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ORIGINAL ARTICLE

Polymorphisms in *p53*, *GSTP1* and *XRCC1* predict relapse and survival of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy

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Abstract
Purpose The aim of this study was to assess whether genetic polymorphisms in *p53*, glutathione *S*-transferase P1 (*GSTP1*), *GSTM1*, excision repair cross complementing group 1 (*ERCC1*) and X-ray repair cross-complementing group 1 (*XRCC1*) genes are associated with clinical outcome of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy.
Methods The genetic polymorphisms in *p53*, *GSTP1, GSTM1* (null), *ERCC1* and *XRCC1* were determined in 102 gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy using polymerase chain reaction-ligation detection reaction method.
Results Among the five studied polymorphisms, *p53* codon 72 Pro/Pro, *GSTP1* codon 105 Ile/Ile, and *XRCC1* codon 399 Gln/Gln + Arg/Gln were associated with poor relapse-free survival and overall survival ($P < 0.05$); and the prognostic effect was retained in the Cox multivariate analysis. Combination analysis with the three polymorphisms using the Kaplan–Meier method and Cox multivariate analysis revealed that the relapse-free and overall survivals significantly increase with the number of favorable genotypes ($P < 0.05$). No significant association was found between the *GSTM1* (null) or the *ERCC1* codon 118 genotypes and the clinical outcome ($P > 0.05$).
Conclusion Testing for *p53* Arg72Pro, *GSTP1* Ile105Val, and *XRCC1* Arg399Gln polymorphisms may allow identification of gastric cancer patients who will benefit from oxaliplatin-based adjuvant chemotherapy. Selecting specific adjuvant treatments according to the individual genetic background may represent an innovative strategy that warrants prospective studies.

Keywords Gastric cancer · Adjuvant chemotherapy · Polymorphism · Oxaliplatin

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Introduction

Gastric cancer is the leading cause of tumor-related deaths in China. Surgery is the primary modality for managing early-stage and locally-advanced diseases. However, even after radical surgery, the majority of gastric cancer patients develop local or distant recurrence. Growing evidence seems to support the use of adjuvant chemotherapy, and surgery alone is no longer the standard treatment for patients with resectable gastric cancer [1, 2]. Fluorouracil coupled with cisplatin has been commonly used in gastric

cancer patients for many years. Recently, additional drugs such as oxaliplatin, taxanes, and irinotecan were introduced into the chemotherapy regimens for treating gastric cancer and indicated promising results and manageable toxicity. However, there is currently no standard regimen for postoperative treatment; and the response rates of these drugs or their combinations were less than 50% [3]. One of the remaining challenges is to identify markers to predict clinical outcome to specific chemotherapeutic protocol beforehand, which may help to prospectively select those patients who are more likely to benefit from the treatment.

Recently, oxaliplatin was shown to be effective in the treatment of advanced gastric cancer and has also been commonly used in adjuvant chemotherapy for gastric cancer. An important mechanism of resistance to platinum drugs has been attributed to enhanced tolerance and repair of DNA damage through the nucleotide-excision-repair (NER) and base excision repair (BER) pathways [4]. Excision repair cross complementing group 1 (ERCC1) and X-ray repair cross-complementing group 1 (XRCC1) are important proteins in NER and BER pathways, respectively. Several polymorphisms of the two genes have been reported to play important role in the response to platinum-based chemotherapy [5–10].

Resistance to platinum agents may also depend on altered detoxification pathways. Growing evidence indicates that glutathione *S*-transferase (GST), a superfamily of dimeric phase II metabolic enzymes, determine cytotoxicity of a variety of chemotherapeutic agents including platinum drugs [11]. It has been suggested that some genetic polymorphisms in *GSTP1* and *GSTM1* genes reduce the efficacy of chemotherapeutic agents. An A/G SNP located within the substrate-binding domain of *GSTP1*, which results in amino-acid substitution of Isoleucine by Valine (Ile105Val), diminishes GSTP1 enzyme activity and is linked to favorable platinum sensitivity [12, 13]. *GSTM1* deletion (null) polymorphism has also been reported to be associated with diminished enzyme activity and increased platinum sensitivity [14].

