Association between Polymorphisms in XRCC1 Gene and Treatment Outcomes of Patients with Advanced Gastric Cancer: A Systematic Review and Meta-Analysis

Zhuo Cao, Jia Song, Jun Wang, Xufeng Guo, Shijie Yu, Weiguo Dong*

Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, PR China

Abstract

**Background:** Many reports have shown inconsistent results on the relationship between single nucleotide polymorphisms (SNPs) of X-ray repair cross complementing protein (XRCC1) gene and platinum-based chemotherapeutic efficacy. This meta-analysis aimed to summarize published data about the association between two SNPs of XRCC1 (Arg194Trp and Arg399Gln) and treatment outcomes of patients with advanced gastric cancer.

**Methodology/Principal Findings:** We retrieved the relevant articles from MEDLINE, Web of Knowledge, and the China National Knowledge Infrastructure (CNKI) databases. Studies were selected according to specific inclusion and exclusion criteria. Study quality was assessed according to the guidelines outlined by Hayden, et al. and PRISMA guidelines. We estimated the odds ratio (OR) for response rate versus no response after platinum-based chemotherapy. Progression-free survival (PFS) and overall survival (OS) were evaluated by pooled Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs). We found that none of the XRCC1 Arg194Trp and Arg399Gln polymorphisms was significantly associated with tumor response. Stratified analysis by ethnicity or sensitivity analysis also showed that XRCC1 SNPs were not related with chemotherapy response. Patients with minor variant A allele were likely to have poorer 2-year survival rate than those with G/G genotype. However, in the group of 5-year follow up, there was no significant association between the A allele and OS yet.

**Conclusions/Significance:** There is no evidence to support the use of XRCC1 Arg194Trp and Arg399Gln polymorphisms as prognostic predictors of TR and PFS in gastric patients treated with platinum-based chemotherapy. The relationship between minor variant A allele and OS requires further verification.

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* E-mail: whdwg@whu.edu.cn

Introduction

Worldwide, gastric cancer is the third most common cause of cancer death among males and the fifth in females [1]. Despite improvements in diagnosis and therapy, the overall survival time of advanced gastric cancer patients is still short. Platinum-based chemotherapy has been a common regimen for patients with advanced gastric cancer. However, chemotherapy sensitivity varied remarkably between different patients.

Up to now, researchers have determined that efficacy of the chemotherapy is multifactorial. Gene polymorphisms of drug target genes, genes involving in DNA repair pathways and detoxification pathways may influence the effect of the anti-cancer agents [2,3].

**XRCC1** gene repairs single-strand breaks by encoding a protein that defends breaks while repairs base excision through interacting with other proteins [4,5]. Another study showed that XRCC1 protein could bind to platinum-containing DNA duplexes [6]. These studies imply that XRCC1 contributes to the repair of platinum-induced DNA damage. The single nucleotide polymorphisms in DNA repair pathways may alter gene expression and activity, therefore influence the effectiveness of cancer therapy and prognosis of patients [7]. The most extensively studied SNPs of XRCC1 gene are Arg399Gln (G > A, rs25487) and Arg194Trp (C > T, rs1799782). The two SNPs have been reported to be associated with an altered DNA repair activity [8,9]. Therefore, these SNPs might alter the activity of DNA repair, thus influence the efficacy of platinum-based chemotherapy and the prognosis of patients.

Some researchers have studied the association between SNPs in XRCC1 gene and clinical outcome of gastric cancer patients [10–23]. However, the results were not consistent. We performed a systemic review and meta-analysis to assess the evidence about effects of XRCC1 SNPs on the efficacy of chemotherapy and overall survival in gastric cancer patients treated with platinum-based chemotherapy.
Methods

Retrieval of Published Studies

This meta-analysis focused on studies dealing with prognostic implication of XRCC1 SNPs in patients with gastric cancer. We searched for relevant publications before June 1st, 2013 by using electronic MEDLINE, Web of Knowledge and CNKI databases with the following terms “XRCC or X-ray repair cross complementing protein”, “gastric or stomach cancer”, “polymorphism or variant”, “chemotherapy or progression-free survival or overall survival”. We searched for studies without any language limitation. Furthermore, we screened the titles and abstracts to identify the relevant studies. The review was limited to the published studies and no contact was made with the authors to obtain unpublished data.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients with advanced, recurrent, or metastatic gastric cancer should be histologically or pathologically confirmed. (2) The gastric cancer patients were treated by any of the platinum drugs. (3) Studies should contain the information to estimate relative risks (i.e., ORs, HRs) and 95% CIs for prognostic effect of gastric cancer. (4) SNPs in XRCC1 gene should be genotyped. Unrelated articles and some types of original studies were not eligible for this meta-analysis, such as review, case report and meta-analysis. Studies were excluded if critical information was missing and not obtained by our repeated requests.

