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Original Article

Role of ERCC1 and ERCC2 genetic polymorphisms in the sensitivity of esophageal squamous cell carcinoma to radiochemotherapy in a Chinese population

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Abstract: Here, we performed a case-control study to assess the relationship between ERCC1 (rs11615 and rs3212986) and ERCC2 (rs13181 and rs1799793) polymorphisms and response to radiochemotherapy and overall survival in esophageal squamous cell carcinoma. This case-control study is comprised of 142 esophageal squamous cell carcinoma patients. The esophageal squamous cell carcinoma patients were selected between February 2010 and February 2012. The ERCC1 (rs11615 and rs3212986) and ERCC2 (rs13181 and rs1799793) polymorphisms was evaluated using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). As determined by a multiple logistic regression analysis, the TT genotype (OR=11.36, 95% CI=3.93-32.81) and CT+TT genotype (OR=6.46, 95% CI=2.92-14.39) of *ERCC1* rs11615 was correlated with more CR+PR when compared with the CC genotype. The median survival times of individuals carrying the TT genotype and CT+TT genotype of ERCC1 rs11615 were significantly higher than those with the CC genotype (*P* value for Log-rank test was 0.048). Multivariate logistic regression analyses revealed that individuals with the TT genotype (HR=0.32, 95% CI=0.13-0.83) and CT+TT genotype (HR=0.39, 95% CI=0.18-0.83) of *ERCC1* rs11615 were at decreased risk for death in esophageal squamous cell carcinoma patients as compared to those with the CC genotype. However, no significant relationship was observed between *ERCC1* rs3212986 and *ERCC2* rs13181 and rs1799793 genomic polymorphisms and response to radiochemotherapy and overall survival of esophageal squamous cell carcinoma patients. In summary, ERCC1 rs11615 genomic polymorphism was markedly correlated with response to radiochemotherapy and overall survival in patients with esophageal squamous cell carcinoma.

Keywords: ERCC1, ERCC2, polymorphism, esophageal squamous cell carcinoma, radiochemotherapy

Introduction

Human esophageal squamous cell carcinoma is one of the most malignant carcinoma all around the world, occurs at a very high frequency in China [1, 2]. Despite advances in combined treatment approaches, such as surgical treatment, radiotherapy and chemotherapy, the prognosis of ESCC remained quite poor [3, 4]. The poor prognosis of this cancer is mainly explained by early node metastasis and invasion of neighboring organs [5]. Recently, molecular targeted therapy has emerged as a focus of research on the treatment of esophageal squamous cell carcinoma [6]. Although extensive research has been conducted to understand the development and progression of esophageal squamous cell carcinoma, the exact mechanism has not been fully elucidated. Presently, no targeted therapeutic drugs are available for the clinical treatment of patients with esophageal squamous cell carcinoma. Therefore, in-depth studies of the molecular pathological mechanisms underlying the prognosis of esophageal squamous cell carcinoma and the search for efficient therapeutic targets are of great importance for improving the clinical prognosis of patients with esophageal squamous cell carcinoma.

It is well known that the current treatment method, such as radiotherapy and chemotherapy, play a role in damage tumor cell DNA and cause tumor cell apoptosis. Previous studies

have indicated that the DNA repair mechanism is an important genetic pathway involving in individualized sensitivity to chemotherapy and radiotherapy [7, 8]. DNA repair gene excision repair cross-complementing group 1 (ERCC1) plays an important role in nucleotide excision repair (NER), and is associated with repairing platinum-induced interstrand and intrastrand DNA cross-links in various cancers. Excision repair cross complementation group 1 (ERCC1) and ERCC2, two DNA repair genes, whose products are important in NER lie on chromosome 19q13.3 [9]. It is reported that since single nucleotide polymorphisms of ERCC1 and ERCC2 gene promoter may affect the expression and secretion of the protein, and subsequently the altered circulating levels might result in relevant biological responses, the ERCC1 and ERCC2 polymorphisms have been regarded as a crucial modulator in sensitivity to radiochemotherapy in various cancers [10-12]. Currently, only several studies reported the relationship between ERCC1 and ERCC2 polymorphisms and response to radiochemotherapy in esophageal squamous cell carcinoma, but the results are conflicting [10, 13-15]. In the present study, we performed a case-control study to assess the relationship between ERCC1 (rs11615 and rs3212986) and ERCC2 (rs13181 and rs1799793) polymorphisms and response to radiochemotherapy and overall survival in esophageal squamous cell carcinoma.

