

# Pharmacogenetic role of *XRCC1* polymorphisms on the clinical outcome of gastric cancer patients with platinum-based chemotherapy: a systematic review and meta-analysis

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**ABSTRACT.** It is still controversial whether X-ray repair cross-complementing group (*XRCC1*) gene polymorphisms (Arg194Trp and Arg399Gln) are associated with the clinical outcome of platinum-based chemotherapy in gastric cancer patients based on published studies. Meta-analysis was performed to provide a systematic review of the findings. Eligible articles from the PubMed, SinoMed, and CNKI databases before September 1, 2012, were selected. Objective response (complete response + partial response *vs* progressive disease + stable disease), progress-free survival (PFS) and overall survival (OS) were applied to evaluate clinical outcomes. We calculated the odds ratio or hazard risk (HR) with 95% confidence interval (CI) using the STATA software. Eleven eligible articles including 1274 gastric cancer patients with platinum-based treatment were enrolled in our meta-analysis. The results indicated that the A allele of the *XRCC1*

Arg399Gln polymorphism was significantly associated with poor OS (HR = 1.40; 95%CI = 1.04-1.90) of gastric cancer but not for platinum-based chemotherapy response or PFS. No significant associations were observed between *XRCC1* Arg194Trp and objective response. The data suggest that the *XRCC1* Arg399Gln polymorphism may be a prognostic biomarker of OS for platinum-based gastric cancer treatment. However, further cohorts with larger sample sizes from different ethnic backgrounds and with improved experimental design are needed to confirm these findings.

**Key words:** Chemotherapy; *XRCC1*; Polymorphism; Meta-analysis; Gastric cancer

## INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide and remains the leading cause of cancer death (Parkin et al., 2005). Although radical surgery combined with platinum-based adjuvant chemotherapy has improved clinical outcomes (Sakuramoto et al., 2007), the approximate 5-year survival rate is merely 20% (Paoletti et al., 2010), and the therapeutic effect differs among individuals.

The DNA repair system plays a critical role in tumorigenesis and treatment resistance (Deans and West, 2011; Wilting and Dannenberg, 2012). *XRCC1*, the key protein of the base excision repair system, serves as a scaffold protein for repairing base lesions induced by reactive oxygen species (David et al., 2007). We previously identified that gastric cancer patients with higher expression of *XRCC1* have a longer survival time than those with low expression (Wang et al., 2012). In addition, *XRCC1* and several other DNA repair proteins were involved in repairing cisplatin-induced DNA interstrand cross-links (Zhu and Lippard, 2009). It is conceivable that interindividual differences in *XRCC1* may contribute to the capacity of repairing platinum-induced DNA damage, thus influencing the chemotherapy efficacy and clinical outcome of gastric cancer patients.

The most common polymorphisms in the *XRCC1* gene are Arg399Gln (rs25487, G>A) and Arg194Trp (rs1799782, C>T). A recent meta-analysis showed that the 2 single nucleotide polymorphisms (SNPs) had predictive value on the clinical outcomes of platinum-based chemotherapy in advanced non-small cell lung cancer (Wu et al., 2012). However, the association between *XRCC1* SNPs and clinical outcomes in gastric cancer is contradictory. We conducted a meta-analysis to assess the efficacy of platinum-based chemotherapy of gastric cancer patients with different *XRCC1* SNPs.

## MATERIAL AND METHODS

### Study selection

We searched the relevant electronic literature from the PubMed, SinoMed, and CNKI databases before September 1, 2012, using the following searching items: “*XRCC1* or X-ray repair cross complementing protein 1”, “stomach cancer or gastric cancer”, and “polymorphism or variant”.

The eligible studies should meet the following criteria:

- a) Advanced, recurrent, or metastatic gastric cancer patients
- b) Histology or pathology confirmed
- c) Treated with any kinds of platinum drugs
- d) Prospective cohort studies of Arg399Gln (G>A) or Arg399Gln polymorphisms
- e) Sample size  $N > 45$ .

We also contacted the corresponding authors for missing information and excluded articles lacking critical information after repeated requests (Ott et al., 2011). If the same research group published multiple papers for the same cohort, we selected the paper containing the largest sample size, using the latest polymorphism data, or presenting the most detailed data that could be extracted more easily.