Data Extraction

The following information was extracted from included publications: first author’s name, year of publication, country, race of patients, source of patients, study design, number of patients, gender distribution, age (median), tumor stage, genotyping method, chemotherapy regimens, clinical outcomes, response criteria and genotype data.

Quality assessment

The quality and risk of bias within the papers were critically appraised separately by two reviewers. Study quality was assessed according to the guidelines outlined by Hayden et al and PRISMA guidelines [24,25]. For every included study, each of the following domains of potential bias was assessed:

1. Study participation: Inclusion and exclusion criteria defined in detail; The key characteristics of study population described in detail; Table sample size > 50
2. Study attrition: Response rate > 80%; Record of reason for loss to follow-up; No impact of loss to follow-up on the results of the study
3. Prognostic factor measurement: Genotyping methods fully described; Genotyping verified by sequence; Blindness of assessment for genotyping
| Study | Country | Source of patients | Race | NO. of patient (male%) | Age (mean) | Stage | Chemotherapy (No.) | Dose of platinum \( \text{m}^2 \) | Study design | Blindness of assessment | Genotype data | Polymorphism detection method | Quality checks | HWE | Outcomes | Quality checks | mPFS (month) | mOS (month) |
|-------|---------|-------------------|------|-----------------------|------------|-------|-------------------|----------------|-------------|------------------|----------------|------------------------|---------------|------|----------|-------------|----------|----------|
| Liu Y | China   | Hospital          | Asian| 126(71.4%)            | 57         | II-IV | L-OHP 85mg/\( \text{m}^2 \) biweekly | U             | U          | Arg399Gln | TaqMan       | Y             | Y          | OS       | /           | 12        | 21       |
| Park S | Korea   | National Cancer   | Asian| 108(68.5%)            | 57         | IV/R  | S-1+DDP           | DDP 60mg/\( \text{m}^2 \) triweekly | P           | U          | Arg399Gln | PCR-RFLP    | Y             | N          | TR/PS/OS | Y           | U         | U        |
| Ji M  | China   | Hospital          | Asian| 59(67.8%)             | 35–75      | IV    | L-OHP+CF+5-FU     | DDP 130mg/\( \text{m}^2 \) triweekly | U           | U          | Arg399Gln | PCR-LDR     | N             | N          | TR       | /           | /         | /        |
| Liang J| China   | Hospital          | Asian| 85(76.5%)             | 55         | IV    | L-OHP+CF+5-FU     | DDP 60mg/\( \text{m}^2 \) triweekly | P           | U          | Arg399Gln | PCR-LDR     | N             | Y          | TR       | /           | /         | /        |
| Gao C | China   | Hospital          | Asian| 91(73.6%)             | 58         | Advanced | L-OHP 100mg/\( \text{m}^2 \) biweekly/100mg/\( \text{m}^2 \) triweekly/60mg/\( \text{m}^2 \) | U           | U          | Arg399Gln/Arg194Gln | PCR-RFLP | Y         | Y          | TR        | /         | 43        | 11.9      |
| Shim H | Korea   | Hospital          | Asian| 200(75.0%)            | 58         | IV/R  | DDP+TAX(188)/DDP+DOC(12) | DDP 75mg/\( \text{m}^2 \) | P           | U          | Arg399Gln/Arg194Gln | PYRO/PCR-RFLP | N         | Y         | TR/PS/OS*| N         | /         | /         |
| Won D | Korea   | Hospital          | Asian| 55(29.1%)             | 65         | Advanced/R | mFOLOX-6 | L-OHP 100mg/\( \text{m}^2 \) biweekly | P           | U          | Arg399Gln | PCR-RFLP   | N             | Y          | TR/OS#   | Y           | 5         | 14       |
| Goekkurt| Germany | Multicenter       | Caucasian| 134(68.7%)          | 64         | Metastatic | FLO(71)/FLP(63) | L-OHP 85mg/\( \text{m}^2 \) biweekly/50mg/\( \text{m}^2 \) triweekly | P           | U          | Arg399Gln | PCR-RFLP   | Y             | Y          | TR/PS//OS* | N         | U         | U        |
| Qiu D | China   | Hospital          | Asian| 68(130)               | 55         | Early/advanced | FOLFOX-4/TS-1/Taxane | L-OHP 130mg/\( \text{m}^2 \) triweekly | P           | P          | Arg399Gln/Arg194Gln | PCR-LDR/PCR-RFLP | N         | N         | Y         | TR/PS/OS| /         | 8          | /          | 30       |
| Huang Z| China   | Hospital          | Asian| 102(71.6%)            | 58         | IB-IV | FOLFOX-4/83/FOLFOX4+TAX/HCP(19) | L-OHP 85mg/\( \text{m}^2 \) biweekly/L-OHP 85mg/\( \text{m}^2 \) biweekly | R           | Y          | Arg399Gln | PCR-LDR    | N             | Y          | OS       | /           | 20        | 26       |
| Keam B | Korea   | II clinical trial | Asian| 73(65.8%)             | 59         | IV/R  | mFOLOX-6 | L-OHP 100mg/\( \text{m}^2 \) biweekly | P           | U          | Arg399Gln | PCR-RFLP   | N             | Y          | TR/PS/OS* | Y           | 6         | 12.6     |
| Ruzzo A| Italy   | Multicenter       | Caucasian| 173(56.6%)           | 61         | IV    | FP       | Unknown | P           | Y          | Arg399Gln/Arg194Gln | PCR-RFLP | N         | Y         | TR/PS//OS*| U         | 6          | 9.8       |

