High expression of TRIM36 is associated with radiosensitivity in gastric cancer

ZHONGSONG MAN[1*], TAO CHEN[1*], ZHONGWEI ZHU[1*], HAITAO ZHANG[1], LEI AO[2], LITING XI[3], JIN ZHOU[1] and ZAIXIANG TANG[2,4]

[1]Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006; [2]Department of Biostatistics, School of Public Health, Medical College of Soochow University, Suzhou, Jiangsu 215123; [3]Department of Gastroenterology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006; [4]Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, Medical College of Soochow University, Suzhou, Jiangsu 215123, P.R. China

Received July 18, 2018; Accepted February 11, 2019

DOI: 10.3892/ol.2019.10122

Abstract. Radiotherapy is one of the main adjuvant treatments for gastric cancer (GC) that can effectively reduce local recurrence and improve survival rates. However, radiotherapy may result in cytotoxicity and not benefit all patients. This highlights the requirement for identifying potential radiosensitivity genes in GC. The current study investigated the association between tripartite motif containing 36 (TRIM36) status and the prognosis of patients with GC receiving radiotherapy. A total of 371 patients with GC were selected from The Cancer Genome Atlas and randomly divided into test and the validation groups. The results revealed that TRIM36 expression was not associated with the overall survival (OS) rate. Patients who received radiotherapy with high TRIM36 expression had an improved OS rate compared with patients who did not receive radiotherapy in the test group, as demonstrated by univariate analysis [hazard ratio (HR), 0.062; 95% confidence interval (CI), 0.008-0.462; P=0.007] and multivariate analysis (HR, 0.095; 95% CI, 0.012-0.748; P=0.025). In the validation group, patients with high TRIM36 expression had decreased mortality risk when they received radiotherapy compared with patients who did not receive radiotherapy, as determined by univariate analysis (HR, 0.190; 95% CI, 0.067-0.540; P=0.002) and multivariate analysis (HR, 0.075; 95% CI, 0.020-0.276; P<0.001). However, for patients with low expression, no significant difference was identified in the overall survival rates between the radiotherapy and non-radiotherapy groups. Chi-squared analysis revealed that the expression status of TRIM36 was an independent factor and was not associated with clinicopathological factors. The results indicated that patients with high TRIM36 expression receiving radiotherapy exhibited an improved OS rate. TRIM36 may therefore be an important factor affecting the clinical prognosis of patients with GC receiving radiotherapy and may be considered as a potential radiosensitivity gene signature.

Correspondence to: Professor Zaixiang Tang, Department of Biostatistics, School of Public Health, Medical College of Soochow University, 199 Renai Road, Suzhou, Jiangsu 215123, P.R. China
E-mail: tangzx@suda.edu.cn

Professor Jin Zhou, Department of General Surgery, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou, Jiangsu 215006, P.R. China
E-mail: 13913506396@163.com

*Contributed equally

Key words: gastric cancer, radiosensitivity gene signature, outcome, tripartite motif containing 36, the cancer genome atlas

Introduction

Gastric cancer (GC) is a common cancer and the second leading cause of cancer mortalities worldwide (1). GC is a multifactorial disease that involves oncogene activation and tumor suppressor gene inactivation (2). The majority of patients are at stage III and IV when diagnosed and the 5-year survival rate is as low as 5% (3). Gene mutations may affect the proliferation, invasion and metastasis of cancer cells and the prognosis of patients with GC (4-6), and elucidating the pathways involved in these mutations may improve the diagnosis, treatment and prognosis of GC.

Radiotherapy serves an important role in the treatment of various types of cancer and the National Comprehensive Cancer Network guidelines recommend adjuvant chemoradiotherapy as a standard treatment for postoperative patients with GC (7). Advances in radiotherapy protocols and precise radiotherapy techniques have improved the efficacy of radiotherapy (8). However, the efficacy can vary for certain patients with similar pathologies and radiotherapy regimens, and radiotherapy is highly toxic to normal tissues (9). Therefore, the identification of genes involved in radiation sensitivity may improve patient outcomes.