Material and methods

Patients

This case-control study is comprised of 142 esophageal squamous cell carcinoma patients. The esophageal squamous cell carcinoma patients were selected from the Inner Mongolia Cancer Hospital and General Hospital of Beijing Military Region between February 2010 and February 2012. All the patients were pathologically confirmed to have esophageal squamous cell carcinoma by two pathologists. Subjects who had received radiotherapy and/or chemotherapy before recruitment were excluded. All patients were followed-up by telephone calls or hospital visits every four weeks. All patients were followed up for 3.2 to 60 months. The mean follow-up time was 33.72±14.89 months.

Neoadjuvant chemotherapy prior to radiotherapy was carried out to 21 patients and the chemotherapy regimen were paclitaxel plus platinum or fluoropyrimidine plus platinum for two weeks for up to three cycles. Concurrent radiochemotherapy was carried out to 57 patients, and the regimen was fluoropyrimidine plus platinum, taxanes plus platinum or irinotecan plus platinum. The adjuvant chemotherapy after radiotherapy was performed for 64 patients, and the regimen was taxanes plus platinum. All the chemotherapy was performed every three weeks less than three cycles. The median dose of radiotherapy was about 60 Gy, and a daily dose was about 1.8 to 2.0 Gy with five times a week.

Response to radiochemotherapy was determined using Computed Tomography (CT) scan after completion of radiotherapy dose or adjuvant chemotherapy, and the tumor response criteria was evaluated according to Response Evaluation Criteria in Solid Tumors (version 1.1), including complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). CR and PR were categorized to be good response, and SD and PD were considered as poor response.

One month after completion of radiotherapy, all patients were examined again with CT scans of the neck and chest in order to evaluate treatment response and toxicity. This study was approved by the Inner Mongolia Cancer Hospital and General Hospital of Beijing Military Region Ethics Committee, and all patients signed an informed consent form before therapy.

General clinical data of esophageal squamous cell carcinoma were collected from medical records, including age, gender, clinical stage, treatment response, and chemotherapy. The overall survival was taken as the end-point index, and the overall survival was calculated from the date of recruitment to the date of death from any cause or the end of follow-up.

DNA extraction and genotyping

Peripheral blood (5 mL) samples were collected weekly for toxicity evaluation after radio-chemotherapy. DNA was extracted from the peripheral blood samples using QIAamp DNA Blood Mini Kit (QIAGEN, USA) based on the manufacturer's protocol. The ERCC1 (rs11615 and rs3212986) and ERCC2 (rs13181 and rs1799793) polymorphisms was evaluated using polyme-

Table 1. The primers, restriction enzymes and digested fragments of ERCC1 rs11615 and rs3212986 and ERCC2 rs13181 and rs1799793

Genes	Primers (5'-3')	Amplified fragments, bp	Restriction enzyme
ERCC1 rs1161	(Forward) GGTGCAAGAAGAGGTGGAG	471	BsrDI
	(Reverse) TCAGATCCCCAGGAGTCC		
ERCC1 rs3212986	(Forward) ACCCCACTCTAGATTTACCCAGGAA	442	MboII
	(Reverse) AAGAAGCAGAGTCAGGAAAGC		
ERCC2 rs13181	(Forward) GCCCGCTCTGGATTATACG	436	PstI
	(Reverse) CTATCATCTCCTGGCCCCC		
ERCC2 rs1799793	(Forward) CTGTTGGTGGTGCCCGTATCTGTTGTCT	748	StyI
	(Reverse) TAATATCGGGGCTCACCCTGCAGCACTTCCT		

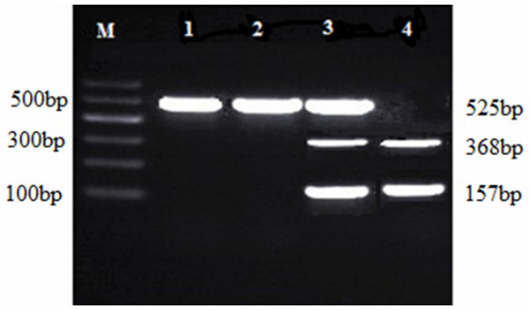

Figure 1. Electrophoretic results of ERCC1 rs11615. M: DNA marker; lane 1: target fragment; lane 2: CC genotype; lane 3: CT genotype; lane 4: TT genotype.