Abbreviation:
- a: R, recurrent.
- b: DDP, cisplatin; S-1, Tegafur Gimeracil Oteracil Potassium Capsule; L-OHP, oxaliplatin; CF, calcium folinate; 5-FU, 5-fluoro-2,4 (1h, 3h) pyrimidinedione; TAX, paclitaxel; DOC, docetaxel; HCPT, hydroxycamptothecin.
- c: U, unsure.
- d: P, prospective; R, retrospective.
- e: Y, yes.
- f: N, no.
- g: *, adjusted for confounders; *, data not given.

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Outcome measurement: WHO or RECIST criteria for tumor response; Outcome measure confirmed by repeat; Blindness of assessment for outcome.

Confounding measurement and account: Adequately valid and reliable measurement used for all important confounders; Important potential confounders adjusted by multiple analysis.

Analysis: Sufficient presentation of data to assess the adequacy of the analysis; No selective reporting of results.

Any differences in opinion were resolved by discussion, then by adjudication to a third reviewer. Studies of acceptable quality for inclusion in the synthesis would at least partly satisfy each of the six biases.

**Statistical methods**

Hardy–Weinberg equilibrium (HWE) was calculated again using a goodness-of-fit test ($\chi^2$ or the Fisher exact tests, significant at the 0.05 level).

We estimated the OR for response rate versus no response after platinum-based chemotherapy (CR+PR vs. PD+SD, using the WHO criteria [26] or the Response Evaluation Criteria inSolid Tumors criteria (RECIST) [27]).

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**Table 2.** Quality assessment of included studies.

| Study          | Study participants | Study attrition | Genotyping method | Outcome measurement | Confounding measurement and account | Analysis |
|----------------|--------------------|-----------------|-------------------|---------------------|-------------------------------------|----------|
| Liu Y 2011     | Y                  | U               | Y                 | /                   | /                                   | /        |
| Park SR 2011   | Y                  | Y               | Y                 | Y                   | Y                                   | /        |
| Ji M 2010      | Y                  | Y               | Y                 | P                   | /                                   | /        |
| Liang J 2010   | Y                  | U               | Y                 | /                   | /                                   | /        |
| Gao C 2010     | P                  | Y               | P                 | P                   | /                                   | /        |
| Shim HJ 2010   | Y                  | Y               | P                 | P                   | /                                   | /        |
| Won DY 2010    | P                  | U               | P                 | Y                   | Y                                   | Y P      |
| Goekkurt E 2009| Y                  | Y               | Y                 | Y                   | Y                                   | Y P      |
| Huang Z 2009   | Y                  | U               | Y                 | /                   | /                                   | /        |
| Tahara T 2011  | Y                  | Y               | P                 | /                   | /                                   | /        |
| Qiu D 2009     | P                  | N               | P                 | P                   | N                                   | N Y      |
| Keam B 2008    | Y                  | U               | Y                 | Y                   | Y                                   | Y Y P    |
| Ruzzo A 2006   | Y                  | Y               | P                 | P                   | Y                                   | Y P      |

Abbreviation: PFS: progression-free survival; OS: overall survival; Y: yes; P: partly; N: no; U: unsure.

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**Table 3.** Allele frequency of XRCC1 Arg194Trp and Arg399Gln.

| Study          | Arg399Gln | Arg194Trp |
|----------------|-----------|-----------|
|                | allele frequency | allele frequency |
|                | % (Gln) | % (Trp) |
| Liu Y 2011     | 20.5     | -        |
| Park SR 2011   | 37.0     | -        |
| Ji M 2010      | 42.4     | -        |
| Liang J 2010   | 25.9     | -        |
| Gao C 2010     | 30.2     | 42       |
| Shim HJ 2010   | 27.5     | 153      |
| Won DY 2010    | 18.0     | 41       |
| Goekkurt E 2009| 38.0     | 8        |
| Huang Z 2009   | 26.5     | -        |
| Tahara T 2011  | 29.3     | -        |
| Qiu D 2009     | 22.1     | -        |
| Keam B 2008    | 20.0     | -        |
| Ruzzo A 2006   | 36.0     | 85       |

Abbreviation: PFS: progression-free survival; OS: overall survival.