In the context of radiation therapy, E3 ubiquitin ligase has been revealed to sensitize tumor cells to radiation, and is thought to be involved in the regulation of apoptosis, the

cell cycle and DNA damage repair (10,11). Tripartite motif containing 36 (TRIM36) has unique E3 ubiquitin ligase activity and serves an important role in transcriptional regulation, cell proliferation, apoptosis and regulation of the p53 signaling pathway (12,13). p53 inactivation may significantly modulate the sensitivity of tumor cells to radiation and chemotherapeutic drugs (14,15). Conventional radiotherapy may cause DNA damage and activation of the DNA damage response, resulting in the expression of the p53 gene (16,17). DNA repair is a regulatory mechanism to overcome cell damage and avoid genomic instability (18). TRIM36 serves a key role in regulating the stability and function of the p53 protein and may therefore affect the efficacy of radiotherapy (19).

In the present study, The Cancer Genome Atlas (TCGA; cancergenome.nih.gov; updated September 2017) database was used to summarize the clinicopathological features that affect the prognosis of patients with GC. TRIM36 mRNA expression levels were used to divide the patients into different groups and cross-validation was performed to analyze the association between TRIM36 status and the prognosis of patients with GC receiving radiotherapy.

Materials and methods

Clinicopathological and RNA-sequencing data. Clinical information and TRIM36 mRNA sequencing data of patients with GC were downloaded from TCGA using the TCGA-Assembler tool on R software (version 3.4.0; www.r-project.org). The data disposal process was as follows: The clinical data were merged to obtain the patient survival information, patients without a survival time or survival outcome were excluded and the data were subsequently merged with other clinical data to obtain a complete clinical document; duplicated individuals were removed; the final 371 patients were included in the statistical analysis. Clinicopathological data included survival time, sex, age at illness and mortality, histology type, Tumor-Node-Metastasis (TNM) stage and grade, residual tumor and chemotherapy and radiotherapy received.

Radiosensitivity gene TRIM36 groups. The 371 samples were divided into the test group and the validation group. The test group and the validation group were further divided into high-expression and low-expression subgroups according to the median level of TRIM36 in the test group. Each group of stage III and IV patients was combined to investigate the association between TRIM36 expression status and radiosensitivity.

Statistical analysis. The digital database of clinicopathological information and TRIM36 expression status of the 371 patients was established using R software. The TRIM36 status below the median was defined as '0' and TRIM36 at or above the median was defined as '1'. The association between TRIM36 expression and clinicopathology was examined using the Chi-squared test. Kaplan-Meier survival analysis was performed to determine the radiotherapy factor for OS and a log-rank test was used to compare the radiotherapy and non-radiotherapy groups. Univariate Cox proportional hazards regression was used to evaluate the effect of a single factor. To control confounding variables, multivariate Cox proportional hazards regression models were generated with the significant clinicopathological factors. Statistical analyses were performed using the packages 'survival' and 'rms' packages in R software. $P<0.05$ was considered to indicate a statistically significant difference. All of the statistical analyses were performed twice to ensure accuracy.

Results

Patients and tumor characteristics. The mean patient age was 65 years (range, 30-90 years). Univariate analysis revealed that TNM-stage (P=0.001), T-stage (P=0.007), N-stage (P=0.001), tumor grade (P=0.001), residual tumor (P=0.001), targeted therapy (P=0.018) and radiotherapy (P=0.001) were statistically significant for the overall survival (OS) rate in all patients. Multivariate analysis revealed that residual tumor (P=0.003) and radiotherapy (P=0.005) served important roles in GC outcome in all patients. TRIM36 expression status was not associated with the OS rate in the three groups (Table I).

Association between TRIM36 expression and clinicopathological parameters. Analysis of the association between TRIM36 status and other clinical factors was performed using the Chi-squared test (Table II). The expression status of TRIM36 was independent of histology (P=0.951), TNM-stage (P=0.750), distant metastasis (P=0.723) and tumor grade (P=0.811). The expression of genes associated with prognosis in patients with a tumor is often associated with clinicopathological factors (20-22). However, in the current study TRIM36 expression status was not associated with clinical and pathological factors.

Analysis of TRIM36 gene expression in the test group. The total number of samples was divided into test and validation groups. Survival rate analysis was performed in the test group. Based on the median value of TRIM36 expression in the test group, the group was divided into high- and low-expression subgroups. In the high TRIM36 expression subgroup, the OS rate of patients treated with radiotherapy was significantly increased compared with patients who did not receive radiotherapy (Fig. 1A). The OS rate was not associated with whether patients had received radiotherapy in the low expression subgroup (Fig. 1B).