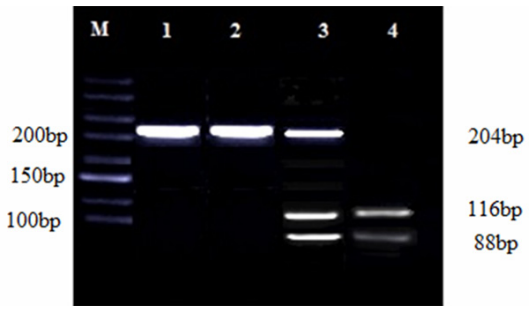

Figure 2. Electrophoretic results of ERCC1 rs3212986. M: DNA marker; lane 1: target fragment; lane 2: CC genotype; lane 3: CA genotype; lane 4: AA genotype.

rase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The primers, restriction enzymes and digested fragments were described in **Table 1**. The PCR was performed in a 25 μl reaction mixture containing 100 ng of DNA, 0.4 μmol/L of each primer, 0.1 mmol/L of dNTP mixtures, 1.5 mmol/L of $MgCl_2$ solution, 1.0 unit of DNA Taq polymerase and of 1× reaction buffer with conditions set at: 95°C for 2

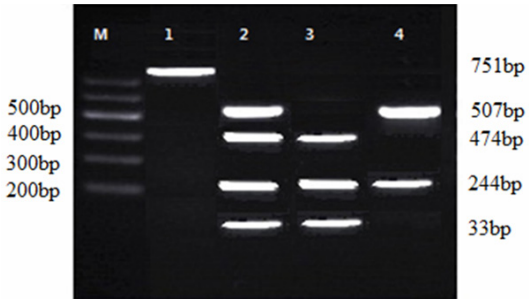

Figure 3. Electrophoretic results of ERCC2 rs13181. M: DNA marker; lane 1: target fragment; lane 2: CA genotype; lane 3: AA genotype; lane 4: CC genotype.

minutes, followed by 35 cycles of 94°C for 30 s, 65°C for 30 s and 72°C for 45 s, and a final elongation of 7 minutes at 72°C. The resulted fragments were electrophoresized on 2% agarose gel stained with ethidium bromide to determine the genotypes of the four polymorphic sites.

For the ERCC1 rs11615, the CC genotype was digested into 525 bp fragment, the CT genotype was digested into 525 bp, 368 bp and 157 bp (**Figure 1**). For ERCC1 rs3212986, the CC genotype was digested into 204 bp, CA genotype was digested into 204 bp, 116 bp and 88 bp, and the AA genotype was digested into 116 bp and 88 bp (**Figure 2**). For ERCC2 rs13181, the AA genotype was digested into 474 bp, 244 bp and 33 bp, the CA genotype was digested into 507 bp, 474 bp, 244 bp and 33 bp, and the CC genotype was digested into 507 bp and 244 bp (**Figure 3**). For the ERCC2 rs1799793, the CC genotype was digested into 227 bp, 146 bp and 63 bp, the AC genotype was digested into 290 bp, 227 bp, 146 bp and 63 bp, and the AA

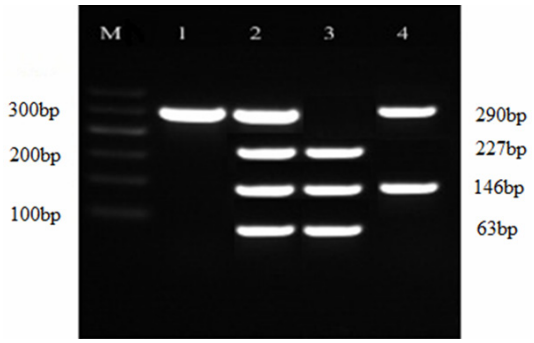

Figure 4. Electrophoretic results of ERCC2 rs1799793. M: DNA marker; lane 1: target fragment; lane 2: AC genotype; lane 3: CC genotype; lane 4: AA genotype.

