A genetic variant in ERCC2 is associated with gastric cancer prognosis in a Chinese population

Haiyan Chu1,2,†, Dongying Gu6†, Ming Xu1,2,†, Zhi Xu1, Yonglin Gong1, Weida Gong1, Yongfei Tang5, Jianwei Zhou1,2, Na Tong1,2, Zhengdong Zhang1,2,*, Jinfei Chen4,5 and Meilin Wang1,2
1Department of Environmental Genomics, Jiangsu Key Laboratory of Cancer Biomarkers, Prevention and Treatment, Cancer Center, Nanjing Medical University, 818 East Tianyuan Road, Nanjing 211166, China, 2Department of Genetic Toxicology, The Key Laboratory of Modern Toxicology of Ministry of Education, School of Public Health, Nanjing Medical University, 818 East Tianyuan Road, Nanjing 211166, China, 3Department of Oncology, Nanjing First Hospital, Nanjing Medical University, 68 Changle Road, Nanjing 210006, China, 4Department of Surgery, Yixing Cancer Hospital, 45 Dongshan Eastern Road, Yixing 214206, China, 5Department of Oncology, Nanjing Medical University, 818 East Tianyuan Road, Nanjing 211166, China
6These authors contributed equally to this work.

†To whom correspondence should be addressed. Department of Environmental Genomics, School of Public Health, Nanjing Medical University, 818 East Tianyuan Road, Jiangning District, Nanjing 211166, China. Tel: +86 25 868 684 23; Fax: +86 25 868 684 99 (Zhengdong Zhang, drdzhang@gmail.com; Jinfei Chen, jinfichen@sohu.com) and Meilin Wang; Department of Oncology, Nanjing First Hospital, Nanjing Medical University, 68 Changle Road, Nanjing 210006, China. Tel: +86 25 877 262 42; Fax: +86 25 877 262 34 (Jinfei Chen). Email: drdzhang@gmail.com (Zhengdong Zhang); jinfichen@sohu.com (Jinfei Chen); mwang@njmu.edu.cn (Meilin Wang)

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Endogenous and exogenous factors can induce DNA damage, leading to increased risk of cancer. Nucleotide excision repair (NER) is considered as the most versatile DNA repair pathway to deal with a variety of different DNA lesions. ERCC1 and ERCC2 are the two important proteins in NER pathway. In this study, we investigated the association of three functional single nucleotide polymorphisms (SNPs) (ERCC1 rs11615, ERCC2 rs13181 and ERCC2 rs1799793) with the clinical outcome of 940 gastric cancer patients in a Chinese population. Multiplex SNaPshot technology was used to genotype these three SNPs. Our results revealed that individuals with ERCC2 rs13181T/GG genotypes had a decreased risk of death compared with those with TT genotype [log-rank P = 0.008; adjusted hazard ratio = 0.68, 95% confidence interval = 0.51–0.91], and this protective effect was more pronounced among the subgroup of patients with tumour size ≤5 cm (0.59–0.39–0.89), non-cardia gastric tumour (0.69, 0.48–0.98), no lymph node metastasis (0.55, 0.32–0.96), no distant metastasis (0.70, 0.52–0.95) and chemotherapy (0.39, 0.21–0.72). We conclude that ERCC2 rs13181 polymorphism could play different roles in the overall survival of gastric cancer. Further larger studies should be conducted to validate our findings.

Introduction

Gastric cancer is the fourth most common cancer worldwide, accounting for 8% of newly diagnosed cancer cases (1), and it is the second leading cause of cancer-related mortality (2). Previous studies had demonstrated that tumour histology, tumour location, environmental exposures, dietary factors, Helicobacter pylori infection status and the treatment of earlier stage tumours could be important factors for the clinical outcome of gastric cancer patients (3,4). At present, surgical resection is still considered as the only effective intervention for cure or long-term survival of gastric cancer patients (5), but the overall 5-year survival for gastric cancer after surgery is <25% (6). Combined usage of 5-Fu/LV plus oxaliplatin (FOLFOX) is considered to improve the survival rate of gastric cancer (4); however, most patients display varying response rate, suggesting that the efficacy of chemotherapies has an obvious variability among the individuals. It is warranted to identify the genetic variants that may play important roles in affecting the clinical outcomes of gastric cancer patients.