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The association between XRCC1 polymorphisms and response rate was estimated by calculating a pooled OR and 95% CI under four genetic models respectively (allele frequency: A vs. G; co-dominant model: A/A vs. G/G, G/A vs. G/G; dominant model: A/A+G/A vs. G/G; recessive model: A/A vs. G+G/A and complete overdominant model: A/A+G/G vs. G/A).

PFS and OS were evaluated by pooled Cox proportional HRs and 95% CIs using published methods [28]. HRs and 95% CIs were estimated directly from the raw [11,13,14,20] or indirectly from the Kaplan–Meier curve of an article [17,22].

We used the Cochran’s Q test, with a significance level of $P_1$, to detect the between-study heterogeneity. We performed primary analyses with a fixed-effect model and confirmatory analyses with a random-effect model, if there was significant heterogeneity. We examined the effect of publication bias using inverted funnel plots and the Egger’s test, and all analysis was carried using the Review Manager 5.2.

### Results

#### Study Characteristics

Overall, 57 studies were selected during the first step of systematic literature review, of which 18 studies seemed to meet the inclusion criteria. Four studies were excluded because the data was inestimable and authors were unreachable [18,29,30,31] (Fig. 1). Finally, the data pool consisted of 13 studies, including 1406 cancer patients.

#### Genotypes were verified by sequencing in all samples in two studies [17,20], partially verified in 20% of samples in one study [12], and not verified in the rest of the studies.

Tumor responses were evaluated using WHO criteria or RECIST criteria. Response rate was confirmed in three studies [11,16,17] and not confirmed in the rest of the studies. Clinical investigators were blind to the results of genotyping in only two studies [10,13] and in the remaining eleven studies this information was not reported.

Potential confounders were fully reported in nine out of 13 identified studies. Statistical analysis was adjusted for confounding variables in seven studies for clinical outcomes.

The frequency for 194Trp was from 6.9% to 32.5% with respect to response rate and that for 399Gln was from 18.0% to 42.4% in Chinese patients and 36.0% to 38.0% in Caucasian patients (Table 3).

Using the frequencies of XRCC1 genotypes, all populations were found to be in HWE except two studies by Ji M et al and Park SR et al [17,19]. Minelli C et al. recently pointed out that studies that appear to deviate from HWE should be investigated further rather than just excluded unless there are other grounds for doubting the quality of the study [32]. In our meta analysis, the HWE-deviant population evaluated by Park SR was not excluded because no genotyping error was detected by PCR-RFLP combined with sequencing [17], while that population evaluated by Ji M was excluded from the study because of small samples and low quality [19].

### Response rate of XRCC1 Arg194Trp polymorphism

Because the study on the association between XRCC1Arg194Trp polymorphism with PFS or OS was too few

### Table 4. Analysis of the association between XRCC1 Arg194Trp and response rate in different models.

| Genetic models | Fixed-effect model (95%CI) | $P_1$ | $I^2$ | $P_2$ |
|----------------|-----------------------------|-------|-------|-------|
| T vs. C        | 1.15 (0.83, 1.61)            | 0.41  | 0%    | 0.73  |
| C/T vs. C/C    | 1.23 (0.79, 1.91)            | 0.36  | 0%    | 0.93  |
| T/T vs. C/C    | 1.22 (0.51, 2.93)            | 0.66  | 10%   | 0.33  |
| T/T+C/T vs. C/C| 1.23 (0.80, 1.87)            | 0.34  | 0%    | 0.99  |
| T/T vs. C/T+C/C| 1.11 (0.48, 2.58)            | 0.81  | 23%   | 0.27  |
| T/T+C/T vs. C/T| 0.84 (0.55, 1.28)            | 0.41  | 0%    | 0.71  |

Abbreviation: $P_1$, p value for difference; $P_2$, p value for heterogeneity.

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Figure 2. Forest plots of response rate in AGC patients treated with chemotherapy by XRCC1 Arg399Gln polymorphism: G/A or A/A vs. G/G.

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to be analyzed, we only analyzed the association of XRCC1 Arg194Trp polymorphism with tumor response in gastric cancer patients in this meta-analysis.

Three studies with a total sample size of 466 patients were eligible for the final analysis. The results from the meta-analysis indicated no statistically significant association between XRCC1 Arg194Trp polymorphism and tumor response under all the genetic models (T vs. G: OR = 1.21, 95% CI 0.80–1.74; recessive model: OR = 1.19, 95% CI 0.95–1.49; Table 4). No significant publication bias was detected by either the inverted funnel plot or Begg’s test (data not shown).