Multivariate Cox proportional hazard regression models for the test group of patients were generated according to the following clinicopathological characteristics: Sex, age, histological type, TNM-stage, tumor grade, residual tumor, positive lymph nodes and targeted therapy. The multivariate Cox proportional hazard regression analysis (Table III) revealed that while the OS rate of patients with GC receiving radiotherapy in the high-expression subgroup was increased [hazard ratio (HR), 0.095; 95% confidence interval (CI), 0.012-0.748; P=0.025], there was no difference in the OS rate in the low-expression subgroup (P=0.643).

Analysis of TRIM36 expression in the validation group. The same statistical analysis as described for the test group was performed in the validation group. The results suggested that radiotherapy was associated with increased OS in the high TRIM36 expression subgroup (Fig. 1C). No difference in the OS rate between patients with GC receiving radiotherapy

Table I. Clinical characteristics in the test, validation and all patients groups.

	Test group (n=185)				Validation group (n=186)				All patients (n=371)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Characteristic	HR	P-value	HR	P-value	HR	P-value	HR	P-value	HR	P-value	HR	P-value
Sex												
Male	1.578 (0.893-2.787)	0.116	1.458 (0.755-2.815)	0.260	1.066 (0.679-1.673)	0.780	1.515 (0.873-2.628)	0.140	1.243 (0.882-1.752)	0.214	1.521 (0.999-2.315)	0.051
Female	1		1		1		1		1		1	
Age (years)												
>60	1.420 (0.862-2.338)	0.168	1.491 (0.797-2.791)	0.210	1.358 (0.793-2.327)	0.265	1.534 (0.769-3.061)	0.224	1.407 (0.979-2.024)	0.065	1.332 (0.849-2.089)	0.212
≤60	1		1		1		1		1		1	
Histology												
MT+DT+ST	0.413 (0.201-0.847)	0.016	0.461 (0.181-1.171)	0.103	1.768 (0.907-3.447)	0.093	1.659 (0.600-4.524)	0.331	0.878 (0.543-1.417)	0.594	1.057 (0.578-1.932)	0.858
NOS	0.830 (0.475-1.450)	0.511	0.978 (0471-2.032)	0.953	1.646 (0.897-3.021)	0.107	1.514 (0.700-3.217)	0.291	1.172 (0.779-1.765)	0.446	1.128 (0.695-1.832)	0.625
PT+TT	1		1		1		1		1		1	
TNM-stage												
II	1.482 (0.592-3.713)	0.401	0.460 (0.111-1.896)	0.282	1.723 (0.634-4.687)	0.286	1.377 (0.283-6.703)	0.690	1.586 (0.807-3.117)	0.181	1.110 (0.349-3.531)	0.859
III	2.158 (0.896-5.196)	0.086	0.419 (0.066-2.635)	0.353	2.773 (1.096-7.017)	0.031	2.680 (0.297-24.14)	0.379	2.448 (1.297-4.622)	0.006	0.967 (0.103-8.918)	0.969
IV	3.390 (1.200-9.575)	0.021	0.274 (0.037-2.015)	0.203	4.025 (1.372-11.80)	0.011	2.925 (0.145-58.96)	0.484	3.636 (1.729-7.646)	0.001	1.215 (0.067-22.05)	0.895
I	1		1		1		1		1		1	
T-stage												
T3	2.154 (1.105-4.200)	0.024	2.808 (1.011-7.796)	0.047	1.467 (0.813-2.647)	0.203	0.546 (0.204-1.465)	0.230	1.756 (1.133-2.273)	0.012	1.559 (0.778-3.128)	0.210
T4	2.413 (1.147-5.074)	0.020	3.052 (0.935-9.956)	0.064	1.574 (0.635-2.937)	0.154	0.551 (0.182-1.668)	0.292	1.917 (1.192-3.083)	0.007	1.756 (0.801-3.847)	0.159
T1-T2	1		1		1		1		1		1	
N-stage												
N1	1.562(0.834-2.926)	0.164	2.853 (1.088-7.478)	0.033	1.900 (0.945-3.823)	0.072	1.078 (0.304-3.817)	0.906	1.694 (1.063-2.697)	0.027	1.635 (0.775-3.452)	0.197
N2	1.051 (0.481-2.298)	0.900	1.580 (0.433-5.769)	0.488	2.418 (1.163-5.025)	0.017	1.295 (0.284-5.902)	0.738	1.640 (0.975-2.758)	0.062	1.908 (0.738-4.926)	0.182
N3	2.421 (1.266-4.629)	0.008	3.985 (1.088-14.59)	0.036	3.039 (1.508-6.125)	0.002	1.358 (0.307-5.988)	0.686	2.652 (1.654-4.250)	0.001	2.777 (1.074-7.179)	0.035
N0	1		1		1		1		1		1	
M-stage												
M1	2.563 (1.223-5.880)	0.014	0.774 (0.183-3.269)	0.728	1.315 (0.692-2.499)	0.403	0.791 (0.095-6.575)	0.829	1.836 (0.991-3.401)	0.054	0.403 (0.123-1.316)	0.132
M0	1		1		1		1		1		1	
Tumor-grade												
G3	1.168 (0.713-1.916)	0.536	1.212 (0.621-2.363)	0.573	1.702 (1.059-2.738)	0.028	1.524 (0.773-3.000)	0.223	1.344 (1.136-1.591)	0.001	1.090 (0.490-2.420)	0.833
G1-G2	1		1		1		1		1		1	
Residual												
R1	3.091 (1.318-7.251)	0.009	4.843 (1.543-15.17)	0.007	1.000 (0.311-7.251)	0.991	0.878 (0.234-3.291)	0.848	1.786 (0.902-3.539)	0.096	2.017 (0.934-4.355)	0.074
R2	10.27 (5.185-20.34)	0.001	8.025 (2.801-22.99)	0.001	3.727 (1.695-8.196)	0.001	3.491 (0.721-16.89)	0.120	6.180 (3.096-12.34)	0.001	4.517 (1.659-12.29)	0.003
R0	1		1		1		1		1		1	

