Significance of lncRNA MALAT1 expression in peripheral blood in the short-term efficacy of radiotherapy for esophageal squamous cancer and its molecular mechanism

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Abstract: Radiotherapy is the main treatment for many advanced esophageal squamous cell carcinoma (ESCC) patients. Recent studies demonstrated that patients with high level of long non-coding RNA (lncRNA) MALAT1 in tumor had poor prognosis. Thus, our study aims to investigate the significance of blood-derived MALAT1 in short-term efficacy of radiotherapy in ESCC and its underlying mechanism. LncRNA MALAT1 expression levels in plasma and serum from 47 ESCC patients were detected by quantitative RT-PCR. ESCC cell line EC9706 was transfected with siRNA to modulate MALAT1 expression. The effect of MALAT1 on cell growth, apoptosis, and radioresistance was studied in vitro. The results showed that there was a linear correlation between both plasma and serum MALAT1 level. MALAT1 level in plasma was associated with TNM stage (P=0.04), differentiation degree (P=0.004), and poor radiotherapy efficacy (P<0.001). Reducing MALAT1 in EC7906 cells inhibited cell growth, promoted apoptosis, alleviated radioresistance, and enhanced caspase-3 activity. The mechanism could be possibly associated with the negative regulation of miR-145 expression by MALAT1. In conclusion, MALAT1

could be used as a potential prognostic marker of ESCC. Reducing MALAT1 was beneficial for enhancing cell radiosensitivity and apoptosis.

Keywords: esophageal squamous cancer, MALAT1, prognosis, redioresistance, miR-145

Introduction

Esophageal cancer is one of the malignant tumors originating from esophageal mucosal epithelia, which is characterized by progressive dysphagia and retrosternal pain. China is a country with a high incidence of esophageal cancer. There were estimated 477900 new cases and 375000 deaths of esophageal cancer reported in 2015, ranking fourth in the mortality of malignant tumors (1). The new cases and deaths of esophageal cancer in China accounted for half of the total number in the world (2). Histologically, esophageal cancer can be divided into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). 90% of esophageal cancer cases in China are ESCC (3). Early detection of esophageal cancer can be cured by endoscopic minimally invasive surgery and the 5-year survival rate can exceed 95% (4). However, most of the patients with esophageal cancer have advanced to the middle and advanced stage at the time of diagnosis, and the 5-year survival rate is about 20% (5). For patients with advanced esophageal cancer, radiotherapy is the main treatment, but the mortality of local recurrence after radiotherapy is as high as 60%-80% (6). Meanwhile, even though different patients have the same age, lesion location, and clinical stages, the efficacy of radiotherapy varies greatly. Therefore, the study of biological factor affecting the radiotherapeutic effect of esophageal cancer and the search for molecular markers with high prognostic value can provide a basis for patients to formulate more favorable individualized treatment programs.

Long (>200 nucleotides) non-coding RNAs (lncRNAs) are a kind of non-coding RNA widely existing in eukaryotic organisms, usually containing more than 200 nucleotides, which occupies at least 80% of the human genome. More and more evidences show that lncRNAs participate in cellular growth, apoptosis, and metastasis in many ways, including transcriptional factor, post-transcription regulator, chromatin remodeling factor, and RNA splicing regulator (7). Dysregulation and dysfunction of lncRNAs can cause many diseases including cancer. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a carcinogenic lncRNA in multiple cancers. Huang *et al.* reported that MALAT1 was a prognostic factor of esophageal cancer;

MALAT1 expression level in cancer tissue was highly associated with distant metastasis and poor survival (8). MALAT1 could bind to miR-200a as ceRNA (competing endogenous RNA) and promote epithelial mesenchymal transition (EMT) process in esophageal cancer EC-109 cells (9).

lncRNAs are relatively stable with their secondary structure in body fluids and they are suitable to be used as biomarkers. Several lncRNAs, namely Linc00152, CFLAR-AS1, and POU3F3, had the potential as plasma biomarkers for early detection of ESCC (10,11). A study in non-small cell lung cancer (NSCLC) evaluated the performance of MALAT1 as a blood-based biomarker and the results suggested that MALAT1 was applicable as a complementary biomarker with high specificity (12). However, the prognostic value of MALAT1 as blood biomarkers in ESCC is not fully understood. A previous study of human papillomavirus-positive cervical cancer suggested that MALAT1 expression was higher in radioresistant cancer cases (13). The impact of MALAT1 on sensitivity to radiotherapy is also unclear in esophageal cancer. Thus, our study aims to investigate the significance of MALAT1 in short-term efficacy of radiotherapy in ESCC and it underlying mechanism.