### Data extraction and quality assessment

Two investigators extracted data independently. In some cases with discrepant results, a discussion was initiated to agree on a common conclusion. Available data extracted from each study included the first author's surname, year of publication, country of origin, ethnicity, sample size, genotyping method, and clinical outcome. In addition, ethnicity was categorized as Asian or Caucasian.

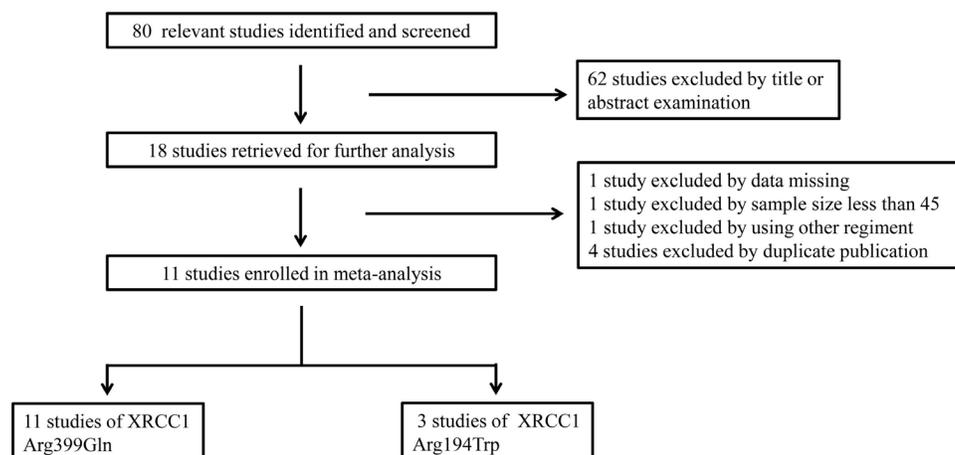
### Statistical analysis

We used the World Health Organization (WHO) criteria (Miller et al., 1981) or Response Evaluation Criteria in Solid Tumors (RECIST; Therasse et al., 2000) to estimate the odds ratio (OR) and corresponding 95% confidence intervals (95% CIs) for objective response *vs* no response after platinum-based chemotherapy [complete response + partial response *vs* progress disease + stable disease]. Pooled Cox proportional hazards ratios (HRs) and 95% CIs were estimated for progression-free survival (PFS) and overall survival (OS), using published methods (Parmar et al., 1998; Tierney et al., 2007). A  $\chi^2$  test-based Q-statistic test was performed to check heterogeneity between studies, and  $P < 0.10$  was considered to be significant (Lau et al., 1997). Initial analyses with a fixed-effect model were used, and if heterogeneity among studies existed, a random-effect model was applied. Funnel plots and the Egger test were utilized to examine the effect of publication bias. All analyses were performed using the STATA software, and P values were two-side with a significance level of 0.05.

## RESULTS

We initially identified 80 relevant articles, among which only 18 studies met our inclusion criteria through reading the title or abstract. By the detailed assessment, we excluded 1 study for missing data, 1 study due to a small sample size, 1 study for using a regimen without platinum, and 4 studies for duplicate publication (Figure 1).

Only 2 studies, from Italy and Germany, investigated the association between *XRCC1* polymorphisms and gastric cancer clinical outcome in the Caucasian population. The patients from the remaining cohorts were Asian, either from China or Korea. In total, 1274 gastric cancer patients had been treated with platinum-based chemotherapy and were included in our analysis (Table 1).