Table I. Continued.

	Test group (n=185)				Validation group (n=186)				All patients (n=371)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Characteristic	HR	P-value	HR	P-value	HR	P-value	HR	P-value	HR	P-value	HR	P-value
Targeted therapy												
Yes	0.545 (0.335-0.886)	0.014	0.557 (0.279-1.112)	0.097	0.810 (0.517-1.271)	0.361	1.017 (0.520-1.989)	0.959	0.672 (0.484-0.933)	0.018	0.863 (0.547-1.362)	0.527
No	1		1		1		1		1		1	
Radiotherapy												
Yes	0.377 (0.186-0.765)	0.007	0.541 (0.212-1.324)	0.178	0.429 (0.230-0.810)	0.008	0.401 (0.163-0.988)	0.047	0.405 (0.253-0.646)	0.001	0.408 (0.217-0.765)	0.005
No	1		1		1		1		1		1	
TRIM36 expression												
High	0.815 (0.512-1.299)	0.390	1.234 (0.691-2.204)	0.476	0.753 (0.468-1.213)	0.244	0.939 (0.520-1.696)	0.837	0.761 (0.553-1.048)	0.095	0.828 (0.565-1.215)	0.335
Low	1		1		1		1		1		1	

HR, hazard ratio; ST, signet ring type; DT, diffuse type; MT, mucinous type; PT, papillary type; TT, tubular type; TRIM36, tripartite motif containing 36; R, residual; T, tumor; G, grade; M, metastasis; N, node; NOS, not otherwise specified; TNM, Tumor-Node-Metastasis.

Table II. Association between TRIM36 expression and clinicopathological features of patients with gastric cancer.

	TRIM36 expression status			
Feature	High	Low	χ^2 value	P-value
Sex			0.032	0.858
Female	64	66		
Male	121	120		
Age (years)			0.166	0.784
≤60	59	56		
>60	124	129		
Histology				
PT+TT	40	42	0.101	0.951
DT+ST+MT	40	47		
NOS	82	94		
TNM-stage			0.101	0.750
I-II	87	84		
III-IV	91	94		
T-stage			0.103	0.748
T1-T2	51	48		
T3-T4	133	135		
N-stage			0.940	0.332
N0-N1	113	104		
N2-N3	67	76		
M-stage			0.125	0.723
M0	170	169		
M1	15	17		
Tumor grade			0.057	0.811
G1-G2	72	69		
G3	110	111		
Residual			0.001	0.972
R0	156	154		
R1-R2	17	17		

