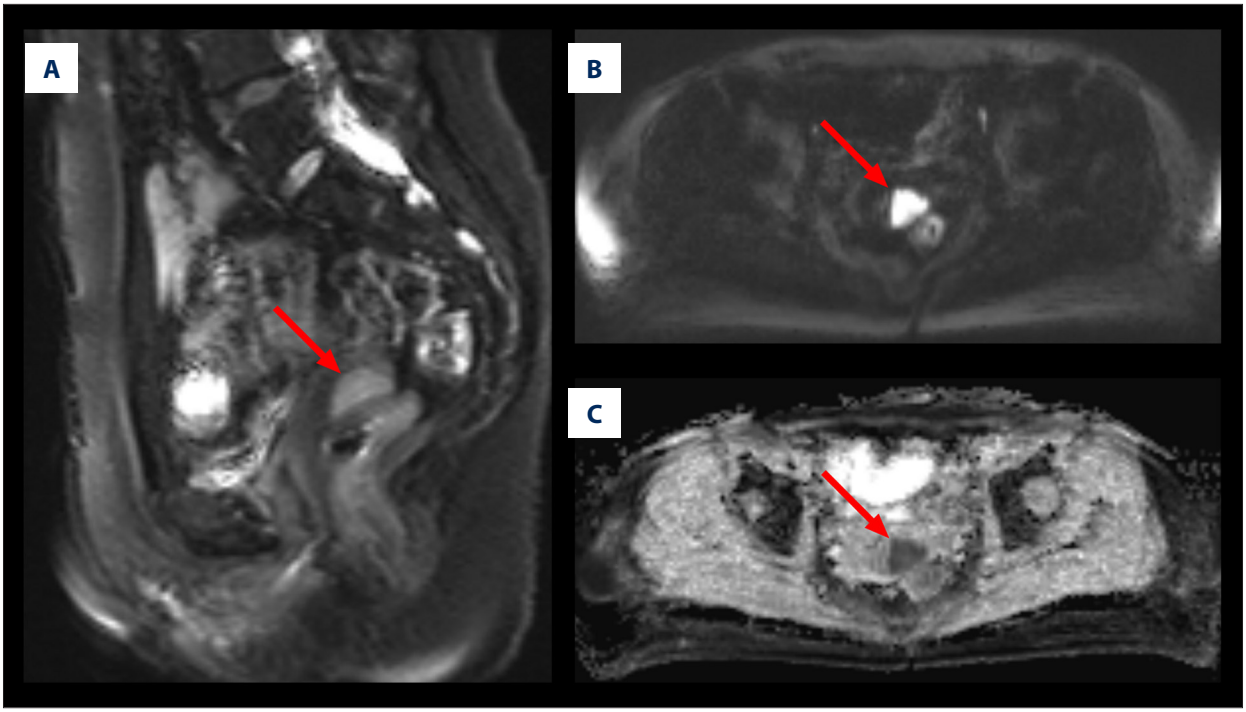

Figure 1. T_2WI-FS, DWI, and ADC images of cervical cancer. The cervical cancer mass is indicated by the red arrow. (**A**) A mass with heterogeneous intensity at the cervix in a T_2WI-FS MR image. (**B**) Cervical cancer showed high intensity in the DWI MR image. (**C**) ADC image of cervical cancer.

Table 1. Clinical characteristics of 42 cervical cancer patients according to miR-145 expression.

Feature	ADC values		Chi-square	*P* value
	Low	High		
All cases	20	20		
Age (year), <45: ≥45	8: 12	10: 10	0.876	0.341
Tumor size (cm), <4: ≥4	4: 16	13: 7	5.278	0.012
FIGO stage, IB: IIA: IIB	3: 7: 10	8: 8: 4	6.982	0.027
Degree of differentiation				
Highly: moderately: poorly	4: 5: 11	6: 9: 5	6.023	0.038
Lymph node metastasis, yes: no	12: 8	10: 10	0.829	0.413

P<0.05 was considered statistically significant.

slight or negligible decrease of cell viability when irradiated (Figure 3B–3D). When given the same radiation dose (6 Gy), the cell viability of cervical cancer cells with high expression of miR-18a and low ADC values was significantly lower than in other groups (Figure 3E). To further verify the role of miR-18a in the radiosensitivity of cervical cancer cells, the expression level of miR-18a was down-regulated through siRNA transfection. As shown in Figure 3F, the down-regulation of miR-18a led to a remarkable radiation resistance.