**Figure 1.** Flow chart of the study selection process for eligible articles.

**Table 1.** Characteristics of the eligible studies considered in this report.

First author	Year	Country	Ethnicity	Sample sizes	Median age [years (min-max)]	Evaluation criterion	Methods	SNPs	Outcomes
Ruzzo	2006	Italy	Caucasian	175	61 (38-79)	WHO	PCR-RFLP	Arg399Gln Arg194Trp	TR TR
Keam	2008	Korea	Asian	73	59 (24-77)	WHO	PCR-PFLP	Arg399Gln	TR, PFS, OS
Qiu	2009	China	Asian	68	55 (38-77)	WHO	PCR-RFLP	Arg399Gln	TR, PFS
Huang	2009	China	Asian	102	58 (34-76)	-	PCR-RFLP	Arg399Gln	OS
Goekkurt	2009	Germany	Caucasian	193	64 (27-86)	WHO	PCR-RFLP	Arg399Gln	TR, OS
Shim	2010	Korea	Asian	200	58 (19-76)	RECIST	PCR-RFLP	Arg399Gln Arg194Trp	TR, PFS, OS TR
Liang	2010	China	Asian	81	55 (32-77)	-	Taqman	Arg399Gln	PFS, OS
Ji	2010	China	Asian	59	-	RECIST	PCR-RFLP	Arg399Gln	TR
Gao	2010	China	Asian	91	58 (21-75)	WHO	PCR-RFLP	Arg399Gln Arg194Trp	TR TR
Park	2011	Korea	Asian	106	57 (26-72)	RECIST	PCR-RFLP	Arg399Gln	PFS, OS
Liu	2011	China	Asian	126	-	-	Taqman	Arg399Gln	OS

TR = therapeutic response; PFS = progression-free survival; OS = overall survival.

## Objective response

There were seven eligible studies covering 809 individuals for the analysis of the predictive value of *XRCC1* Arg399Gln concerning the objective response of gastric cancer to platinum-based treatment (Ruzzo et al., 2006; Keam et al., 2008; Goekkurt et al., 2009; Qiu and Wang, 2009; Gao et al., 2010; Ji et al., 2010; Shim et al., 2010). However, in the dominant model, the A allele did not show any positive association between polymorphism and treatment response in all patients (G/A+A/A vs G/G: OR = 0.97; 95%CI = 0.49-1.26) (Table 2) or stratified analysis by ethnicity (Asian: OR = 0.84; 95%CI = 0.42-1.70; Caucasian: OR = 0.75; 95%CI = 0.38-1.48). No publication bias was observed, either by the Funnel test or the Egger test (data not shown).

**Table 2.** Analysis of the association among *XRCC1* Arg399Gln and Arg194Trp polymorphisms and objective response, progression-free survival (PFS), and overall survival (OS).

	Objective response			PFS			OS		
	Study <sup>a</sup> (cases)	OR (95%CI)	P <sub>het</sub> <sup>b</sup>	Study <sup>a</sup> (cases)	HR (95%CI)	P <sub>het</sub> <sup>b</sup>	Study <sup>a</sup> (cases)	HR (95%CI)	P <sub>het</sub> <sup>b</sup>
Arg399Gln									
G/A+A/A vs G/G	7 (809)	0.79 (0.49-1.26) <sup>c</sup>	0.03	5 (528)	1.32 (0.84-2.07) <sup>c</sup>	0.00	7 (823)	1.40 (1.04-1.90) <sup>c</sup>	0.01
Arg194Trp									
C/T+T/T vs C/C	3 (466)	0.92 (0.60-1.41)	0.68	-	-	-	-	-	-

<sup>a</sup>The number of the studies included in the analysis. <sup>b</sup>P<sub>het</sub> = P value of between-study heterogeneity. <sup>c</sup>If P value for heterogeneity <0.10, the random-effect model was used.

Three eligible studies including 466 individuals were selected to confirm whether the *XRCC1* Arg194Gln polymorphism was correlated with platinum-based chemotherapy response (Ruzzo et al., 2006; Gao et al., 2010; Shim et al., 2010). Unfortunately, there was no association between genetic variations and treatment response in any population (C/T+T/T vs C/C: OR = 0.92; 95%CI = 0.60-1.41) (Table 2) or stratified analysis by ethnicity (Asian: OR = 0.94; 95%CI = 0.59-1.52; Caucasian: OR = 0.84; 95%CI = 0.33-2.12). No publication bias was observed either by the Funnel test or the Egger test (data not shown).