Most anti-cancer agents including fluorouracil, platinum, and taxanes, regardless of distinct mechanisms of action, ultimately kill tumor cells by inducing apoptosis [15]. Thus, the activity of apoptosis-related genes may influence cytotoxicity of chemotherapeutic drugs. The tumor suppressor gene *p53*, participates in numerous homeostatic activities such as cell cycle checkpoint control, repair of DNA damage, and induction of apoptosis. Recent studies have shown that *p53* 72 Arg/Pro polymorphism plays a crucial role in modulating wild-type *p53* apoptotic capacity [16]. A limited number of studies have shown that the prognosis is worse when the *p53* 72 Pro/Pro genotype is present compared with the other two genotypes [17–19].

Some reports [10, 13, 19–21] have suggested that polymorphisms in genes involved in DNA repair, drug metabolism, detoxification pathways, and apoptosis may influence the effect of chemotherapeutic agents on gastric cancer. However, most of those studies focused on the potential influence of genetic polymorphisms on the effect of drugs in advanced (metastatic) disease, the results of which could not be transferred to adjuvant chemotherapy without reservation. Little is known about the effect of those polymorphisms on adjuvant chemotherapy [19, 20]. In the current study, we examine a panel of five genetic polymorphisms within genes involved in the detoxification of oxaliplatin (*GSTP1* and *GSTM1*), DNA repair (*ERCC1* and *XRCC1*) and apoptosis (*p53*), and clarify the impact of these polymorphisms on clinical outcome of gastric cancer patients receiving oxaliplatin-based adjuvant treatment.

Materials and methods

Patients

From May 2001 to November 2006, 102 patients with histologically confirmed gastric cancer were consecutively enrolled in this retrospective study at the 4th Affiliated Hospital of Suzhou University. All patients underwent radical surgery and were then treated with at least four courses of oxaliplatin-based adjuvant treatment, including 83 treated with 5-FU/leukovorin/oxaliplatin (FOLFOX4: oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 followed on days 1 and 2 by 5-FU 400 mg/m^2 intravenous (IV) bolus, then 600 mg/m^2 IV over 22 h continuous infusion. This schedule was repeated every 2 weeks.) and 19 treated with 5-FU/leukovorin/oxaliplatin/other regimens (taxanes or hydroxycamptothecin) (paclitaxel 135 mg/m^2 or docetaxel 75 mg/m^2 on day 1, hydroxycamptothecin 8 mg/m^2 on days 1–5; and the usage of 5-FU and leucovorin was the same as that in FOLFOX4). If patients had hematologic toxic effects of grade 3 or grade 4 or nonhematologic toxic effects of grades 2–4, their daily dose was reduced properly. Gastric carcinoma was diagnosed and staged according to the World Health Organization classifications and TNM classifications defined by the American Joint Committee on Cancer. This study was approved by the ethics and research committee of our hospital.

DNA extraction and genotyping

Genomic DNA was isolated from peripheral blood lymphocytes using a Axygene genomic DNA purification Kit (Axygen Biotechnology, China). Genotyping was performed using the multiplex polymerase chain reaction-ligation detection reaction (PCR-LDR) method, as described previously [19]. The primers and probes are listed in Supplementary Table 1. The genotyping of the five

polymorphisms were performed using two multiplex PCR-LDRs, one for *XRCC1* Arg399Gln, *GSTM1* null and *GSTP1* Ile105Val, the other for *ERCC1* C118T and *p53* Arg72Pro.