Materials and methods

Study subjects

In this study, 47 ESCC patients who were unable to undergo surgery or concurrent radiotherapy and chemotherapy were collected from Affiliated Cancer Hospital of Xinjiang between January 2015 and January 2018. All patients underwent pathological examination and confirmed ESS without secondary malignancy. The use of human specimen was done following all applicable international, national, and institutional ethical guidelines. Written informed consent was signed and obtained from each patient. The baseline data were collected: age, sex, TNM stage, clinical stage, lesion location, lesion length, X-ray typing. The TNM stage was determined according to the 8^{th} edition of tumor-node-metastasis classification for esophageal carcinoma (UICC, 2016) (14). Five ml of peripheral blood was drawn from each

ESCC patient in anticoagulant blood tube and was processed for plasma collection within 1 h. Blood samples were set at room temperature for 1 h to clot and serum was collected. Plasma and serum samples were removed of cellular nucleic acids by a two-step centrifugation protocol (2000 g for 10 min and 12000 g for 10 min).

Radiotherapy was divided into two periods. In the first period, 2.0 Gy/5 d/wk was given and continued for 4 weeks; in the next 2 weeks, 2.2 Gy/5 d/wk was given. Clinical target volume (CTV) extended 3.0 cm beyond the proximal and distal extent of gross tumor volume (GTV), and the lateral borders extended 0.6 cm beyond the GTV; Radiation fields extended 1.0 cm beyond the proximal and distal extent of CTV, and the lateral borders extended 0.8 cm beyond the CTV. For upper and middle thoracic tumors, involved-field irradiation (including tumors and positive lymph nodes) was used. For cervical tumors, radiation fields included bilateral supraclavicular region. If one side has supreclavicular lymph node metastasis, one station of regional lymph nodes was extended on the same side.

Evaluation of therapeutic efficiency

Esophageal barium meal radiography and chest CT were reviewed before radiotherapy, 4 weeks after radiotherapy, and at the end of radiotherapy. According to the revised RECIST guideline (version 1.1) (15) and literature (16), the short-term therapeutic efficiency was evaluated and divided into:1) complete remission (CR), all lesions disappeared completely and lasted for at least 4 weeks, esophageal mucosa returned to normal; 2) partial remission (PR), the sum of maximum diameter decreased by more than 50% and lasted for at least 4 weeks, barium passes through the esophagus smoothly; 3) no change (NC), the lesions remained large or did not improve significantly, barium meal examination showed that the esophagus still had filling-defect or stricture.

Cell culture and transfection

ESCC cell line EC9706 (ATCC, Manassa, USA) was cultured with RPMI 1640+10% FBS (all from HyClone, Logan, USA) and used for cellular experiments. Cells were maintained in an atmosphere with 5% CO_2 at 37 ℃. To interfere MALAT1

expression, siRNA against human MALAT1 (product ID: 272231, Life Technologies, Santa Cruz, USA) was used for transfection as described (17). Scrambled siRNA (product ID: AM 4635, Life Technologies) was also transfected as control. The transfection was done using Lipofectamine 2000 reagent (Invitrogen, Carlsbad, USA). Transfection with siRNA yielded about 50% reduction of MALAT1 expression. Transfected cells were harvested after 48 hours and used for further assays.

RNA extraction and quantification

Total RNA was extracted from plasma or serum using mirVana PARIS kit (Ambion, Austin, USA). RNA extraction from cells was done using TRIzol reagent (Invitrogen) and followed by isopropanol precipitation. RNA concentration was determined by NanoDrop 1000 spectrophotometer (Thermo Fisher, Wilmington, USA). RNA was reverse-transcribed into cDNA using PrimeScript RT reagent (Takara, Beijing, China). Expression of MALAT1 and miR-145 was quantified by real-time PCR and normalized to U6 housekeeping gene using $2^{-\Delta\Delta Ct}$ method. $\Delta Ct=Ct_{target}-Ct_{U6}$; $\Delta\Delta Ct$=(sampleΔCt-controlΔCt). Real-time PCR was performed using SYBR green PCR Master Mix (Takara) in ABI7500 PCR system (Applied Biosystems, Foster City, USA). The primer sequences are: forward CTTAAGCGCAGCGCCATTTT and reverse CCTCCAAACCCCAAGACCAA for MALAT1; forward ATCGTCCAGTTT TCCCAGG and reverse CGCCTCCACACACTCACC for miR-145; forward CTCGC TTCGGCAGCACA and reverse AACGCTTCACGAATTTGCGT for U6.