Table 2. Baseline information of included subjects

Characteristics	Patients	%
Age, years	68.66±5.82	
Gender		
Males	104	73.24
Females	38	26.76
Clinical stage		
I-II	51	35.92
III-IV	91	64.08
Treatment response		
CR+PR	65	45.77
SD+PD	77	54.23
Neoadjuvant chemotherapy		
No	121	85.21
Yes	21	14.79
Concurrent chemotherapy		
No	85	59.86
Yes	57	40.14
Adjuvant chemotherapy		
No	78	54.93
Yes	64	45.07

genotype was digested into 290 bp and 146 bp (**Figure 4**).

Statistical analysis

Data were statistically analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The distributions of quantitative variables were shown by mean and standard deviation, and categorical variables were expressed by frequencies and percentage. The differences between response and non-response were analyzed with a χ^2 test. Unconditional regression analysis was conducted to analyze the correlation between response to chemotherapy and ERCC1 rs11615 and rs3212986 and ERCC2 rs13181 and rs1799793 genetic polymorphisms, and the results was expressed using odds ratios (ORs) along with their 95% confidence Intervals (CIs). The correlation between ERCC1 rs11615 and rs3212986 and ERCC2 rs13181 and rs1799793 genomic polymorphisms and overall survival of esophageal squamous cell carcinoma was estimated using Cox proportional hazards model, and the results was expressed by hazard ratios (HR) along with their confidence intervals (CI). A survival analysis was performed using the Kaplan-Meier method. A *P* value of less than 0.05 was considered to indicate a significant difference.

Results

The baseline information of esophageal squamous cell carcinoma patients were shown in **Table 2**. Of the 142 esophageal squamous cell carcinoma patients, 104 (73.24%) cases were males, 38 (26.76%) were females, 51 (35.92%) were shown grade I-II, 91 (64.08%) presented grade III-IV, 65 (45.77%) showed CR+PR treatment response, and 77 (54.23%) showed SD+PD.

As determined by Chi-square test, a significant difference in the frequency of *ERCC1* rs11615 was observed between CR+PR and SD+PD in esophageal squamous cell carcinoma patients (χ^2=28.66, P<0.001) (**Table 3**). However, no significant differences were observed in the frequencies of *ERCC1* rs3212986 and *ERCC2* rs13181 and rs1799793 between CR+PR and SD+PD groups. As determined by a multiple logistic regression analysis, the TT genotype (OR=11.36, 95% CI=3.93-32.81) and CT+TT genotype (OR=6.46, 95% CI=2.92-14.39) of *ERCC1* rs11615 was correlated with more CR+PR when compared with the CC genotype. However, we did not observe any significant associations between *ERCC1* rs3212986 and *ERCC2* rs13181 and rs1799793 genomic polymorphisms and response to radiochemotherapy in esophageal squamous cell carcinoma patients.

The median survival times of individuals carrying the TT genotype and CT+TT genotype of ERCC1 rs11615 were significantly higher than

Table 3. Relationship between genomic polymorphisms of ERCC1 and ERCC2 and response to therapy in esophageal squamous cell carcinoma patients