Response rate of XRCC1 Arg399Gln Polymorphism

Eight studies including 903 patients were qualified for the final analysis. The results from the meta-analysis indicated no statistically significant association between XRCC1 Arg399Gln polymorphism and tumor response under all the genetic models (T vs. G: OR = 1.17, 95% CI 0.83–1.69; recessive model: OR = 1.19, 95% CI 0.96–1.49; Table 5), and no single study altered the result substantially by the sensitivity test. Stratified analysis by ethnicity showed the 399Gln allele was not associated with response rate neither in Asians or in Caucasians. No significant publication bias was detected by either the inverted funnel plot or Begg’s test (data not shown).

Progression free survival and Overall survival of XRCC1 Arg399Gln Polymorphism

Three studies were eligible for analyzing the relationship between the minor variant A allele and progression-free survival. In dominant model, the XRCC1 399 A allele was not associated with high risks of disease progression for gastric cancer patients (G/A + A/A versus G/G: HR, 1.04; 95%CI, 0.49–2.25; I² = 85%, p = 0.001 for heterogeneity) (Fig. 3).

Six studies with a total number of 569 patients were eligible for the final analysis. In dominant model, the XRCC1 Arg399Gln SNPs was not associated with increasing risk of death in all patients (G/A + A/A versus G/G: HR, 1.28, 95%CI, 0.82–2.01; I² = 76%, p = 0.007 for heterogeneity) (Fig. 4).

There was significant heterogeneity when these six studies were combined. Stratified analysis by follow-up time, the A allele was associated with more risk of death in the subgroup of 2-year follow up (G/A or A/A versus G/G: HR, 2.32; 95%CI, 1.72–3.13; I² = 0%, p = 0.38 for heterogeneity) (Fig. 4). However, there was no significant association between the A allele and survival in the group of 5-year follow up. No significant publication bias was detected by either the inverted funnel plot or Begg’s test (data not shown).

Discussion

In this meta-analysis, there was not any evidence for an association nor an ethnic difference between the XRCC1 194 and 399 polymorphisms and tumor response in all patients. However, the minor variant A allele of XRCC1 399 polymorphism was negatively associated with progression-free survival and 2-year survival in gastric cancer patients.

Platinum agents are activated intracellularly, covalently binding to DNA to induce DNA adducts and finally leading to cell death. Various signal transduction pathways, including DNA damage recognition and repair, cell-cycle arrest and cell apoptosis, involves in this process to exert anticancer effects. Cancer cells with

### Table 5. Stratified analysis of the association between XRCC1 Arg399Gln and response rate.

| Study groups | No. studies | OR (95%CI) | P1 | P2 | No. studies | OR (95%CI) | P1 | P2 | No. studies | OR (95%CI) | P1 | P2 |
|--------------|-------------|------------|----|----|-------------|------------|----|----|-------------|------------|----|----|
| A vs. G      |             |            |    |    | G/A vs. A   |            |    |    | G/G vs. A   |            |    |    |
| All          | 6           | 1.17[0.94,1.46] | 0.16 | 0.07 | 8            | 1.30[0.99,1.71] | 0.06 | 0.54 | 6            | 1.19[0.74,1.90] | 0.47 | 0.06 |
| Caucasians   | 2           | 1.12[0.80,1.57] | 0.51 | 0.94 | 2            | 1.21[0.73,2.01] | 0.46 | 0.28 | 2            | 1.06[0.33,3.35] | 0.93 | 0.09 |
| Asians       | 4           | 1.21[0.90,1.62] | 0.20 | 0.84 | 6            | 1.36[0.97,1.89] | 0.07 | 0.46 | 4            | 1.33[0.79,2.54] | 0.38 | 0.05 |
| G/G vs. A/A  |             |            |    |    | G/A vs. G   |            |    |    | A/A vs. G   |            |    |    |
| All          | 6           | 0.88[0.61,1.28] | 0.51 | 0.33 | 0.19 | 6            | 1.29[0.86,1.65] | 0.28 | 0.06 | 6            | 1.30[0.79,2.14] | 0.30 | 0.08 |
| Caucasians   | 2           | 0.81[0.29,2.31] | 0.70 | 0.80 | 0.32 | 2            | 1.27[0.53,3.07] | 0.59 | 0.08 | 2            | 1.38[0.70,2.71] | 0.35 | 0.06 |
| Asians       | 4           | 0.89[0.60,1.30] | 0.54 | 0.04 | 0.47 | 4            | 1.19[0.80,1.77] | 0.39 | 0.05 | 0.50 | 4            | 1.21[0.58,2.53] | 0.35 | 0.06 |

Abbreviation: P1, p value for difference; P2, p value for heterogeneity.