Cell growth

Cells were seeded in 96-well plate at 1000 cells/well density and cultured as usual. Cell growth was determined by Cell Counting Kit-8 (CCK8, Beyotime Biotechnology, Shanghai, China) as instructed. Absorbance at 450 nm was measured as an indicator of cell density.

Cell apoptosis

Cells were seeded in 6-well plate at 2×10^5 cells/well density and cultured for 48 hours. Cells were collected and stained with fluorescein isothiocyanate (FITC)-Annexin V and propidium iodide (PI, BD Biosciences, Franklin Lakes, USA)

for apoptosis assay. Stained cells were detected by flow cytometer CytoFlex (Beckman Coutler, Miami, USA). The fraction of cells appeared in the upper right quadrant and the lower right quadrant were considered as apoptotic cells

Irradiation sensitivity

Cells were irradiated 5 times with a linear accelerator at room temperature. The radiation dose was 5 Gy per time; the absorbed dose rate was 300 cGy/min; the radiation distance was 1 m. After irradiation, the cells continued to be cultured routinely for 48 h. CCK-8 method was used to detect the survival of the cells. Meanwhile, caspase-3 activities were also measured. Cells were lysed on ice to release caspase-3 into supernatant. Cell debris was collected and reacted with Ac-DEVD-*p*NA at 37 ℃. Absorbance at 405 nm was measured to calculate hydrolytic activities.

Statistics

Statistical analyses were performed by SPSS software version 17.0 (Chicago, USA). Continuous data were expressed as mean ± standard deviation or median (interquartile range) as noted in the results. Comparisons of categorical data between two groups were analyzed by χ^2 test. Comparisons of continuous data between two groups were analyzed by *t*-test or Mann-Whitney rank sum test; comparisons of continuous data among multiple groups were analyzed by one-ANOVA followed by Tukey's test. *P* value <0.05 was considered as statistically significant.

Results

MALAT1 expression was correlated with poor short-term efficacy of radiotherapy in ESCC patients

Firstly we measured MALAT1expression in plasma and serum samples from ESCC patients. The results were showed in Figure 1A. There was a linear correlation between plasma and serum MALAT1 level (R^2=0.891), as shown in Figure 1B. The results suggested that either sample was acceptable for detection of blood-based MALAT1 expression. We then investigated the relationship between MALAT1 level

in plasma and specific clinicopathologic parameters. The results were shown in Table 1. MALAT1 expression was associated with TNM stage and differentiation degree. The plasma MALAT1 level in the patients with stage III-IVESCC was significantly higher than that in patients with stage I-II (P=0.04). Higher MALAT1 level was also observed in the patients with highly differentiated ESCC (P=0.004). However, there was no significant association between MALAT1 level (either plasma or serum sample) and age, gender, length of diseased esophagus, location of lesion, and X-ray typing.