Genotypes	CR+PR N=65	%	SD+PD N=77	%	χ^2 test	*P* value	OR (95% CI)[1]	*P* value
ERCC1 rs11615								
CC	19	29.23	56	72.73			1.0 (Ref.)	-
CT	24	36.92	15	19.48			4.87 (2.07-11.43)	<0.05
TT	22	33.85	6	7.79	28.66	<0.001	11.36 (3.93-32.81)	<0.05
CT+TT	46	70.77	21	27.27			6.46 (2.92-14.39)	<0.05
ERCC1 rs3212986								
CC	21	32.31	29	37.66			1.0 (Ref.)	-
CA	25	38.46	30	38.96			1.21 (0.55-2.67)	0.64
AA	19	29.23	18	23.38	0.75	0.69	1.58 (0.65-3.82)	0.31
CA+AA	44	67.69	48	62.34			1.27 (0.60-2.70)	0.51
ERCC2 rs13181								
TT	38	58.46	45	58.44			1.0 (Ref.)	-
TG	20	30.77	22	28.57			1.14 (0.53-2.43)	0.74
GG	7	10.77	10	12.99	0.20	0.90	1.01 (0.34-3.00)	0.98
TG+GG	27	41.54	32	41.56			1.00 (0.48-2.06)	0.99
ERCC2 rs1799793								
AA	33	50.77	41	53.25			1.0 (Ref.)	-
AC	22	33.85	28	36.36			1.10 (0.52-2.30)	0.81
CC	10	15.38	8	10.39	0.80	0.67	1.55 (0.54-4.48)	0.42
AC+CC	32	49.23	36	46.75			1.10 (0.54-2.25)	0.77

[1]Adjusted for age, gender and clinical stage.

those with the CC genotype (*P* value for Log-rank test was 0.048) (**Table 4**; **Figure 5**). Multivariate logistic regression analyses revealed that individuals with the TT genotype (HR=0.32, 95% CI=0.13-0.83) and CT+TT genotype (HR=0.39, 95% CI=0.18-0.83) of ERCC1 rs11615 were at decreased risk for death in esophageal squamous cell carcinoma patients as compared to those with the CC genotype. However, no significant relationship was observed between *ERCC1* rs3212986 and *ERCC2* rs13181 and rs1799793 genomic polymorphisms and overall survival of esophageal squamous cell carcinoma patients.

Discussion

Esophageal squamous cell carcinoma is one of the most common cancers and is associated with high morbidity and mortality all over the world, especially in China [16]. Esophageal squamous cell carcinoma patients are always too late to receive treatment because they are usually diagnosed in the final stages. Although traditional therapies, such as surgical resection, chemotherapy, and radiotherapy, have been widespread used to patients, the overall survival of esophageal squamous cell carcinoma is always not satisfied [17]. It also has been reported that esophageal squamous cell carcinogenesis is a multistep, multifactorial process involving genetic alterations in oncogenes, DNA repair genes and cell cycle regulators [18]. Therefore, a deeper understanding of the molecular events associated with esophageal squamous cell carcinoma was greatly required. In the present study, we carried out a study to investigate the relationship between ERCC1 and ERCC2 genomic variants and response to radiochemotherapy and prognosis of esophageal squamous cell carcinoma, and we observed that the T allele of ERCC1 rs11615 genomic polymorphism was associated with a better response to radiochemotherapy and longer overall survival of esophageal squamous cell carcinoma patients.

The ERCC1 protein is a major component of the NER complex, acting as the rate-limiting enzyme in the NER pathway. ERCC1 has the ability of repairing DNA adducts and other DNA helix-

Table 4. Relationship between genomic polymorphisms of ERCC1 and ERCC2 and overall survival in esophageal squamous cell carcinoma patients

Genotypes	Death N=54	%	Alive N=88	%	Median survival time	Log-rank test	HR (95% CI)[1]	*P* value
ERCC1 rs11615								
CC	29	53.70	28	31.82	38.19		1.0 (Ref.)	-
CT	18	33.33	37	42.05	41.19		0.76 (0.41-1.41)	0.38
TT	6	11.11	23	26.14	48.23	0.048	0.32 (0.13-0.83)	0.02
CT+TT	24	44.44	60	68.18	44.10		0.39 (0.18-0.83)	0.01
ERCC1 rs3212986								
CC	24	44.44	36	40.91	37.32		1.0 (Ref.)	-
CA	23	42.59	39	44.32	42.85		0.68 (0.37-1.26)	0.22
AA	7	12.96	13	14.77	41.61	0.56	0.65 (0.32-1.34)	0.25
CA+AA	30	55.56	52	59.09	41.73		0.87 (0.41-1.82)	0.68
ERCC2 rs13181								
TT	28	51.85	41	46.59	43.60		1.0 (Ref.)	-
TG	23	42.59	40	45.45	35.02		1.67 (0.94-2.95)	2.95
GG	3	5.56	7	7.95	44.47	0.10	0.83 (0.32-2.19)	0.71
TG+GG	26	48.15	47	53.41	38.78		0.81 (0.39-1.69)	0.54
ERCC2 rs1799793								
AA	32	59.26	46	52.27	40.42		1.0 (Ref.)	-
AC	18	33.33	31	35.23	41.08		0.82 (0.45-1.49)	0.52
CC	4	7.41	11	12.50	43.26	0.79	0.74 (0.31-1.77)	0.49
AC+CC	22	40.74	42	47.73	41.46		0.75 (0.36-1.58)	0.42