The nucleotide excision repair (NER) pathway plays an important role in DNA repair and is involved in recognising and repairing the DNA kinking due to chemotherapy-related DNA adducts (7). ERCC1 and ERCC2 are two key genes in the NER pathway. ERCC1 is a highly conserved enzyme of the NER process, which can recognise and remove DNA adducts (8). In advanced head and neck squamous cell carcinoma (9) and bladder cancer (10), the low levels of ERCC1 expression are associated with increased survival following platinum-based treatments compared with high ERCC1 expression. ERCC2 is an ATP-dependent DNA helicase and is involved in repairing DNA damage induced by UV light by removing the DNA adducts (11,12). Lunn et al. (13) suggested that rare mutation of ERCC2 can decrease the efficiency of NER, resulting in hypersensitivity to UV light and increased risk of skin cancer.

Several functional single nucleotide polymorphisms (SNPs) of ERCC1 and ERCC2 involved in cancer have been identified. For ERCC1 rs11615C>T (Asn118Asn) polymorphism, a single base change did not affect the amino acid coding (asparagine); however, it can reduce 50% codon usage for asparagines (14); polymorphism at codon 118 can also reduce DNA repair capacity in platinum resistance. Recently, Hao et al. (15) reported that the ERCC1 rs11615 C to T substitution was associated with poor survival of osteosarcoma patients. In addition, for ERCC2 rs13181T>G (Lys751Gln) and rs1799793C>T (Asp312Asn) polymorphisms, the substitutions of Asp to Asn at position 312 and Lys to Gln at position 751 were first identified in 1996 (16). Previous studies had proposed that amino acid substitutions of these two polymorphisms had a moderate effect in decreasing DNA repair capacity (17). Seker and colleagues (18) found that the 312Asp allele diminished apoptotic response and increased cancer risk by prolonging carcinogen-damaged cell survival and proliferation. ERCC2 Lys751 allele may influence ERCC2 protein expression, resulting in suboptimal repair of X-ray-damaged DNA (13). Many studies have also demonstrated that ERCC2 rs1799793 and rs13181 are associated with the clinical outcome of multiple cancers (19–22). In this study, we hypothesised that functional genetic variants of ERCC1 and ERCC2 (i.e. ERCC1 rs11615, ERCC2 rs13181 and ERCC2 rs1799793) are associated with clinical outcome of gastric cancer and may serve as potential prognostic markers for gastric cancer.
Materials and methods

Study population
This study was approved by the institutional review board of Nanjing Medical University. Since January 1999 to December 2006, a total of 1022 gastric cancer patients were recruited from the Cancer Clinical Research Base of Nanjing Medical University, which had been described previously (23,24). All patients had histopathologically confirmed gastric cancer without previous chemotherapy or radiotherapy before surgery. Of these patients, 940 (92.0%) were entered into the survival analysis and 82 (8.0%) were excluded (78 had no complete epidemiological and clinical information, 4 were not adenocarcinoma). Gastric cancer patients’ characteristics and clinical features are summarised in Table I. The maximum follow-up time was 119.0 months (last follow-up in March 2009) and the median follow-up time was 68.5 months. According to Lauren’s criteria, the histopathology of gastric cancer was classified into diffuse or intestinal types (25). The tumour-node-metastasis (TNM) stages were evaluated according to the TNM classification of the American Joint Committee on Cancer (AJCC cancer staging manual, sixth edition).

SNP selection and genotyping
We selected three functional SNPs of two crucial genes in NER pathway, namely ERCC1 rs11615C>T, ERCC2 rs1799793C>T and ERCC2 rs13181T>G polymorphisms, which have frequently been reported to be associated with diseases. Genomic DNA was obtained from paraffin sections of gastric cancer patients’ tissues. In this study, multiplex SNAPSHOT technology was used to genotype the selected three SNPs based on an ABI fluorescence assay allelic discrimination method (Applied Biosystems, Foster city, CA, USA) as described previously (26). SNP analysis was performed using an ABI1300 genetic analyser. Additionally, Genemapper4.0 software was applied to automatically determine genotypes (Applied Biosystems). Genotyping was validated by sequencing randomly selected 10% of the samples and the results were 100% concordant. However, several samples that failed in genotyping due to DNA quality were excluded from further analysis (Table II).