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![Figure 3. Forest plots of PFS in AGC patients treated with chemotherapy by XRCC1 Arg399Gln polymorphism: G/A or A/A vs. G/G.](https://www.plosone.org/doi/10.1371/journal.pone.0085357.g003)
enhanced ability to repair DNA damage caused by platinum agents, may be resistant to the chemotherapy. There is evidence that cancer patients with a lower DNA repair capacity had an increased overall survival after platinum-based chemotherapy [33,34].

X-Ray repair cross-complementing groups are important proteins of the DNA repair pathways. The XRCC1 protein associates with other proteins to facilitate the processes of base excision repair or single-strand break repair [5]. XRCC1 SNPs have been reported to be associated with an altered DNA repair activity [33,34]. Arg194Trp and Arg399Gln are the most common SNPs in XRCC1 gene, and the 399Gln polymorphism was considered of increasing chemotherapy sensitivity [35].

With a pooled dataset of 903 patients treated with platinum-based regimens, we made a comprehensive assessment of prognosis of gastric cancer patients by response rate, PFS and OS. We found 399Gln allele of XRCC1 polymorphism was negatively associated with progression-free survival and overall survival. Heterogeneity was detected in the analysis of XRCC1 Arg399Gln to overall survival, which indicated variability. Heterogeneity may have been caused by different characteristics, such as ethnicity, tumor stage, sample size, or follow-up time [39]. By subanalysis on follow-up time, there was significant subgroup difference between studies followed up by 2-year and 5-year (P = 0.04). The minor variant A allele was obviously associated with poor OS in studies with 2-year follow up, while not in the studies with 5-year follow up. However, heterogeneity was not removed yet by subanalysis. Our findings suggested that the effect of XRCC1 Arg399Gln polymorphism in clinical outcomes might need to be explored more carefully in future studies incorporating more criteria in the design and experimentation to ensure a more accurate and robust conclusion.

There were several limitations in our meta-analysis. Firstly, the total sample size for analysis of association between progression-free survival and overall survival and XRCC1 SNPs was small, therefore, subgroup analysis for influence of Arg194Trp on response rate and Arg399Gln on PFS and OS could not be performed in the present meta-analysis. Also, some of the findings in subgroups may have been undervalued because of the smaller sample size available for analyses. Secondly, significant heterogeneity between-study was obtained. Most of the eligible studies differed significantly in the study designs, such as patient selection, chemotherapeutic protocol and follow-up time. These may have caused significant heterogeneity between studies. Thirdly, our analysis used published international studies, of which studies [18,29–31] was excluded from the analysis because of loss of contact for original data. We did not include the data of overall survival of XRCC1 Arg399Gln from the study by Shim HJ et al, Goekkurt E et al and Ruzzo A et al [10,12,15], because we can’t get required information to estimate HR for 399Gln allele neither from the raw or indirectly from the Kaplan–Meier curve of an article. This could cause some bias in our estimates, but it is unlikely to change our main conclusions. In addition, we were unable to analyze the association between XRCC1 SNPs and

### Table 1: Forest plots of OS in AGC patients treated with chemotherapy by XRCC1 Arg399Gln polymorphism: G/A or A/A vs. G/G, stratified by follow-up time.

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|------------------|----|--------|--------------|--------------|
| Huang ZH 2009     | 0.6429           | 0.2868 | 16.4% | 1.90 [1.08, 3.34] |             |
| Liu YP 2011       | -0.4813          | 0.2872 | 16.4% | 0.62 [0.35, 1.09] |             |
| Park SR 2011      | -0.2744          | 0.2345 | 17.9% | 0.76 [0.48, 1.20] |             |
| TAHARA T 2011     | 0.1906           | 0.244  | 17.6% | 1.21 [0.75, 1.95] |             |
| Subtotal (95% CI) |                 |     | 68.2% | 1.01 [0.64, 1.61] |             |

Heterogeneity: Tau² = 0.16; Chi² = 9.81, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 0.06 (P = 0.95)

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|------------------|----|--------|--------------|--------------|
| Keam B 2008       | 0.4543           | 0.3238 | 15.3% | 1.58 [0.83, 2.97] |             |
| Liang J 2010      | 1.0152           | 0.2814 | 16.5% | 2.76 [1.59, 4.79] |             |
| Subtotal (95% CI) |                 |     | 31.8% | 2.13 [1.23, 3.69] |             |

Heterogeneity: Tau² = 0.07; Chi² = 1.71, df = 1 (P = 0.19); I² = 42%
Test for overall effect: Z = 2.71 (P = 0.007)