[1]Adjusted for age, gender and clinical stage.

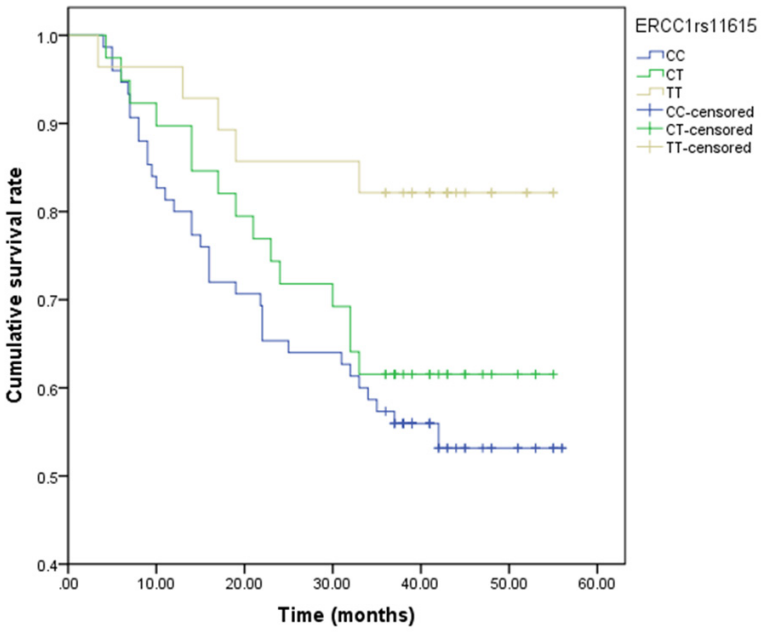

Figure 5. Kaplan-Meier estimates of overall survival of esophageal squamous cell carcinoma with ERCC1 rs11615.

distorting lesions [19], and high expression of ERCC1 has been demonstrated to be correlated with poor response to esophageal squamous cell carcinoma receiving radiochemotherapy via reducing radiochemotherapy-induced DNA damage [19-22]. In our study, we observed that the T allele of ERCC1 rs11615 had a significantly higher complete response and partial response to radiochemotherapy in comparison with the CC genotype.

The results of our study are consistent with previous studies [10, 19-23]. Warnecke-Eberz et al. carried out in 52 esophageal cancer patients, and reported that the C/T genotype of ERCC1 rs11615 showed better response to chemoradiation [19]. Metzger et al. carried out a study with 153 patients with esophageal adenocaricnoma, and they reported that ERCC1 rs11615 genomic polymorphism were cor-

related with response and survival in patients with adenocarcinoma of the esophagus treated with a neoadjuvant radiochemotherapy [22]. Sebio et al. carried out a study in 84 stages II and III rectal cancer, and reported that the ERCC1 variants could be a promising predictive biomarkers of response to chemoradiation in rectal cancer [23]. Yu reported a study with 118 esophageal squamous cell carcinoma patients of a Chinese population, and they reported that T allele of ERCC1 rs11615 was a predictive factor for the response to radiochemotherapy, and this genomic polymorphism was associated with better overall survival in esophageal cancer patients [10]. However, some studies reported inconsistent results. Balboa et al. conducted a study with 65 stage II/III rectal patients, and they did not observe an significant association between ERCC1 rs11615 genomic polymorphism and response to chemoradiotherapy [20]. Yoon et al. carried out a study with 81 new diagnosed resectable esophageal adenocarcinoma patients, and they did not find a significant relationship between ERCC1 rs11615 genomic variation and response to radiochemotherapy and survival of patients [21]. The discrepancies in results between various studies may be attributed to differences in study ethnicities, subject selection, design of study and sample size as well as by chance.