Statistical analysis

The genotypes for each polymorphism were analyzed first as a three-group categoric variable (referent model), and if it was necessary some SNPs were further grouped according to the dominant and recessive model. The relationship between genotype frequencies and clinical characteristics was assessed by χ^2 or Fisher's exact probability tests. Follow-up of these patients was performed at 3-month intervals after chemotherapy at outpatient clinics or by routine phone calls. Relapse-free survival (RFS) was defined as the time interval between the date of surgery and the date of relapse of disease or the date of the last follow-up. Overall survival (OS) was defined as the time between surgery and either death or the time of the last follow-up. Survival curves were generated by the Kaplan–Meier method and the log-rank test was adopted to compare survival time between patients with different genotypes. Cox's proportional hazards model was used to estimate Hazard Ratios (HRs) and their 95% confidence intervals (CIs), representing the overall relative risk of relapse or death associated with polymorphisms. All *P*-values were two-sided. Statistical significance was defined as $P < 0.05$. Data analysis was performed using the computer software SPSS13.0.

Results

Patients

A total of 102 gastric cancer patients with a median age of 58 years (range 34–76), were enrolled in this study. Of the patients, 11 curatively resected patients with stage IV (M0) disease were included based on following consideration: complete resection of the tumor with D (2–3) resection, defined as resection performed with curative intent and resulting in negative resection margins. The patient characteristics are presented in Table 1. The median follow-up period was 26.0 months (range 5.2–75.1). No significant association was found between the age, gender, TNM stage or tumor differentiation and any of the polymorphisms investigated (data not shown). Patients' characteristics and their clinical outcomes were unknown to investigators performing the genetic analyses.

Table 1 Patient characteristics

Characteristics	*n* (%)
Age (median age 58)	
≥58	57 (55.9)
<58	45 (44.1)
Gender	
Male	73 (71.6)
Female	29 (28.4)
Histotype	
Intestinal	66 (64.7)
Diffuse	36 (35.3)
Differentiation	
Well and moderated	52 (51.0)
Poor	50 (49.0)
Nodal stage	
Negative	21 (20.6)
Positive	81 (79.4)
Tumor stage	
T1	1 (1.0)
T2	3 (2.9)
T3	82 (80.4)
T4	16 (15.7)
TNM stage	
IB	3 (2.9)
II	15 (14.7)
IIIA	54 (52.9)
IIIB	19 (18.6)
IV (M0)	11 (10.8)

TNM tumor–node–metastasis classifications

Polymorphisms and clinical outcome

By the time of the final analysis, 61.8% (63/102) of all patients relapsed and 52.9% (54/102) had died. Of the whole group, the median RFS time was 20.0 months (range 3.2–67.3) and the median OS time was 26.0 months (range 5.2–75.1).

The distribution of genotypes of the five polymorphisms is listed in Table 2. Among the five studied polymorphisms, significantly lower RFS and OS were observed in patients with the *p53* codon 72 Pro/Pro, *GSTP1* codon 105 Ile/Ile and *XRCC1* codon 399 Gln/Gln + Arg/Gln genotypes ($P < 0.05$) (Figs. 1a–c, 2a–c). After adjusting for age, gender, TNM stage, and tumor differentiation, Cox multivariate analysis demonstrated that the *p53* Pro/Pro, *GSTP1* Ile/Ile, and *XRCC1* Gln/Gln + Arg/Gln genotypes were potential prognostic factors for poor RFS and OS (Table 3; $P < 0.05$).

Combined analysis of genotypes and clinical outcome

Based on individual results for these polymorphisms, we performed a combined analysis to investigate whether a pattern of favorable genotypes (*p53* codon 72 Arg/Arg or

Table 2 The distribution of genotypes

Genotypes	Cases (%)
p53 codon 72	
Arg/Arg	20 (19.6)
Arg/Pro	56 (54.9)
Pro/Pro	26 (25.5)
ERCC1 codon 118	
C/C	53 (52.0)
C/T	43 (42.2)
T/T	6 (5.9)
GSTP1 codon 105	
Ile/Ile	59 (57.8)
Ile/Val	35 (34.3)
Val/Val	8 (7.8)
GSTM1	
Positive	49 (48.0)
Negative	53 (52.0)
XRCC1 codon 399	
Arg/Arg	62 (60.8)
Arg/Gln	35 (34.3)
Gln/Gln	5 (4.9)