### Progression-free survival

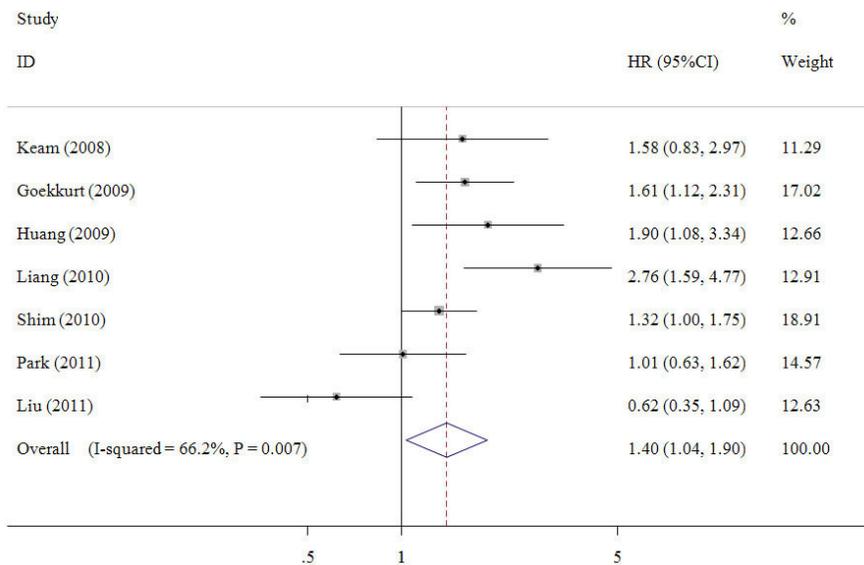
Five studies concerning the predictive value of the *XRCC1* Arg399Gln polymorphism with respect to PFS to the platinum-based treatment were selected for the final analysis (Keam et al., 2008; Qiu and Wang 2009; Liang et al., 2010; Shim et al., 2010; Park et al., 2011). Five hundred and twenty-eight gastric cancer patients enrolled in our studies were Asian. Unfortunately, the A allele did not have a higher PFS than the G allele when tested using the random-effect model (G/A+A/A vs G/G: HR = 1.32; 95%CI = 0.84-2.07) (Table 2). No publication bias was observed either by the Funnel test or the Egger test (data not shown).

### Overall survival

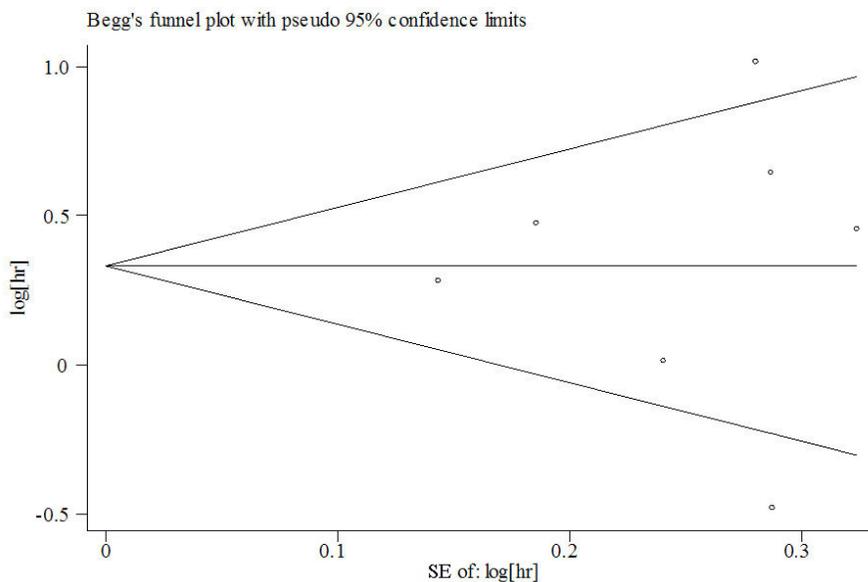
Seven studies covering 881 patients were eligible for the analysis of the association between the *XRCC1* Arg399Gln polymorphism and OS (Keam et al., 2008; Goekkurt et al., 2009; Huang et al., 2009; Liang et al., 2010; Shim et al., 2010; Liu et al., 2011; Park et al., 2011). Only 1 study was based on the Caucasian population (Goekkurt et al., 2009). Patients with the A allele had a shorter overall survival time than those with the G allele when tested with the random-effect model (G/A+A/A vs G/G: HR = 1.40; 95%CI = 1.04-1.90) (Figure 2 and Table 2). No publication bias was observed either by the Funnel test or the Egger test (Figure 3).