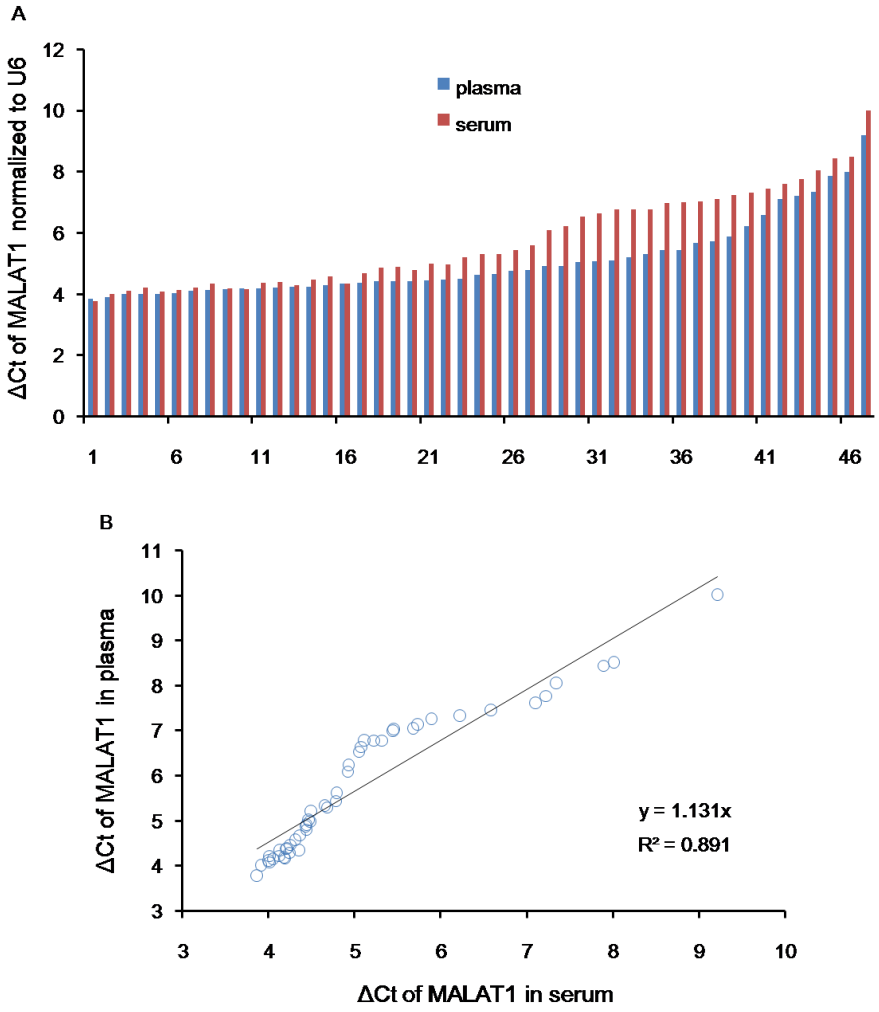

Figure 1. Expression of MALAT1 in plasma and serum of ESCC patients.

A, ΔCt of MALAT1 expression normalized to U6. B, Correlation between plasma level and serum level.

According to the outcomes of radiotherapy, 17 patients achieved CR, 26 patients

achieved PR, and 4 patients remained NC. The expression levels of MALAT1 (expressed as ΔCt normalized to U6) in plasma of the three groups were 4.28 (4.12, 4.48), 4.93 (4.40, 5.57), and 7.95 (7.73, 8.31), respectively; the levels in serum were 4.38 (4.17, 5.07), 6.23 (4.75, 7.04), and 8.48 (8.28, 8.88), respectively. The MALAT1 expression level was positively correlated with poor radiotherapy efficacy (P<0.001), as shown in Figure 2.

Table 1. Relationship between MALAT1 level in plasma and specific clinicopathologic parameters

	ΔCt of MALAT1 in plasma median (interquartile range)	***P***
Age		
>60	4.78 (4.34, 5.71)	0.309
≤60	4.47 (4.17, 5.15)	
Gender		
Male	4.46 (4.21, 5.63)	0.798
Female	4.93 (4.36, 5.32)	
Length of diseased esophagus		
> 7 cm	4.50 (4.24, 5.56)	0.604
≤ 7 cm	4.78 (4.27, 5.39)	
TNM stage		
I-II	4.44 (4.18, 5.04)	0.040
III-IV	4.99 (4.34, 5.98)	
Degree of differentiation		
Low-medium	4.41 (4.17, 4.82)	0.004
High	5.12 (4.44, 6.85)	
Location		
Cervical	4.28 (4.15, 4.71)	0.344
Upper thoracic	4.68 (4.40, 5.41)	
Middle thoracic	5.23 (4.43, 5.60)	
Lower thoracic	4.93 (4.38, 5.29)	
X-ray typing		
Medullary	4.26 (4.13, 4.44)	0.089
Fungating	5.08 (4.44, 6.43)	

Ulcerative	4.78 (4.42, 5.73)
Constrictive	4.78 (4.48, 5.18)

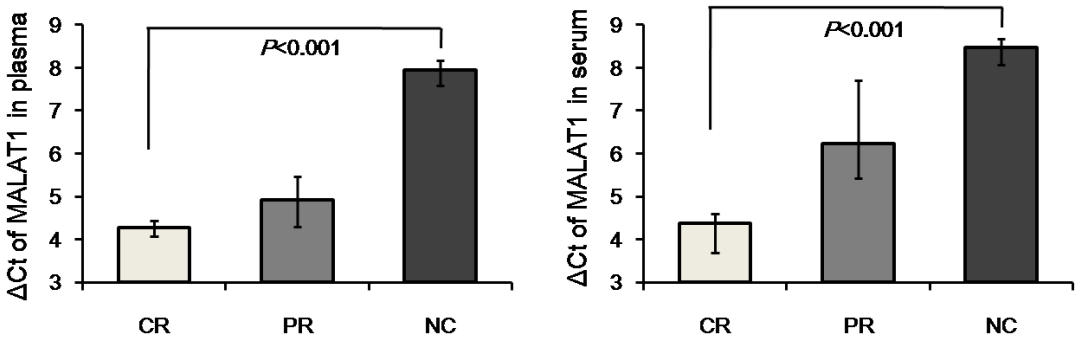

Figure 2. Relationship between MALAT1 expression and short-term efficacy of radiotherapy. CR, complete remission; PR, partial remission; NC, no change.