Arg/Pro, *XRCC1* codon 399 Arg/Arg, *GSTP1* codon 105 Val/Val or Val/Ile) could be used to determine clear-cut differences of clinical outcomes. Of the 102 patients, 11 had no favorable genotype, 31 had one favorable genotype, 30 had exactly two, and 30 had three favorable genotypes. Patients with two or three favorable genotypes had prolonged RFS and OS compared with patients with zero or one favorable genotype (25.5 vs. 16.7 months, $\chi^2 = 13.926$, $P < 0.001$; 30.3 vs. 23.8 months, $\chi^2 = 9.601$, $P = 0.002$). The Kaplan–Meier plots with log-rank comparisons are shown in Figs. 1d and 2d. In addition, a statistically significant difference, with respect to RFS and OS, were also found among the four groups of patients ($\chi^2 = 18.100$, $P < 0.001$; $\chi^2 = 11.008$, $P = 0.012$).

Using the group of patients with two or three favorable polymorphisms as the reference group in the Cox multivariate analysis, the relative risks of dying and relapse were 2.512 (95% CI = 1.389–4.544, $P < 0.001$) and 2.918 (95% CI = 1.707–4.988, $P = 0.002$) for the group of patients with only one or zero favorable genotype, respectively (Table 3). The RFS and OS significantly increase with the number of favorable genotypes (HR = 1.637, 95% CI = 1.183–2.266, $P = 0.003$; HR = 1.538, 95% CI = 1.086–2.179, $P = 0.015$).

Discussion

The results of the present study support the pharmacogenetic role of *p53* Arg72Pro, *GSTP1* Ile105Val, and *XRCC1* Arg399Gln polymorphisms in patients with gastric cancer