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|------------------|----|--------|--------------|--------------|
| Huang ZH 2009     | 0.6429           | 0.2868 | 16.4% | 1.90 [1.08, 3.34] |             |
| Liu YP 2011       | -0.4813          | 0.2872 | 16.4% | 0.62 [0.35, 1.09] |             |
| Park SR 2011      | -0.2744          | 0.2345 | 17.9% | 0.76 [0.48, 1.20] |             |
| TAHARA T 2011     | 0.1906           | 0.244  | 17.6% | 1.21 [0.75, 1.95] |             |
| Subtotal (95% CI) |                 |     | 68.2% | 1.01 [0.64, 1.61] |             |

Heterogeneity: Tau² = 0.16; Chi² = 9.81, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 0.06 (P = 0.95)

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|------------------|----|--------|--------------|--------------|
| Keam B 2008       | 0.4543           | 0.3238 | 15.3% | 1.58 [0.83, 2.97] |             |
| Liang J 2010      | 1.0152           | 0.2814 | 16.5% | 2.76 [1.59, 4.79] |             |
| Subtotal (95% CI) |                 |     | 31.8% | 2.13 [1.23, 3.69] |             |

Heterogeneity: Tau² = 0.07; Chi² = 1.71, df = 1 (P = 0.19); I² = 42%
Test for overall effect: Z = 2.71 (P = 0.007)

Total (95% CI)

Heterogeneity: Tau² = 0.24; Chi² = 21.10, df = 5 (P = 0.0008); I² = 76%
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Chi² = 4.11, df = 1 (P = 0.04), I² = 75.7%

Figure 4. Forest plots of OS in AGC patients treated with chemotherapy by XRCC1 Arg399Gln polymorphism: G/A or A/A vs. G/G, stratified by follow-up time.

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platinum adverse effects, because few studies provided this information.