PT, papillary type; TT, tubular type; ST, signet ring type; DT, diffuse type; MT, mucinous type; NOS, not otherwise specified; T, tumor; N, node; M, metastasis; G, grade; R, residual; TRIM36, tripartite motif containing 36; TNM, Tumor-Node-Metastais.

and those not receiving radiotherapy was observed in the low TRIM36 expression subgroup (Fig. 1D). Multivariate Cox proportional hazard regression analysis (Table III) revealed that patients with GC that received radiotherapy displayed improved OS rates when compared with patients with GC that did not receive radiotherapy in the high expression group (HR, 0.075; 95% CI, 0.020-0.276; P<0.001). However, in the low expression subgroup, the OS rate of patients with GC that received radiotherapy was not different compared with patients with GC that did not receive radiotherapy (P=0.661).

Analysis of TRIM36 expression in all patients. The 371 samples were divided into high and low expression subgroups according to the median expression level of TRIM36 in the test group. Univariate analysis revealed that patients with high expression that received radiotherapy had a lower risk of mortality (Fig. 1E) compared with those that did not receive radiotherapy, and that radiotherapy did not affect mortality in the low expression

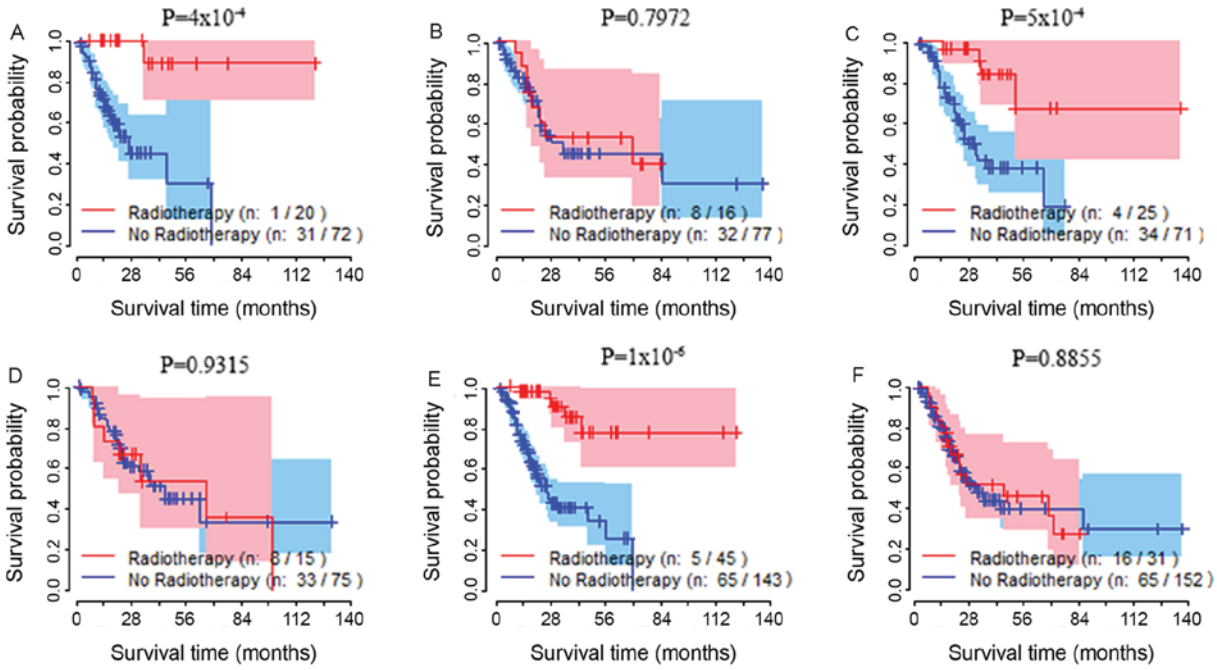

Figure 1. OS rate curves plotted for patients treated with radiotherapy and without radiotherapy with high and low tripartite motif containing 36 expression. (A) High expression in the test group. (B) Low expression in the test group. (C) High expression in the validation group. (D) Low expression in the validation group. (E) High expression in all patients. (F) Low expression in all patients. The colored areas denote the 95% confidence intervals for the OS rate. n, number of patients; OS, overall survival.

subgroup (Fig. 1F). Multivariate analysis revealed that there was no difference in OS rates in patients that received radiotherapy compared with those that did not receive radiotherapy in the low expression subgroup (P=0.658; Table III). However, the OS rate of patients that received radiotherapy was significantly improved when compared with those that did not receive chemotherapy in the high expression subgroup (HR, 0.094; 95% CI, 0.030-0.296; P<0.001). Univariate and multivariate analysis revealed that radiotherapy significantly increased the OS rate of patients with high expression of TRIM36 compared with patients with low expression.