Our study has some strengthens. First, our results were based on adjusted estimates, and the accurate analysis may be achieved with the adjustment of confounders, such as age, gender and clinical stage. Second, the follow-up of study was carried out by telephone calls or hospital visits every four weeks, which may reduce the lose-to-follow-up of study subjects. Several possible limitations should be acknowledged in this study. Firstly, the sample was selected from only one hospital, which may induce selection bias into our study. Second, subgroup analyses stratified by environmental factors were not done in the present study, because relevant data was unavailable from medical records. Third, the sample size is relatively small in this study, which may reduce the statistical power to find differences between groups. Further studies with more sample sizes are required to confirm the results of our findings.

In summary, ERCC1 rs11615 genomic polymorphism was markedly correlated with response to radiochemotherapy and overall survival in patients with esophageal squamous cell carcinoma. ERCC1 could be used as a predictive marker for therapy response to radiochemotherapy, and may help to predict the prognosis of esophageal squamous cell carcinoma.

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Disclosure of conflict of interest

None.

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References

[1] Maddams J, Parkin D and Darby S. The cancer burden in the United Kingdom in 2007 due to radiotherapy. Int J Cancer 2011; 129: 2885-2893.

[2] Zhu J, Ji L, Zhang J, Yang L, Guan C, Wang Y, Zhu J, Liang L and Ni R. Upregulation of SYF2 in esophageal squamous cell carcinoma promotes tumor cell proliferation and predicts poor prognosis. Tumour Biol 2014; 35: 10275-10285.

[3] Siegel R, Ma J, Zou Z and Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[4] Zhang L, Wu Y, Li P, Tu J, Niu Y, Xu C and Zhang S. Effects of cyclooxygenase-2 on human esophageal squamous cell carcinoma. World J Gastroenterol 2011; 17: 4572-4580.

[5] Mitin T, Hunter J and Thomas CJ. Esophageal carcinoma. N Engl J Med 2015; 372: 1471-1472.

[6] Tsai S, Wang P, Liou N, Lin P, Chen C and Chang W. ICAM1 Is a Potential Cancer Stem Cell Marker of Esophageal Squamous Cell Carcinoma. PLoS One 2015; 10: e0142834.

[7] Kim MK, Cho KJ, Kwon GY, Park SI, Kim YH, Kim JH, Song HY, Shin JH, Jung HY, Lee GH, Choi KD, Kim SB. Patients with ERCC1-negative locally advanced esophageal cancers may benefit from preoperative chemoradiotherapy. Clin Cancer Res 2008; 14: 4225-4231.

[8] Leichman L, Goldman B, Bohanes P, Lenz H, Thomas C, Billingsley K, Corless C, Iqbal S,

Gold P, Benedetti J, Danenberg K and Blanke C. S0356: A phase II clinical and prospective molecular trial with oxaliplatin, fluorouracil, and external-beam radiation therapy before surgery for patients with esophageal adenocarcinoma. J Clin Oncol 2011; 29: 4555-4560.

[9] Smith JS, Tachibana I, Pohl U, Lee HK, Thanarajasingam U, Portier BP, Ueki K, Ramaswamy S, Billings SJ, Mohrenweiser HW, Louis DN and Jenkins RB. A transcript map of the chromosome 19q-arm glioma tumor suppressor region. Genomics 2000; 64: 44-50.

[10] Yu X, Xiao H, Zhao B, Zhang X and Wang G. DNA repair gene ERCC1 C118T polymorphism predicts sensitivity of recurrent esophageal cancer to radiochemotherapy in a Chinese population. Thorac Cancer 2015; 6: 741-748.

[11] Liang R, Lin Y, Liu Z, Liao X, Yuan C, Liao S and Li Y. Correlation between ERCC1 expression and concurrent chemotherapy and radiotherapy in patients with locally advanced nasopharyngeal cancer. Genet Mol Res 2015; 14: 5804-5811.