Evaluation of radiosensitivity *in vivo*

To further evaluate the radiosensitivity *in vivo*, the xenograft cervical cancer model was established by the subcutaneous injection of cancer cells from original tumor tissues with different ADC values and expression levels of miR-18a. As shown in Figure 4A and 4B, the xenograft cervical cancer model built from the cancer cells with low ADC values and high expression of miR-18a exhibited an impressive tumor inhibition after irradiation, while the tumor masses in other groups all were remarkably enlarged.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

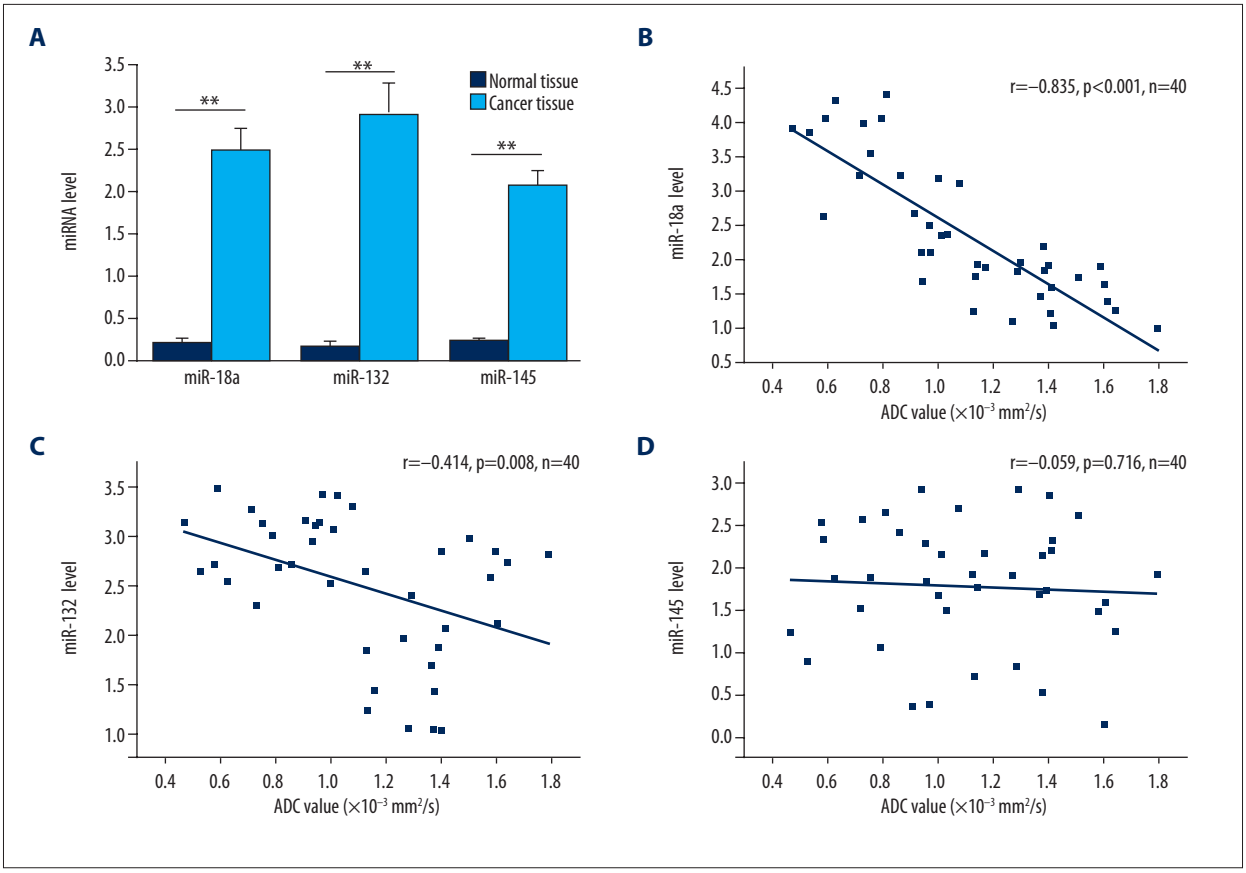

Figure 2. miRNAs expressions in tumor tissues and their relationships with ADC values of cervical cancer. (**A**) The expression level of 3 kinds of miRNAs (miR-18a, miR-132, and miR-145) in cancer tissues and adjacent normal tissues. (**B**) Correlation between levels of miR-18a and ADC values of cervical cancer. (**C**) Correlation between levels of miR-132 and ADC values of cervical cancer. (**D**) Correlation between levels of miR-145 and ADC values of cervical cancer. (** $p<0.001$)

Discussion

Recently, the morbidity and mortality rates of cervical cancer have decreased with the development of early screening and medical techniques [2,14]. However, cervical cancer remains the third most common cancer in women, especially in the developing countries [15]. Radiotherapy that destroys cervical cancer cells by high-energy rays is a common but effective method used to treat this malignancy [4]. A recent study showed that patients who received radiotherapy were 40–90% less likely to relapse within 5 years than those who did not receive radiotherapy [16]. Unfortunately, radioresistance often results in the clinical failure of radiotherapy [3]. In the present study we developed reliable predictive indicators for cervical cancer, which is urgently needed after comprehensive treatment.

DWI technology has been widely used in the diagnosis of malignant tumors[17]. For cervical cancer, DWI can perfectly distinguish tumor tissues from normal cervical tissue [18]. Quantitative ADC values are also used to evaluate the pathological type or grading of cervical cancer [6]. In our study, cervical cancers with more advanced stages, larger tumor size, and worse differentiation showed lower ADC values. Earlier studies indicated that ADC values can predict tumor treatments [5], and it has been reported that ADC values obviously change in the patients with good curative response, suggesting the predictive effect of ADC values in the chemotherapy response [19]. Previous studies also demonstrated that ADC values significantly changed in the patients with satisfactory radiotherapy response, indicating that ADC values may be a reliable predictive indicator of radiosensitivity for cervical cancer patients [9].

miRNAs can play important roles in tumor proliferation, progression, and metastasis by modulating the expression of certain target genes [20,21], and some of them can be regarded as reliable biomarkers for prediction of prognosis and curative response in various cancers [22]. miR-18a, miR-132, and miR-145 have been reported to affect the radiosensitivity of cervical cancer [11–13]. In the present study, we compared the expression of these miRNAs between cervical cancer tissues and normal tissues. Our results indicate that all 3 of these