Association between tumor stage, TRIM36 status, radiotherapy and OS rate. Patients with TNM-stage I, II, III and IV cancer were analyzed separately. Patients with stage III and IV cancer were grouped together, due to the small sample size of patients with stage IV cancer. According to the aforementioned statistical methods, for each subgroup analysis, survival analysis revealed that patients presenting with stage III/IV, a high TRIM36 expression level and had received radiotherapy had significantly increased OS rates compared with patients with a high expression level that did not receive radiotherapy. The survival curves of the test group, the validation group and the total sample group are presented in Fig. 2A, C and E, respectively. In the test, validation and total sample groups, there was no difference in the OS rates of patients with stage III/IV that had low TRIM36 expression and had received radiotherapy compared to those that did not receive radiotherapy (Fig. 2B, D and F).

Discussion

Personalized radiotherapy an important factor in the development of radiology (23). In the present study, the OS rate of patients with high TRIM36 expression receiving radiotherapy was increased compared with patients with low TRIM36 expression receiving radiotherapy. This suggested that the TRIM36 gene may be a useful prognostic biomarker for patients with GC receiving radiotherapy. To the best of the authors' knowledge, the current study is the first to establish an association between radiosensitivity and TRIM36 expression status in patients with GC.

The American Joint Committee on Cancer staging system is a widely used clinical prognostic indicator for malignant tumors (24). In the current study, an association between high TRIM36 expression and sensitivity to radiotherapy was established. The majority of patients receiving postoperative radiotherapy for GC were patients with TNM-stage III and IV. To avoid interference of TNM-stage on OS, patients with III-IV cancer in the three groups were analyzed separately. Survival analysis was performed on high and low TRIM36 expression subgroups with and without radiotherapy in patients with stage III/IV GC. The OS rate of patients with stage III/IV GC that had high TRIM36 expression was increased in those that received radiotherapy compared with those who did not receive radiotherapy. This suggested that TRIM36 may be involved in radiotherapy sensitivity in GC.

Gene expression in tumor tissues is usually associated with clinicopathological factors (20-22). The overexpression of programmed death-ligand 1 was beneficial in patients with breast carcinoma that received radiotherapy and the expression status was affected by intrinsic subtypes (20). Previous studies have reported that high expression levels of chromosomal maintenance 1 (CRM1) or cyclin dependent kinase 5 (CDK5) in GC lead to increased OS rates when compared with low expression levels. The expression level of CRM1 was associated with lymph node metastasis and the TNM-stage, and

Table III. Association between RT and overall survival rate in tripartite motif containing 36 high and low expression subgroups.

A, Test group

		Univariate analysis (RT vs. no RT)		Multivariate analysis (RT vs. no RT)	
Expression level	Number of patients	HR	P-value	HR	P-value
High	92	0.062 (0.008-0.462)	0.007	0.095 (0.012-0.748)	0.025
Low	93	0.902 (0.411-1.981)	0.797	0.786 (0.283-2.183)	0.643

B, Validation group

		Univariate analysis (RT vs. no RT)		Multivariate analysis (RT vs. no RT)	
Expression level	Number of patients	HR	P-value	HR	P-value
High	96	0.190 (0.067-0.540)	0.002	0.075 (0.020-0.276)	<0.001
Low	90	1.035 (0.467-2.294)	0.931	0.804 (0.304-2.127)	0.661

C, All patients

		Univariate analysis (RT vs. no RT)		Multivariate analysis (RT vs. no RT)	
Expression level	Number of patients	HR	P-value	HR	P-value
High	188	0.133 (0.053-0.334)	<0.001	0.094 (0.030-0.296)	<0.001
Low	183	0.959 (0.549-1.674)	0.884	1.079 (0.421-1.725)	0.658

RT, radiation therapy; HR, hazard ratio.