Table I. Gastric cancer patients’ characteristics and clinical features

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 940) n (%)</th>
<th>Deaths (n = 439) n (%)</th>
<th>MST (months)</th>
<th>Log-rank P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>≤60</td>
<td>441 (46.9)</td>
<td>202</td>
<td>90.1</td>
<td>0.225</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;60</td>
<td>499 (53.1)</td>
<td>237</td>
<td>60.0</td>
<td>1.12 (0.93–1.36)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>724 (77.0)</td>
<td>335</td>
<td>75.5</td>
<td>0.461</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>216 (23.0)</td>
<td>104</td>
<td>64.3</td>
<td>1.09 (0.87–1.35)</td>
<td></td>
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<tr>
<td>Tumour size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 cm</td>
<td>579 (61.6)</td>
<td>245</td>
<td>99.9</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>361 (38.4)</td>
<td>194</td>
<td>49.1</td>
<td>1.44 (1.19–1.74)</td>
<td></td>
</tr>
<tr>
<td>Tumour site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardia</td>
<td>318 (33.8)</td>
<td>143</td>
<td>79.1</td>
<td>0.282</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-cardia</td>
<td>622 (66.2)</td>
<td>296</td>
<td>64.3</td>
<td>0.90 (0.73–1.09)</td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intestinal</td>
<td>399 (42.5)</td>
<td>156</td>
<td>57.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Diffuse</td>
<td>541 (57.5)</td>
<td>283</td>
<td>51.1</td>
<td>1.46 (1.20–1.78)</td>
<td></td>
</tr>
<tr>
<td>Depth of invasion&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>148 (15.8)</td>
<td>45</td>
<td>48.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>T2</td>
<td>200 (21.3)</td>
<td>83</td>
<td>90.1</td>
<td>1.56 (1.09–2.25)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>545 (58.1)</td>
<td>264</td>
<td>51.1</td>
<td>2.17 (1.58–2.97)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>45 (4.8)</td>
<td>27</td>
<td>26.9</td>
<td>2.79 (1.73–4.50)</td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>374 (39.8)</td>
<td>131</td>
<td>60.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>N1/N2/N3</td>
<td>566 (60.2)</td>
<td>308</td>
<td>44.4</td>
<td>1.86 (1.51–2.28)</td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>882 (93.8)</td>
<td>404</td>
<td>75.5</td>
<td>0.003</td>
<td>1.00</td>
</tr>
<tr>
<td>M1</td>
<td>58 (6.2)</td>
<td>35</td>
<td>27.5</td>
<td>1.67 (1.18–2.37)</td>
<td></td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>261 (27.8)</td>
<td>88</td>
<td>60.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>II</td>
<td>186 (19.8)</td>
<td>75</td>
<td>90.1</td>
<td>1.28 (0.94–1.75)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>396 (42.1)</td>
<td>220</td>
<td>42.9</td>
<td>2.04 (1.59–2.62)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>97 (10.3)</td>
<td>56</td>
<td>42.1</td>
<td>2.14 (1.53–3.00)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>635 (67.5)</td>
<td>301</td>
<td>61.5</td>
<td>0.653</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>305 (32.5)</td>
<td>138</td>
<td>75.2</td>
<td>1.05 (0.86–1.28)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for age and sex.
<sup>b</sup>Mean survival time was provided when MST could not be calculated.
<sup>c</sup>Information was not available for two patients.

Survival analysis
Survival time was calculated from the date of surgery to the date of death or the last follow-up time. Mean survival time was chosen when the median survival time could not be calculated. The different survival time of gastric cancer patients’ characteristics, clinical features and genotypes were evaluated by using log-rank test. The crude or adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated by univariate or multivariate Cox regression analysis. In order to identify the predictors of gastric cancer patients’ outcome, we used the Cox stepwise regression to calculate with a significance level of P < 0.05 for entering and P > 0.10 for removal of the respective explanatory variables. A goodness-of-fit chi test was used to evaluate the Hardy–Weinberg equilibrium of the genotype distribution. All statistical analyses were performed with SAS software (version 9.1; SAS Institute, Inc., Cary, NC, USA) with two-sided P value, unless indicated otherwise.

Results
Gastric cancer patients’ characteristics and clinical features
The distribution of characteristics and clinical features of the gastric cancer patients are shown in Table I. Of the 940 gastric cancer patients with the complete clinical follow-up information, we observed a total of 439 gastric cancer patients died during the 119.0 months of follow-up. The mean age was 60.68 ± 10.25 years and the median age was 62.0 years (range, 28–83 years). In this study, there were 724 males (77%) and 216 females (23.0%), and all patients were gastric adenocarcinoma cases.

All patients were treated with the surgical resection, of which 305 had undergone chemotherapy. Tumour size (≤5 or >5 cm),
histological type (intestinal or diffuse), depth of invasion (T1 or T2 or T3 or T4), lymph node metastasis (N0 or N1/N2/N3), distant metastasis (M0 or M1) and TNM stage (I or II or III or IV) were associated with survival time (all log-rank \( P < 0.01 \)).