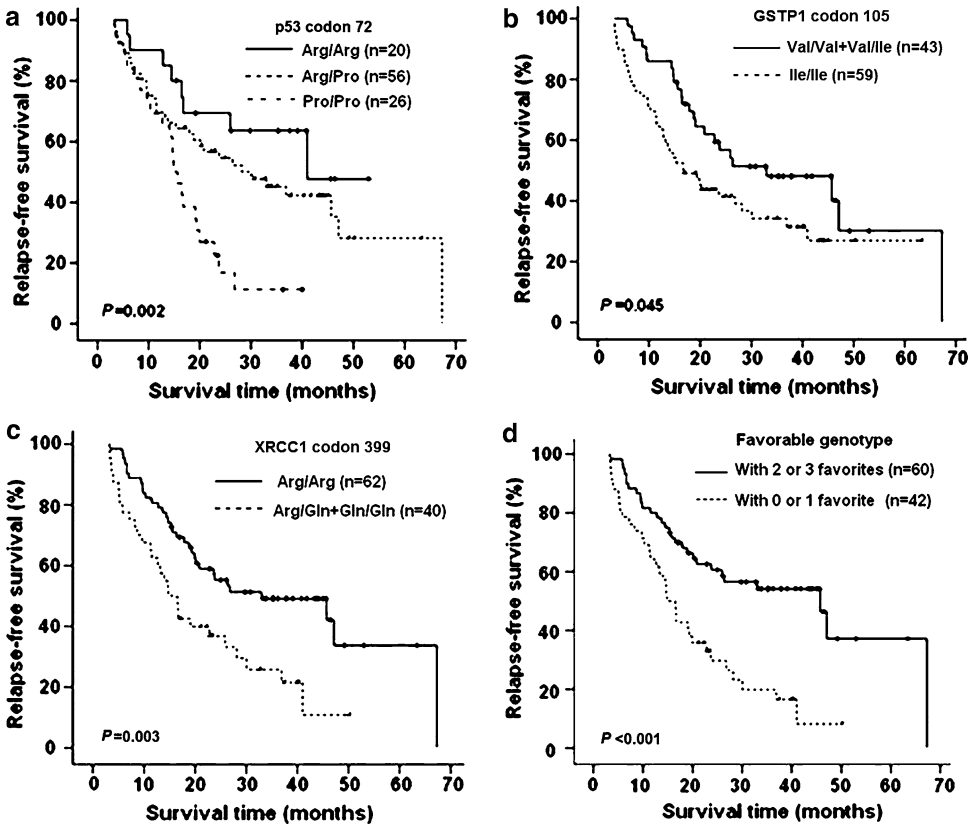

Fig. 1 Kaplan–Meier curves of relapse-free survival according to the genotypes of *p53*, glutathione *S*-transferase P1 (*GSTP1*), and X-ray repair cross-complementing group 1 (*XRCC1*) genotypes. **a–d** Kaplan–Meier estimates of relapse-free by the *p53* codon 72, *GSTP1* codon 105, *XRCC1* codon 399 genotypes and the number of favorable genotypes, respectively. Favorable genotypes include *p53* codon 72 Arg/Arg or Arg/Pro, *XRCC1* codon 399 Arg/Arg, *GSTP1* codon 105 Val/Val or Val/Ile

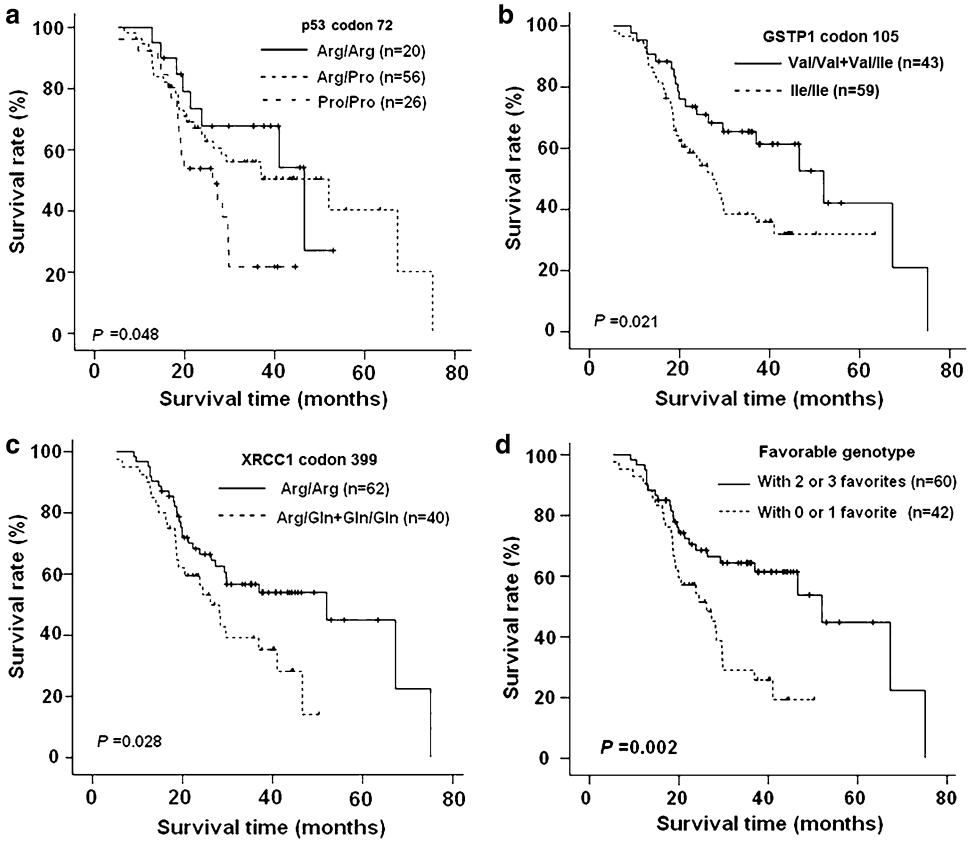

Fig. 2 Kaplan–Meier curves of overall survival according to the genotypes of *p53*, glutathione *S*-transferase P1 (*GSTP1*), and X-ray repair cross-complementing group 1 (*XRCC1*) genotypes. **a–d** Kaplan–Meier estimates of overall survival by the *p53* codon 72, *GSTP1* codon 105, *XRCC1* codon 399 genotypes and the number of favorable genotypes, respectively. Favorable genotypes include *p53* codon 72 Arg/Arg or Arg/Pro, *XRCC1* codon 399 Arg/Arg, *GSTP1* codon 105 Val/Val or Val/Ile