[12] Ciaparrone M, Caspiani O, Bicciolo G, Signorelli D, Simonelli I, de Campora L, Mazzarella G, Mecozzi A, Pianelli C, Camaioni A, Catalano P, Pasqualetti P, Fabiano A, Radici M, Marmiroli L and Corsi DC. Predictive Role of ERCC1 Expression in Head and Neck Squamous Cell Carcinoma Patients Treated with Surgery and Adjuvant Cisplatin-Based Chemoradiation. Oncology 2015; 89: 227-234.

[13] Tanaka K, Mohri Y, Ohi M, Yokoe T, Koike Y, Morimoto Y, Miki C, Tonouchi H and Kusunoki M. Excision-repair cross-complementing 1 predicts response to cisplatin-based neoadjuvant chemoradiotherapy in patients with esophageal squamous cell carcinoma. Mol Med Rep 2009; 2: 903-909.

[14] Okumura H, Uchikado Y, Setoyama T, Matsumoto M, Owaki T, Ishigami S and Natsugoe S. Biomarkers for predicting the response of esophageal squamous cell carcinoma to neoadjuvant chemoradiation therapy. Surg Today 2014; 44: 421-428.

[15] Chen W, Xin P, Pan Q, Chen Y, Wang C, Zhang Z, Chen Y, Zhang C and Cai W. ERCC1 Single Nucleotide Polymorphism C8092A, but Not Its Expression Is Associated with Survival of Esophageal Squamous Cell Carcinoma Patients from Fujian Province, China. PLoS One 2014; 9: e106600.

[16] (IARC) IAfRoC. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. 2012.

[17] Zhu H, Wang Q, Hu C, Zhang W, Quan L, Liu M, Xu N and Xiao Z. High expression of survivin predicts poor prognosis in esophageal squamous cell carcinoma following radiotherapy. Tumour Biol 2011; 32: 1147-1153.

[18] Ling Z, Li P, Ge M, Hu F, Fang X, Dong Z and Mao W. Aberrant methylation of different DNA repair genes demonstrates distinct prognostic value for esophageal cancer. Dig Dis Sci 2011; 59: 2992-3004.

[19] Warnecke-Eberz U, Vallbohmer D, Alakus H, Kutting F, Lurje G, Bollschweiler E, Wienand-Dorweiler A, Drebber U, Holscher AH and Metzger R. ERCC1 and XRCC1 gene polymorphisms predict response to neoadjuvant radiochemotherapy in esophageal cancer. J Gastrointest Surg 2009; 13: 1411-1421.

[20] Balboa E, Duran G, Lamas M, Gomez-Caamaño A, Celeiro-Muñoz C, Lopez R, Carracedo A and Barros F. Pharmacogenetic analysis in neoadjuvant chemoradiation for rectal cancer: high incidence of somatic mutations and their relation with response. Pharmacogenomics 2010; 11: 747-761.

[21] Yoon HH, Catalano PJ, Murphy KM, Skaar TC, Philips S, Powell M, Montgomery EA, Hafez MJ, Offer SM, Liu G, Meltzer SJ, Wu X, Forastiere AA, Benson AB, Kleinberg LR and Gibson MK. Genetic variation in DNA-repair pathways and response to radiochemotherapy in esophageal adenocarcinoma: a retrospective cohort study of the Eastern Cooperative Oncology Group. BMC Cancer 2011; 11: 176.

[22] Metzger R, Warnecke-Eberz U, Alakus H, Kutting F, Brabender J, Vallbohmer D, Grimminger PP, Monig SP, Drebber U, Holscher AH and Bollschweiler E. Neoadjuvant radiochemotherapy in adenocarcinoma of the esophagus: ERCC1 gene polymorphisms for prediction of response and prognosis. J Gastrointest Surg 2012; 16: 26-34; discussion 34.

[23] Sebio A, Salazar J, Paez D, Berenguer-Llergo A, Del Rio E, Tobena M, Martin-Richard M, Sullivan I, Targarona E, Balart J, Baiget M and Barnadas A. EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. Pharmacogenomics J 2015; 15: 77-83.