Approximately, 38.4% of the patients had larger tumours (\( \geq 5 \) cm, median survival time (MST) = 49.1 months), which had a 44% significantly higher risk of death (aHR = 1.44, 95% CI = 1.19–1.74), than the patients with smaller tumours (\( \leq 5 \) cm, 99.9 months). We found that diffuse tumour of patients were associated with increased risk of death, compared with intestinal tumour (MST, 51.1 versus 57.2 months; 1.46, 1.20–1.78). In addition, we also observed that 566 (60.2%) patients developed lymph node metastasis and 58 (6.2%) patients developed distant metastasis, which were associated with the risk of death (1.86, 1.51–2.28 and 1.67, 1.18–2.37, respectively).

**Effects of ERCC1 and ERCC2 polymorphisms on gastric cancer survival**

These three SNPs in the subjects were consistent with Hardy–Weinberg equilibrium (\( P > 0.05 \)) and the genotyping success rate for these SNPs ranged from 94.4 to 97.6% (Table II). As shown in Table III, Cox regression analyses revealed the association of \( \text{ERCC1 rs11615, ERCC2 rs1799793 and } \text{ERCC2 rs13181} \) polymorphisms with gastric cancer survival in different genetic models. Results showed that \( \text{ERCC2 rs13181} \) was associated with the survival of gastric cancer patients in codominant models (log-rank \( P = 0.028 \)). Additionally, we found that \( \text{rs13181TG} \) genotype could increase the survival of gastric cancer patients compared with TT genotype (aHR = 0.69, 95% CI = 0.51–0.93; Table III). Kaplan–Meier plot also showed that compared with the \( \text{rs13181TT} \) genotype, individuals with \( \text{rs13181TG/GG} \) genotypes had a significantly decreased risk of death (\( P = 0.008; 0.68, 0.51–0.91; \) Figure 1). However, there was no significant association between \( \text{rs11615C>T} \) or \( \text{rs1799793C>T} \) polymorphism and survival from gastric cancer in any genetic models (Table III).

Next, we assessed the association of \( \text{rs13181T>G} \) polymorphism with gastric cancer survival by stratified analysis of tumour size, tumour site, histological type, depth of invasion, lymph node metastasis, distant metastasis, TNM stage and chemotherapy (TG/GG versus TT; Table IV). As presented in Table IV, we did not observe any significant association between the \( \text{rs13181 TG/GG} \) genotypes and gastric cancer survival among the subgroups of histological type and TNM stage, compared with TT genotypes. However, the protective effect of these genotypes was more significant in the subgroups of patients with tumour size \( \leq 5 \) cm (aHR = 0.59, 95% CI = 0.39–0.89, \( P_{\text{heterogeneity}} = 0.330 \)), non-cardia gastric tumour (0.69, 0.48–0.98, 0.817), non-lymph node metastasis (0.55, 0.32–0.96, 0.308), no distance metastasis (0.70, 0.52–0.95, 0.503) and chemotherapy (0.39, 0.21–0.72, 0.029).

Next, we performed the stepwise Cox regression analysis to assess the associations between the included demographic characteristics, clinical features, the three included SNPs and gastric cancer survival. As shown in Table V, three variables (lymph node metastasis: N1/N2/N3 versus N0, TNM stage: TNM III/IV versus I/II and \( \text{rs13181: TG/GG versus TT} \) were finally included in the Cox regression model with a significance level for \( P < 0.05 \) entering and \( P > 0.10 \) for removing a variable (\( P = 0.042, 0.011 \) and 0.023, respectively).

**Discussion**

In this study, we investigated the genetic variants of two key genes in the NER pathway (\( \text{ERCC1 rs11615, ERCC2 rs1799793 and } \text{ERCC2 rs13181} \)) with the survival of gastric cancer patients. The results showed that the \( \text{ERCC2 rs13181TG/GG} \) genotypes were associated with the increased survival from gastric cancer in a Chinese population.