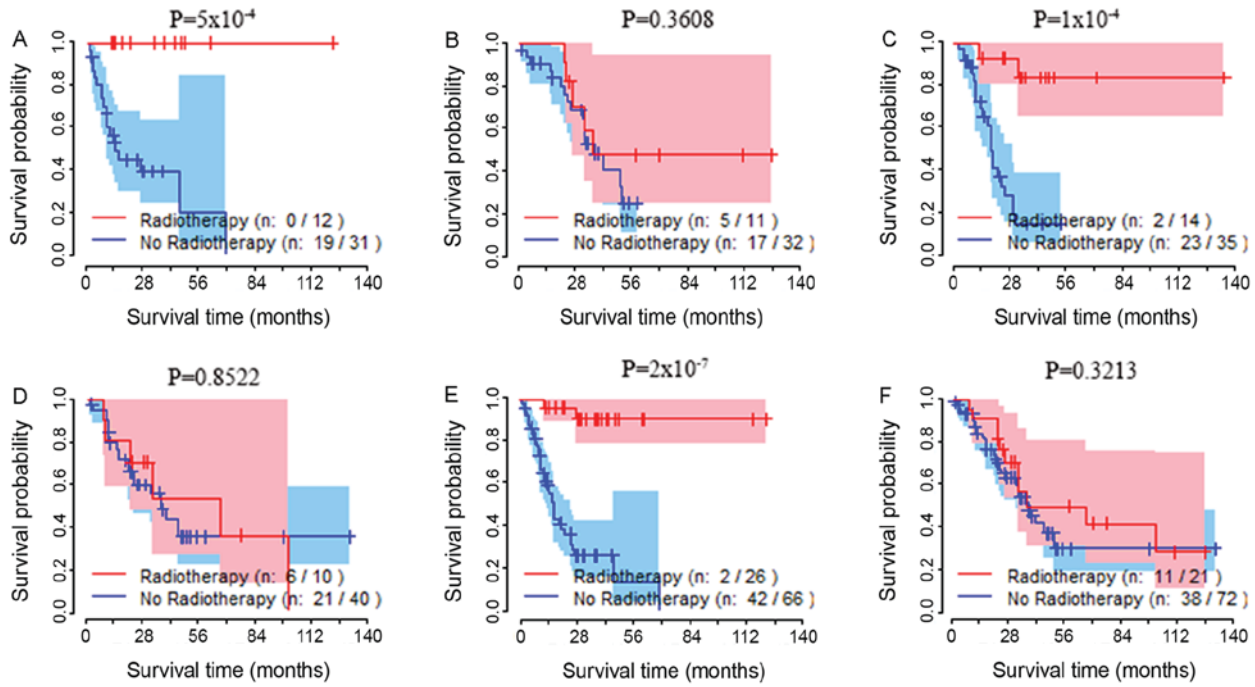

Figure 2. Overall survival rate curves plotted for patients with stage III/IV gastric cancer treated with radiotherapy and without radiotherapy with high and low tripartite motif containing 36 expression. (A) High expression in the test group with stage III/IV cancer. (B) Low expression in the test group with stage III/IV cancer. (C) High expression in the validation group with stage III/IV cancer. (D) Low expression in the validation group with stage III/IV cancer. (E) High expression in all patients with stage III/IV cancer. (F) Low expression in all patients with stage III/IV cancer. n, number of patients.

CDK5 expression levels were associated with sex and Lauren's classification (21). In the present study, TRIM36 expression levels were an independent factor, suggesting that TRIM36 may be a radiosensitivity gene signature in GC radiotherapy.

E3 ubiquitin ligases are divided into two major groups: The homologous to the E6-AP carboxyl terminus family and the really interesting new gene finger-containing protein family (25). The latter is the larger group and binds to E2 ubiquitin ligase to promote ubiquitination (26-28). Studies have revealed that E3 ubiquitin ligases may be involved in the occurrence of GC, and that they are highly expressed in malignant gastric tumors (4,29). E3 ubiquitin ligase is an oncogene that is highly expressed in patients with GC with a poor prognosis (29). However, studies have shown that E3 ubiquitin ligase may have a tumor suppressor function in GC (30,31) as E3 ubiquitin ligase is often deregulated during the development of GC. The specific mechanism and role of E3 ubiquitin ligase in the treatment of GC requires further study.