MALAT1 regulates cell proliferation, apoptosis, and radioresistance via targeting miR-145

Next, we investigated the molecular function of MALAT1 in ESCC cell line EC9706. siRNA approach was employed to knock down endogenous MALAT1 expression in EC9706 cell. As shown in Figure 3A, depletion of MALAT1 resulted in decreased cell growth curve. Knockdown of MALAT1 also promoted cell apoptosis (Figure 3B). The fraction of apoptotic cells in siRNA group was 24.81%, significantly higher than that in control group (15.64%). Clinical data suggested that MALAT1 played a role in radiotherapy efficacy. We then tested the effect of MALAT1 expression on cell radioresistance. As shown in Figure 3C, irradiation damaged cells and slowed down the growth rate of cells in all groups. On the other hand, the cells transfected with siRNA were the slowest growing cells in all groups, and it was more difficult to recover from irradiation damage. Caspase-3 activity plays an important role in radioresistance of cells. The caspase-3 activity in siRNA group increased more after irradiation than that in control group (P<0.001). Previous studies indicated that MALAT1 could negatively regulate miRNA-145 expression in cervical cancer, and miRNA-145 has anti-cancer role in esophageal cancer (13,18). We tested the

relationship between MALAT1 and miR-145 expression in EC9706 cell. There was also a negative correlation between these two molecular. The results suggested that reducing MALAT1 was beneficial for enhancing cell radiosensitivity, probably via targeting miR-145.