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

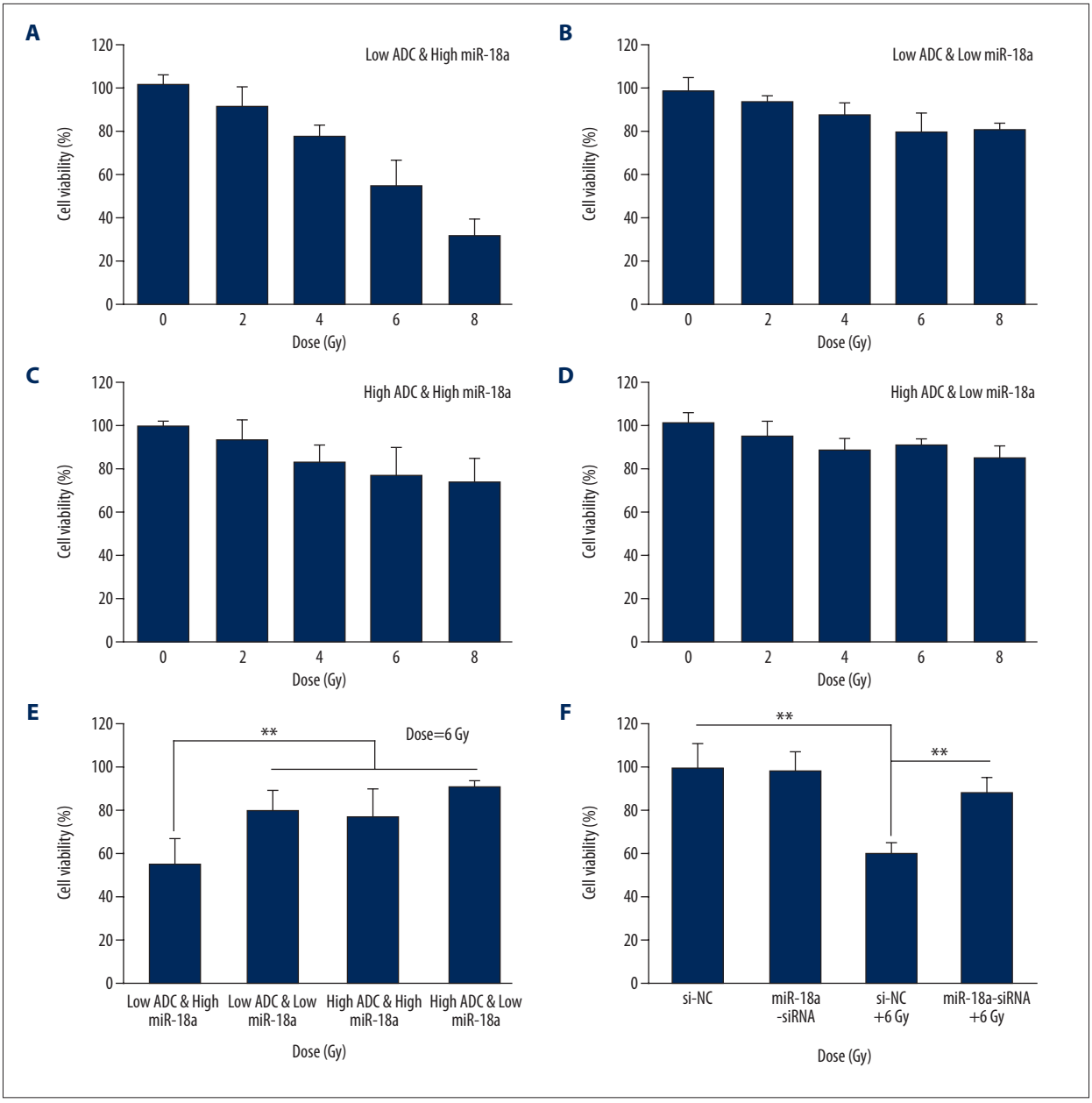

Figure 3. Higher expression of miR-18a in cervical cancer cells leads to more radiosensitivity. (**A**) Cell viability of cervical cancer cells with low ADC value and high expression of miR-18a under irradiation exposure at different doses. (**B**) Cell viability of cervical cancer cells with low ADC value and low expression of miR-18a under irradiation exposure at different doses. (**C**) Cell viability of cervical cancer cells with high ADC value and high expression of miR-18a under irradiation exposure at different doses. (**D**) Cell viability of cervical cancer cells with high ADC value and low expression of miR-18a under irradiation exposure at different doses. (**E**) Cell viability of cervical cancer cells in the 4 groups under irradiation exposure at 6 Gy. (**F**) Cell viability of cervical cancer cells with down-regulated expression of miR-18a under irradiation exposure at 6 Gy. (** $p<0.001$)

miRNAs were up-regulated in cervical cancer tissues. In particular, miR-18a showed a more marked negative correlation with ADC values. In previous reports, miR-18a has been found to be overexpressed in bladder cancer, colon carcinoma, nasopharynx cancer, and hepatocellular carcinoma [13,23,24]. Some reports indicated that miR-18a can increase cellular radiosensitivity of cervical cancer. Overexpression of miR-18a suppressed the level of ataxia-telangiectasia mutated (ATM) and attenuated DNA double-strand break (DSB) repair, which re-sensitized the cervical cancer cells to radiotherapy by promoting apoptosis [10,25]. In our research, we found that higher expression of miR-18a in cervical cancer cells resulted in more radiosensitivity. Among these cancer cells with high miR-18a expression, the cells from the cervical cancer tissues with lower