Endogenous and exogenous factors can induce DNA damage, leading to an increased risk of cancer (27). DNA damage repair mechanisms play important roles in preserving DNA integrity. Of these DNA repair mechanisms, NER is considered to be the most versatile DNA repair pathway to deal with a variety of different DNA lesions (28). \( \text{ERCC1 and ERCC2 proteins} \) involved in the NER pathway act as the rate-limiting enzymes. \( \text{ERCC1} \) is a highly conserved protein and is crucial for removing the DNA adducts induced by platinum (29). Functional polymorphism of the \( \text{ERCC1 rs11615} \) has been demonstrated to influence the clinical outcome of patients with platinum-based chemotherapy (30,31). The \( \text{ERCC1 rs11615TT} \) genotype was considered to be associated with the decreased survival of patients, which may be due to reduced drug sensitivity from the low levels of \( \text{ERCC1} \) expression, resulting in the low efficient repair of the DNA adducts induced by platinum (30). However, Ozcan et al. (10) reported that high \( \text{ERCC1 expression} \) contributed to the poor overall survival and shorter disease-free time in bladder cancer patients with platinum-based chemotherapy. Recently, a systematic review found no significant association between the \( \text{ERCC1 rs11615} \) polymorphism and clinical outcomes (32), which is consistent with our findings.

\( \text{ERCC2 protein} \) is an important component of the NER complex, which is involved in the DNA helicase process during NER and transcription (11), and contributes to repair of ionising radiation-induced DNA damage (12). The \( \text{ERCC2 rs1799793 and rs13181 polymorphisms} \) have been extensively studied and Xue et al. (33) concluded that these two SNPs were associated with gastric cancer risk in Asian populations. For the \( \text{rs13181T>G} \) polymorphism, the G allele was associated with reduced response, progression-free survival and overall survival among Caucasians and this SNP could be a useful prognostic marker in oxaliplatin treatment of gastric and colorectal cancers (22). Giovannetti et al. (19) also observed
that rs13181G allele was associated with shorter progression-
free survival of pancreatic cancer patients for platinum-based
regimens, whereas no similar association was found between
rs1799793 and pancreatic patients’ survival. In advanced oral
cancer patients, the rs1799793 variant allele showed significant
protection in both disease-specific survival and relapse-free
survival, and significantly prolonged relapse-free survival was
found in patients with the rs13181 variant allele (20). Herein,
we focused on investigating the associations between these two
SNPs and clinical outcome of gastric cancer patients. Results
suggest that the rs13181TG/GG genotypes contribute to a good
survival for gastric cancer, which is consistent with findings
of Zárate et al. (21). However, for rs1799793, we did not
observe a similar association. A previous study indicated that
the rs13181 may influence the ERCC2 protein product leading
to suboptimal repair of X-ray-induced DNA damage; however,
the rs1799793 did not appear to affect DNA repair capacity (13). In addition, Hou et al. (34) revealed that the variant allele of rs13181 can reduce repair of DNA adducts (34). These could be the possible reasons to explain these findings. The exact mechanism of the phenomenon is not yet clear.

In this study, we found that different tumour size, tumour site and distant metastasis of gastric cancer can affect the survival of gastric cancer patients. Some studies have also reported that the gastric cancer clinical characteristics are associated with the survival of gastric cancer patients (23,35). Our findings demonstrate that the ERCC2 rs13181 TG/GG genotypes could predict better survival of patients with tumour size ≤ 5 cm, non-cardia gastric tumour, no lymph node metastasis and no distant metastasis, compared with the TT genotype. Interestingly, we also observed that, compared with the TT genotype, TG/GG genotypes contributed to the good survival of gastric cancer patients, who were undergoing chemotherapy. A possible explanation is that ERCC2 rs13181TG>G polymorphism is associated with the reduced ERCC2 messenger RNA levels, leading to the lower DNA repair efficiency of tumour cells’ DNA damage induced by chemotherapy.

Some limitations should be addressed in this study. First, we only have data for overall survival of included gastric cancer patients, and lack information on disease-specific survival and relapse-free survival. We can confirm that the majority of gastric cancer patients died of a gastric cancer–related cause, but we do not have reliably denoted causes of death. Second, we had no detailed information for the chemotherapy of the gastric cancer patients. We observed that the ERCC2 rs13181 TG/GG genotypes contributed to the good survival of gastric cancer patients, who were undergoing chemotherapy. Third, we only investigated several common reported polymorphisms of ERCC1 and ERCC2 genes. More polymorphisms or genes should be investigated as possible useful markers to predict the clinical outcome of gastric cancer.

Finally, the maximum follow-up time was 119.0 months and the median follow-up time was 35.0 months, which were mainly explained by gas tract patients recruited from 2005 to 2006 (20.1% in 2005 and 79.9% in 2006). Therefore, further studies with longer follow-up time are warranted to validate our results.

In conclusion, we observed that the ERCC2 rs13181 TG/GG can prolong the survival time of gastric cancer, suggesting that the rs13181 polymorphism can be used as a predictor of overall survival of gastric cancer patients in a Chinese population. Further studies should be conducted to validate our findings.
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Conflict of interest statement: The authors declare no conflict of interest.

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