## DISCUSSION

In this meta-analysis, we found that only gastric cancer patients with the *XRCC1* 399Gln allele, who were treated by platinum-based chemotherapy, had a negative association with overall survival time.



**Figure 2.** Forest plot of overall survival in gastric cancer patients treated with platinum-based chemotherapy by the *XRCC1* Arg399Gln polymorphism (G/A+A/A vs G/G, reference group = G/G).



**Figure 3.** Funnel plot of overall survival in gastric cancer patients treated with platinum-based chemotherapy by the *XRCC1* Arg399Gln polymorphism (G/A+A/A vs G/G, reference group = G/G).

Patients with more resistance to platinum therapy have poorer clinical outcomes (d'Amato et al., 2009). Various mechanisms underlie platinum resistance, among which the DNA repair is one of the most predominant mechanisms (Rabik and Dolan, 2007; Galluzzi et al.,

2012; Shen et al., 2012). *XRCC1* is an indispensable protein involved in DNA repair, playing a critical role in base-excision repair (Parsons et al., 2010), homologous recombination (Fan et al., 2007), and non-homologous end joining (Audebert et al., 2004). The *XRCC1* Arg194Trp and Arg399Gln polymorphisms are the most studied SNPs and contribute to altering the DNA repair capacity, thus altering chemotherapy sensitivity and clinical outcome. Previous studies showed that *XRCC1* polymorphisms had predictive value of the clinical outcomes of lung cancer patients undergoing platinum-based chemotherapy (Cui et al., 2012; Wu et al., 2012). However, the predictive value for gastric cancer patients is still controversial, which prompted us to conduct the present meta-analysis to comprehensively evaluate the role of the *XRCC1* polymorphisms.

In this meta-analysis, we assessed the *XRCC1* polymorphisms on the clinical outcomes of patients treated with platinum-based chemotherapy based on objective response, PFS, and OS. Because the objective response does not always correlate with survival outcome (Lokich, 2004), we analyzed objective response, PFS, and OS together for a comprehensive assessment. The *XRCC1* Arg194Trp and Arg399Gln polymorphisms were not associated with the objective response, in the overall population or stratified by ethnicity. In addition, the *XRCC1* Arg399Gln polymorphism did not show the predictive role in PFS. Interestingly, we found that patients with the *XRCC1* Arg399 allele might have a shorter OS time when treated with platinum-based drugs, which was consistent with 4 of the included studies (Goekkurt et al., 2009; Huang et al., 2009; Liang et al., 2010; Shim et al., 2010). Because only 1 in 7 studies was conducted in Caucasians, additional studies with larger sample sizes and different ethnic backgrounds are needed to make a more definitive conclusion.

Above all, we should clarify that there were several limitations in this meta-analysis, despite that Egger and Begg tests suggested that potential publication bias may not exist. First, only 2 studies were based on the Caucasian population (Table 1), which might cause bias. Moreover, there were no associations between the *XRCC1* Arg194Trp and Arg399Gln polymorphisms, objective response, and PFS in Caucasian patients. Although we repeatedly contacted the corresponding author for their original data, we could not get the data for final analysis of PFS (Ruzzo et al., 2006; Goekkurt et al., 2009; Ott et al., 2011). The conclusion was unlikely to change, as the results of the PFS outcome in the 3 studies with missing data were consistent with ours. However, the OS outcome conclusion might be altered marginally. Secondly, different chemotherapy regimens combined with platinum may affect the outcomes. However, we were not able to estimate the impact on the conclusions when different chemotherapy drugs were applied in the recruited data. Thirdly, due to the differences in study design, we could not perform detailed stratification analysis.

In conclusion, our meta-analysis indicated that the *XRCC1* Arg399Gln polymorphism may be a prognostic biomarker for OS for platinum-based gastric cancer treatment. However, well-designed studies with larger sample sizes using individuals with different genetic backgrounds are needed to confirm these findings.

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## Conflicts of interest

The authors declare no conflict of interest.

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