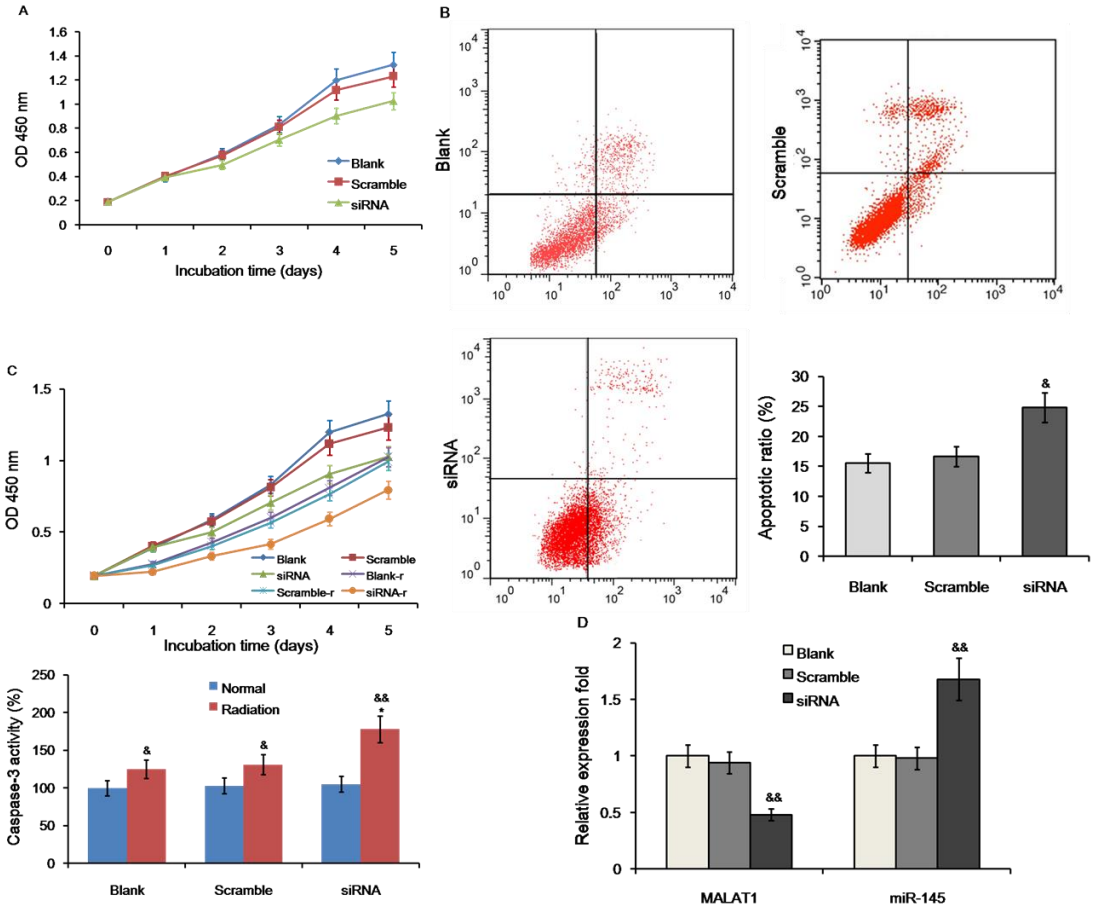

Figure 3. MALAT1 regulates cell proliferation, apoptosis, and radioresistance of EC9706 cells. Knockdown of MALAT1 inhibited cell proliferation (A), promoted cell apoptosis (B), and enhanced radiosensitivity (C). D: There was a genitive correlation between MALAT1 and miR-145 expression. &, P<0.05 vs. blank (of normal); &&, P<0.01 vs. blank (of normal); *, P<0.05 vs. blank of radiation.

Discussion

Numerous studies have indicated that miRNAs could be used as biomarkers of cancer diagnosis and prognosis. The utility of lncRNAs as tumor biomarkers is in the

ascendant. Radiotherapy is the first line therapy for advanced ESCC patients. Our study explored the possibility of applying blood-based MALAT1 in predicting short-term efficacy of radiotherapy in ESCC. The results showed that high MALAT1 expression level in either plasma or serum was associated with poor prognosis. Molecular experiments showed that knockdown of MALAT1 inhibited cell growth, promoted apoptosis, and enhanced radiosensitivity, probably via targeting miR-145.

MALAT1 is a lncRNA which over express in a wide range of cancers such as NSCLC, breast cancer, and prostate cancer (19-21). Generally MALAT1 can predict poor prognosis and is especially associated with tumor metastasis (22,23). In ESCC, MALAT1 was tightly related to lymphatic invasion and distant metastasis (8). Our study also showed that MALAT1 was associated with tumor differentiation. Numerous studies have reported that MALAT1 could drive tumorigenesis through promoting tumor cell proliferation, increasing cell migration and invasion (24-27). Our study showed consistent results that depletion of MALAT1 could inhibit cell growth and promote apoptosis in ESCC. A previous study showed that overexpression of MALAT1 inhibited irradiation-induced cell damage in ESCC (28), which illustrated the tumorigenesis role of MALAT1 in ESCC on the other hand.

Current studies indicate that MALAT1 is involved in chemoresistance and radioresistance. In many cases, lncRNA functions as a miRNA sponge to effect chemoresistance. In gastric cancer, MALAT1 regulated chemoresistance through influencing autophagy and miR-23b-3p sequestration mediated this process (29). MALAT1 modulated chemoresistance of lung adenocarcinoma cells by sponging miR-200b (30). MALAT1 was associated with poor response to oxaliplatin treatment of colorectal cancer via interacting with miR-218 (31). Knockdown of MALAT1 could reverse chemoresistance to temozolomide via promoting miR-101 regulatory network in glioblastoma (32). A MALAT1/miR-145-5p/AKAP12 axis existed in docetaxel sensitivity of prostate cancer cells (33). Knockdown of MALAT1 could sensitize nasopharyngeal carcinoma cells to radiation by modulating miR-1/slug axis (34). MALAT1 expression was significantly higher in radioresistant than in

radiosensitive cervical cancer cases; MALAT1 and miR-145 had reciprocal repression and synergistically affected cell growth [13]. The MALAT1/miR-145 axis also existed in our study. miR-145 has been reported in many studies to inhibit cell proliferation, promote apoptosis, suppress migration and risk of metastasis in ESCC (35-37).

Overall, our study identified the role of MALAT1 in short-term efficacy of radiotherapy in ESCC patients and radioresistance of ESCC cells. MALAT1 could be used as a potential prognostic marker of ESCC. However, the value of MALAT1 as a prognostic marker needs to be further clarified by long-term follow-up studies. The sensitivity and specificity of MALAT1 needs to be explored by large sample population studies.

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