Table 3 Results of Cox multivariate analyses for overall and relapse-free survivals

Variables	Relapse-free survival		Overall survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (≥58 vs. <58)	0.996 (0.971–1.022)	0.761	1.003 (0.975–1.032)	0.836
Gender (male vs. female)	1.029 (0.591–1.794)	0.919	1.221 (0.682–2.189)	0.502
Differentiation (well and moderated vs. poor)	1.236 (0.736–2.075)	0.423	1.121 (0.642–1.959)	0.688
TNM stage (IB–II vs. III–IV)	1.666 (0.811–3.422)	0.164	2.621 (1.096–6.266)	0.030
p53 codon 72 (Arg/Arg + Arg/Pro vs. Pro/Pro)	2.476 (1.435–4.271)	0.001	2.006 (1.107–3.634)	0.022
ERCC1 codon 118 (T/T + C/T vs. C/C)	1.083 (0.655–1.791)	0.756	0.933 (0.539–1.614)	0.805
XRCC1 codon 399 (Arg/Arg vs. Arg/Gln + Gln/Gln)	2.186 (1.312–3.644)	0.003	1.902 (1.084–3.336)	0.025
GSTP1 codon 105 (Val/Val +Val/Ile vs. Ile/Ile)	2.003 (1.152–3.482)	0.014	2.125 (1.139–3.966)	0.018
GSTM1 (negative vs. positive)	1.291 (0.774–2.154)	0.329	1.425 (0.822–2.469)	0.207
No. of favorable genotypes (≥2 vs. 0 or 1)*	2.918 (1.707–4.988)	<0.001	2.512 (1.389–4.544)	0.002

HR hazard ratio; *CI* confidence interval; *TNM* tumor–node–metastasis classifications

* Favorable genotypes include *p53* Arg/Arg or Arg/Pro at codon 72, *XRCC1* codon 399 Arg/Arg, *GSTP1* Val/Val or Val/Ile at codon 105

treated with oxaliplatin-based adjuvant chemotherapy. The *p53* condon 72 Pro/Pro, *GSTP1* codon 105 Ile/Ile and *XRCC1* codon 399 Gln alleles were associated with poor RFS and OS, highlighting its potential value in the individualized tailoring chemotherapy for gastric cancer. To the best of our knowledge, this is the first report that identifies a pharmacogenetic profile that may predict the clinical outcome to oxaliplatin-based adjuvant chemotherapy in gastric cancer.

The NER system is a major DNA repair system in mammalian cells and plays a significant role in repairing a variety of distorting lesions, including platinum-induced DNA adducts. In fact, NER is the only known mechanism in mammalian cells for the removal of bulky, helix distorting DNA adducts produced by platinum agents. *ERCC1* is the primary enzyme in the NER pathway, and seems to be mainly involved in the repair of oxaliplatin-induced DNA damage [4]. High *ERCC1* levels are associated with

increased removal of platinum-induced DNA adducts and platinum resistance. The in vitro studies suggest that the *ERCC1* codon 118 T allele is associated with higher *ERCC1* mRNA levels than the C allele, resulting in resistance to platinum drugs [22]. However, the clinical data regarding the assumed relationship between *ERCC1* codon 118 polymorphism and platinum sensitivity is controversial [5–9, 23]. In this study, no significant association was found between the *ERCC1* 118 polymorphism and the relapse or survival, which is consistent with the results of other reports in advanced gastric cancer [21, 24] and lung cancer [8]. Thus, the predictive role of the codon 118 polymorphism in platinum-treated patients warrants additional study.