Conclusions

Genetic polymorphisms in XRCC1 gene were not likely to be associated with response to platinum-based chemotherapy in advanced cancer patients. However, the relationship between XRCC1 SNPs and overall survival need larger sample size studies to make a further confirmation.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global Cancer Statistics. Ca-Cancer J Clin 61: 69–90.
2. Nagasubramanian R, Inocêncio F, Ratain MJ (2005) Pharmacogenetics in cancer treatment. Annual Review of Medicine-Selected Topics in the Clinical Sciences 54: 437–452.
3. McCord JL (2003) Cancer pharmacogenetics. Brit J Cancer 90: 8–11.
4. Savas S, Kim DY, Alamd MF, Shariff M, Ozekli H (2004) Identifying functional genetic variants in DNA repair pathway using protein conservation analysis. Cancer Epidem Biomar 13: 801–807.
5. Castronuevo KW, Aminof G, Johnson P (1996) XRCC1 polypeptide interacts with DNA polymerase beta and possibly poly (ADP-ribose) polymerase-1 and DNA ligase III is a novel molecular ‘nick-sensor’ in vitro. Nucleic Acids Res 24: 4387–4394.
6. Zhu GY, Lippard SJ (2009) Photoaffinity Labeling Reveals Nuclear Proteins That Uniquely Recognize Cisplatin-DNA Interstrand Cross-Links. Biochemistry-Us 48: 4916–4925.
7. Bernig T, Chanocek SJ (2006) Challenges of SNP genotyping and genetic variation: its future role in diagnosis and treatment of cancer. Expert Rev Mol Diag 6: 319–331.
8. Abdel-Rahman SZ, El-Zein RA (2000) The 399Gln polymorphism in the DNA repair gene XRCC1 modulates the genotoxic response induced in human lymphocytes by the tobacco-specific nitrosamine NNK. Cancer Lett 150: 63–71.
9. Manullo G, Palli D, Peluso M, Guarrera S, Curtarolo S, et al. (2001) XRCC1, XRCC3, XPD gene polymorphisms, smoking and P-32-DNA adducts in a sample of healthy subjects. Carcinogenesis 22: 1437–1445.
10. Ruzzo A, Graziano F, Kawakami K, Watanabe G, Santini D, et al. (2006) Pharmacogenetic profiling and clinical outcome of patients with advanced gastric cancer treated with palliative chemotherapy. J Clin Oncol 24: 1883–1891.
11. Keam B, Im S, Han S, Ham HS, Kim MA, et al. (2008) Modified FOLFOX-6 chemotherapy in advanced gastric cancer: Results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. Bmc Cancer 8: 148–163.
12. Goekkurt E, Al-Batran S, Hartmann JT, Mogck U, Schuch G, et al. (2009) Genetic polymorphisms and response to platinum-based chemotherapy in advanced gastric cancer. Chin J of Oncol 18: 2688–2698.
13. Liang J, Li Q, Yao R, Lv H, Jiang J, et al. (2010) Association between genetic polymorphisms of ERCC1, XRCC1, GSTP1 and survival of advanced. Gastric cancer patients treated with oxaplatin-based chemotherapy. Mol Med Rep 7: 1904–1911.
14. Azavant M, Al-Batran S, Hartmann JT, Mogck U, Schuch G, et al. (2009) Genetic polymorphisms in XRCC1 gene were not likely to be associated with response to platinum-based chemotherapy in advanced gastric cancer patients receiving oxaplatin-based adjuvant chemotherapy. Mod Med Rep 7: 1904–1911.
15. Gao C, Chen H, Lu J, Ding J, Li S, et al. (2010) Relationship between polymorphisms of XRCC1 gene and sensitivity to chemotherapy in advanced gastric cancer. Chin J of Clinical Rational Drug Use 3: 4–6.
16. Won DY, Kim SH, Hur H, Jung H, Jeon HM (2010) Chemotherapeutic responses in advanced gastric cancer: a meta-analysis. J Korean Chem Soc 101: 1247–1254.
17. Shim HJ, Jang SW, Eom KY, Park TR, Park SY. Contributed reagents/materials/analysis tools: ZC. Wrote the paper: ZC. Retrieved published studies: ZC JW.
18. GenoKurt E, Al-Batran S, Hartmann JT, Mogck U, Schuch G, et al. (2009) Genetic polymorphisms and response to platinum-based chemotherapy in advanced gastric cancer patients treated with oxaplatin-based chemotherapy. Chin J of Oncol 18: 2688–2698.
19. Shim HJ, Jang SW, Eom KY, Park TR, Park SY. Contributed reagents/materials/analysis tools: ZC. Wrote the paper: ZC. Retrieved published studies: ZC JW.
20. Liu Y, Ling Y, Qi Q, Zhang Y, Zhang C, et al. (2013) Genetic polymorphisms of ERCC1–118, XRCC1–399 and GSTP1–105 are associated with the clinical outcome of gastric cancer patients receiving oxaplatin-based adjuvant chemotherapy. Mod Med Rep 7: 1904–1911.
21. Gao C, Chen H, Lu J, Ding J, Li S, et al. (2010) Relationship between polymorphisms of XRCC1 gene and sensitivity to chemotherapy in advanced gastric cancer. Chin J of Clinical Rational Drug Use 3: 4–6.
22. Tahara T, Shibata T, Nakamura M, Yamashita H, Yoshida D, et al. (2011) Effect of Genetic Polymorphisms Related to DNA Repair and the Xenobiotic Pathway on the Prognosis and Survival of Gastric Cancer Patients. Anticancer Res 31: 765–710.
23. Qin D, Wang F (2009) Polymorphism of XRCC1 Gene influences response to OXAPlatin-based chemotherapy in patients with advanced gastric cancer. J of Radioimmunology 22: 630–637.
24. Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognostic studies in systematic reviews. Ann Intern Med 147: 427–437.
25. Malker D, Liberati A, Tetzeli J, Altman DG (2006) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6: e1000097.
26. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207–214.
27. Therasse P, Arbuck SG, Eisenhaur EA, Wanders J, Kaplan RS, et al. (2000) New guidelines to evaluate the response to treatment in solid Tumors, J Natl Cancer I 92: 205–216.
28. Tierney JE, Stewart LA, Gherai D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. TRIALS 8: 16–25.
29. Ott K, Rachakonda PS, Panzram B, Keller G, Lordick F, et al. (2011) DNA Repair Gene and MTHFR Gene Polymorphisms as Prognostic Markers in Locally Advanced Adenocarcinoma of the Esophagus or Stomach Treated with Cisplatin and 5-Fuorouracil-Based Neoadjuvant Chemotherapy. Ann Surg Oncol 18: 2688–2698.
30. Jin B, Wei J, Zou Z, Qian X, Nakamura T, et al. (2007) Polymorphism of XRCC1 predicts overall survival of gastric cancer patients receiving oxaplatin-based chemotherapy in Chinese population. Eur J Hum Genet 15: 1049–1053.
31. Wei J, Zhang W, Zou Z, Qian X, Yu L, et al. (2007) Single nucleotide polymorphisms in XRCC1, XRCC3 and ERCC1 genes in gastric cancer patients receiving oxaplatin based chemotherapy. Chin J Public Health Jul 23: 839–840.
32. Minelli C, Thompson JR, Abrams KR, Thakkarinistan A, Attia J (2000) How should we use information about HWE in the meta-analyses of genetic association studies? Int J Epidemiol 37: 156–156.
33. Bosken CH, Wei QY, Amos CI, Spitz MR (2002) An analysis of DNA repair as a gene-disease associations requires appropriate methodological and statistical approaches. J Clin Epidemiol 61: 634–645.