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

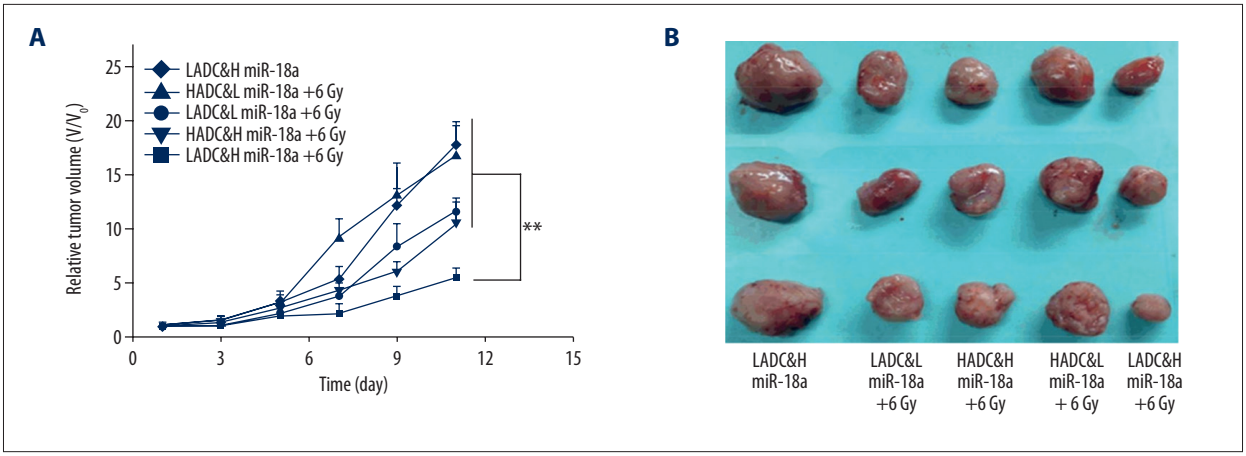

Figure 4. Evaluation of radiosensitivity *in vivo*. (**A**) Tumor size curves in different groups. (**B**) Image of tumor masses excised from nude mice. (** $p<0.001$).

ADC values exhibited more impressive radiosensitivity, both *in vitro* and *in vivo*. Therefore, use of ADC values combined with miR-18a expression has good potential to predict radiosensitivity in cervical cancer patients.

This research was limited by its small sample size, and more patients should be involved to prove the conclusions. In addition, the potential mechanism involved in the association between ADC value and miR-18a expression needs further study.

Conclusions

In a summary, we found that the combination of ADC values and expression level of miR-18a is a new and reliable predictor for radiosensitivity of cervical cancer. Cervical cancer patients with low ADC values and high expressions of miR-18a would receive a better outcome in radiotherapy. This finding is helpful for doctors to guide the clinical treatments of cervical cancer.

Conflict of interest

None.

References:

1. Saslow D, Solomon D, Lawson HW et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for clinical pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol, 2012; 137: 516–42
2. Tewari KS, Sill MW, Long HJ et al: Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med, 2014; 370: 734–43
3. Massad LS, Einstein MH, Huh WK et al: 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis, 2013; 17: S1–27
4. Ronco G, Dillner J, Elfstrom KM et al: Efficacy of HPV-based screening for prevention of invasive cervical cancer: Follow-up of four European randomised controlled trials. Lancet, 2014; 383: 524–32
5. Vozenin M-C, Lord H-K, Hart D, Deutsch E: Unravelling the biology of human papillomavirus (HPV) related tumours to enhance their radiosensitivity. Cancer Treat Rev, 2010; 36: 629–36
6. Huang Z, Mayr NA, Lo SS et al: Inter-patient variation of radiosensitivity and dead-cell resolving time in cervical cancer. International Journal of Radiation Oncology Biology Physics, 2010; 78: S411
7. Chvetsov AV, Yartsev S, Schwartz JL, Mayr N: Assessment of interpatient heterogeneity in tumor radiosensitivity for nonsmall cell lung cancer using tumor-volume variation data. Medical Physics. 2014; 41: 064101
8. Tsoutsou P, Annibaldi A, Viertl D et al: TAT-RasGAP(317-326) enhances radiosensitivity of human carcinoma cell lines *in vitro* and *in vivo* through promotion of delayed mitotic cell death. Radiat Res, 2017; 187: 562–69
9. Ni X, Tong Y, Xiao Y et al: Diffusion-weighted magnetic resonance imaging in predicting the radiosensitivity of cervical cancer. Int J Clin Exp Med, 2015; 8: 13836–41
10. Liang S, Ju X, Zhou Y et al: Downregulation of eukaryotic initiation factor 4A1 improves radiosensitivity by delaying DNA double strand break repair in cervical cancer. Oncol Lett, 2017; 14: 6976–82
11. Liu G-F, Zhang S-H, Li X-F et al: Overexpression of microRNA-132 enhances the radiosensitivity of cervical cancer cells by down-regulating Bmi-1. Oncotarget, 2017; 8: 80757–69
12. Ye C, Sun N-x, Ma Y et al: MicroRNA-145 contributes to enhancing radiosensitivity of cervical cancer cells. FEBS Lett, 2015; 589: 702–9
13. Liu S, Pan X, Yang Q et al: MicroRNA-18a enhances the radiosensitivity of cervical cancer cells by promoting radiation-induced apoptosis. Oncol Rep, 2015; 33: 2853–62
14. Arbyn M, Ronco G, Anttila A et al: Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine. 2012; 30: F88–99
15. Rijkaart DC, Berkhof J, Rozendaal L et al: Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: Final results of the POBASCAM randomised controlled trial. Lancet Oncol, 2012; 13: 78–88
16. Moyer VA, U.S. Preventive Services Task Force: Screening for cervical cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med, 2012; 156: 880–91
17. Chen G-P, Ahunbay E, Schultz C, Li XA: Development of an inverse optimization package to plan nonuniform dose distributions based on spatially inhomogeneous radiosensitivity extracted from biological images. Med Phys, 2007; 34: 1198–205
18. Huang T, Chen M, Wu M, Wu X: Image analysis of DNA content and nuclear morphometry for predicting radiosensitivity of nasopharyngeal carcinoma. Anal Quant Cytol Histol, 2008; 30: 169–74

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

19. Yuh WC, Huang Z, Mayr NA et al: Hemoglobin influences tumor cell radiosensitivity in patients with cervical cancer. Int J Radiat Oncol Biol Phys, 2010; 78: S119
20. Liu SS, Leung RCY, Chan KYK et al: P73 expression is associated with the cellular radiosensitivity in cervical cancer after radiotherapy. Clin Cancer Res, 2004; 10: 3309–16
21. Li X-l, Meng Q-h, Fan S-j: Adenovirus-mediated expression of UHRF1 reduces the radiosensitivity of cervical cancer HeLa cells to gamma-irradiation. Acta Pharmacol Sin, 2009; 30: 458–66
22. Shin H-J, Kim J-Y, Hampson L et al: Human papillomavirus 16 E6 increases the radiosensitivity of p53-mutated cervical cancer cells, associated with up-regulation of aurora A. Int J Radiat Biol, 2010; 86: 769–79
23. Chen M, Xing L-N: siRNA-mediated inhibition of hTERC enhances radiosensitivity of cervical cancer. Asian Pac J Cancer Prev, 2012; 13: 5975–79
24. Luo J, Zhu W, Tang Y et al: Artemisinin derivative artesunate induces radiosensitivity in cervical cancer cells *in vitro* and *in vivo*. Radiat Oncol, 2014; 9: 84
25. Herd O, Francies F, Kotzen J et al: Chromosomal radiosensitivity of human immunodeficiency virus positive/negative cervical cancer patients in South Africa. Mol Med Rep, 2016; 13: 130–36

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]