XRCC1 plays a prominent role in BER to efficiently repair DNA damage caused by ionizing radiation, oxidative stress, and DNA alkylating agents. In a small size study of advanced colorectal cancer, *XRCC1* 399 polymorphism was associated with resistance to oxaliplatin/5-FU chemotherapy [25], however, the predictive value of the polymorphism was not always observed in several subsequent studies [9, 10, 21, 23, 26]. In a recent study on advanced gastric cancer receiving oxaliplatin-based chemotherapy, Liu et al. [10] demonstrated that patients harboring *XRCC1* 399 Gln/Gln had a significant shorter survival than patients carrying the other two genotypes. In the present study, similar results were observed in gastric cancer receiving oxaliplatin-based adjuvant chemotherapy.

Increasing evidence has suggested an important role for drug-metabolizing enzymes in determining interindividual variations in therapeutic response. GSTs make up a family of multifunctional enzymes that detoxify a variety of electrophilic compounds. A limited number of studies suggested that genetic polymorphisms in *GSTP1* and *GSTM1* genes (conducted primarily in Western populations) influence the efficacy of detoxifying cytotoxins generated by chemotherapeutics such as platinum agents. However, the results of those studies have been contradicting. Due to impairment of the GSTP1 capacity caused by the A → G substitution, patients with the Val variant allele may be less capable of detoxifying oxaliplatin compared to patients with wild-type allele. Our data suggests that patients with the *GSTP1* Val allele have favorable RFS and OS, which is in agreement with previous reports in breast [27] and colorectal cancers [28]. Similar results were also observed in a recent study on advanced gastric cancer treated with 5-FU/cisplatin [13] in spite that a recent study showed that *GSTP1* codon 105 polymorphism is not associated with oxaliplatin efficacy in advanced colorectal cancer patients [29]. Conversely, the deletion polymorphism of *GSTM1* that is associated with abolished enzyme activity was not associated with clinical outcomes in the present study, which parallels previous studies on advanced gastric cancer by other groups [13, 21]. The lack of a predictive role for the *GSTM1* polymorphism may be due to the difference in tissue-specificity and drug-specificity of GSTM1 isoenzymes [11]. Although deletion polymorphism was also found in GSTT1, another member of GSTs, most published works did not support its pharmacogenetic role, especially in gastrointestinal tumors [13, 21, 30]. So we did not assess the *GSTT1* polymorphism in this study.

There is an increasing recognition that an intact *p53* pathway is crucial for the cellular response to chemotherapeutic agents. Several studies [17, 18] have shown that the *p53* 72 Arg variant is associated with better anti-tumor efficiency of different drugs including cisplatinum, paclitaxel and anthracycline compared with the Pro variant. However, little is known about the effect of this polymorphism in gastric cancer. In our former report, we demonstrated that *p53* codon 72 polymorphism could predict the efficacy of 5-FU in gastric cancer [19]. In this work, we further reveal that the Pro/Pro genotype is an independent risk factor in gastric cancer patients receiving oxaliplatin-based adjuvant chemotherapy. However, because *p53* gene is frequently mutated in tumors, the possible effect of other *p53* mutations on the codon 72 polymorphism should be further assessed before this polymorphism could be used for clinical application.

Based on individual results of the five polymorphisms, we further analyzed clinical outcomes according to the numbers of favorable genotype. We demonstrate that a patient's benefit from oxaliplatin-based adjuvant chemotherapy significantly increases with the number of favorable genotypes. A combined analysis may more accurately identify patients with maximum benefit from oxaliplatin-based chemotherapy.

In conclusion, our data show that the polymorphisms of *p53* Arg72Pro, *GSTP1* Ile105Val, and *XRCC1* Arg399Gln polymorphisms appear to be independent prognostic factors in gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy, which merits detailed investigation as an innovative strategy for prediction of treatment outcome in clinical oncology. Due to the limited number of samples, this study needs to be regarded as exploratory and results need to be confirmed in an independent study.

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