The p53 signaling pathway is a central regulator of cell proliferation that directly regulates the transcription of genes involved in the cell cycle and DNA repair (32-34). The primary mechanism of p53 signaling in the repair of cellular DNA is ubiquitination (35). The E3 ubiquitin ligase is a negative regulator of p53 and mainly exerts its effects via degradation of p53 and inhibition of the transcriptional target of p53 (10,11). It can be speculated that high expression of TRIM36 may enhance sensitivity to radiotherapy by inhibiting the p53 signaling pathway via its own unique E3 ubiquitin ligase structure. The extracellular signal-regulated kinase (ERK) signaling pathway regulates cell proliferation, differentiation and survival, and mediates and amplifies signals during tumor invasion and metastasis (36). Previous studies have demonstrated that the extracellular signal-regulated kinase (ERK) signaling pathway is associated with tumor radiation resistance (37,38). In addition, previous studies have indicated that TRIM36 serves an inhibitory effect on the ERK signaling pathway in prostate cancer (39). Based on these studies, TRIM36 may increase radiosensitivity by inhibiting the ERK signaling pathway in GC.

Radiosensitivity of the tumor is linked to the immune response, and radiation itself is considered to be immunosuppressive (40,41). The TRIM family is involved in immunity and carcinogenesis in cellular processes. TRIM36 may serve an important role in the process of radiation immunity by inducing cancer cells to undergo apoptosis. TRIM proteins have been studied in numerous types of cancer, and TRIM overexpression has been observed in GC. However, the molecular mechanism linking TRIM overexpression and GC pathology remains unclear. A previous study suggested that the TRIM25 gene enhanced cell migration and invasion by activating the transforming growth factor β pathway in GC, and that overexpression of TRIM25 resulted in poor outcomes (42). TRIM44 and TRIM59 are also associated with GC, and a high expression was associated with poor outcome (22,43). Previous research has demonstrated that TRIM59 promotes gastric tumorigenesis through suppression of downstream signals of p53 (43). The results obtained from these studies suggested that high expression of TRIM resulted in poor GC prognosis. However, the current study revealed that the expression of TRIM36 is not associated with the prognosis of GC; however, high expression may be associated with improved OS rates of patients receiving radiotherapy. Based on the results obtained in the current study, TRIM36 may be associated with the radiosensitivity in GC. However, the biological pathways involved remain to be explored.

The current study has certain limitations. First, a sample size of 371 is relatively small. However, this limitation was partially overcome using a cross-validation strategy to investigate the association between TRIM36 expression and radiosensitivity. Second, TRIM36 is located on chromosome 5q22.3, which frequently contains DNA alterations in tumor (44). The mRNA level of TRIM36 may not accurately represent the expression of the TRIM36 gene. Therefore, using the median mRNA expression level of TRIM36 to divide groups could cause a bias. Finally, potential bias could arise from variation in the follow-up information obtained from TCGA due to the retrospective nature of the TCGA cohort.

In conclusion, the current study demonstrated the potential predictive and prognostic value of TRIM36 expression status in a TCGA dataset of patients with GC that received radiotherapy. However, further studies are required to validate the predictive value of this potential biomarker. High TRIM36 expression levels were associated with improved clinical prognosis in patients with GC receiving radiotherapy, possibly through the downregulation of the p53 signaling pathway. The results obtained in the current study provide novel insights into the treatment of GC, any may be particularly useful for clinical trials determining radiation resistance and sensitivity in patients.

Acknowledgements

Not applicable.

Funding

This work was supported in part by the National Natural Science Foundation of China (grant nos. 81773541 and 81573253), Jiangsu Provincial Key Project in Research and Development of Advanced Clinical Technique (BL2018657), Key Investigation and Development Program of China (2016YFC0904700 and 2016YFC0904702) and the Jiangsu Provincial Medical Youth Talent Project of Invigorating Health Care through Science Technology and Education (grant no. QNRC2016733).

Availability of data and materials

The datasets generated and analyzed during the current study are available in The Cancer Genome Atlas repository (http://cancergenome.nih.gov/).

Authors' contributions

ZM, JZ, ZT, TC and ZZ conceived and designed the study. ZM, TC and ZZ drafted the manuscript. TC and ZZ collected data for the manuscript from the TCGA database. ZM, TC and ZZ drafted the manuscript. HZ, LA and LX performed the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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