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Original Article

Polymorphisms of ERCC1 and XRCC1 predict the overall survival of advanced gastric cancer patients receiving oxaliplatin-based chemotherapy

Lijian Zhang[1,2], Ruyong Yao[2], Shibao Fang[3], Xiuwen Wang[1], Xin Li[4]

[1]Department of Oncology, Qilu Hospital of Shandong University, Jinan 250012, China; [2]Department of Oncology, The Affiliated Hospital of Medical College, Qing Dao University, Qingdao 266003, China; [3]Department of Ultrasound, The Affiliated Hospital of Medical College, Qing Dao University, Qingdao 266003, China; [4]Department of Oncology, The People's Hospital of Jimo, Qingdao 266200, China

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Abstract: The aim of the present study was to evaluate the clinical outcome of excision repair cross-complementing protein 1 (ERCC1) and X-ray repair cross-complementing protein 1 (XRCC1) gene polymorphisms in 89 patients receiving oxaliplatin/5-fluorouracil-based chemotherapy as a first-line treatment regimen for advanced gastric cancer. ERCC1 codon 118C/T and XRCC1 codon 399A/G polymorphisms were identified using quantitative polymerase chain reactions, and the associations between disease control rate (DCR), median overall survival (mOS) and gene polymorphisms were analyzed. Following two cycles of chemotherapy, a complete response was observed in two patients, a partial response in 18 patients, stable disease in 38 patients and progressive disease in 31 patients. It was determined that ERCC1 and XRCC1 polymorphisms are not associated with DCR (P=0.662 and P=0.631, respectively). The mOS of patients exhibiting ERCC1 and XRCC1 polymorphisms was eight months, and although no significant association was identified between ERCC1 codon 118 genotypes and mOS (P>0.05), the combination of ERCC1 and XRCC1 polymorphisms, as well as the specific presence of the XRCC1 codon 399A/G polymorphism, was associated with mOS (P<0.05). Thus, the present study indicated that the XRCC1 polymorphism and the combination of XRCC1 and ERCC1 polymorphisms were independent predictors for mOS; however, the XRCC1 and ERCC1 genes were not able to predict the DCR.

Keywords: Stomach neoplasm, polymorphism, excision repair cross-complementing protein 1, X-ray repair cross-complementing protein 1, Oxaliplatin

Introduction

Gastric cancer is the second most frequent cause of cancer-related mortality worldwide, with the highest incidence in China, Japan and Eastern European countries [1]. It is commonly diagnosed at an advanced stage, however, chemotherapy may exhibit a palliative effect in symptomatic patients. For example, fluoropyrimidines and platinum were identified to be effective in the treatment of gastric cancer, however, the response rates of these individual agents or their combinations was <50% [2, 3]. Therefore, the identification of novel biomarkers that can predict the response of a specific therapeutic agent are required to facilitate the selection of patients who may benefit from a specific chemotherapeutic regimen.

Oxaliplatin is a third generation platinum analogue, the structure of which contains a 1,2-diaminocyclohexane ring. It has demonstrated antitumor efficacy in the treatment of advanced gastric cancer and can cause DNA damage by forming DNA-platinum monoadducts with guanines; however, nucleotide-excision-repair (NER) and base excision repair (BER) pathways can cause resistance to platinum-based drugs by repairing DNA damage [4]. Excision repair cross-complementing protein 1 (ERCC1) and X-ray repair cross-complementing protein 1 (XRCC1) are key proteins in NER and BER pathways, respectively; and have been identified as critical factors in the response to platinum-based chemotherapy [5-10]. However, the predictive value of the corresponding genes in advanced gastric cancer patients treated

with oxaliplatin-based chemotherapy remains controversial. Therefore, additional studies are required to improve the understanding of the roles of these genes in advanced gastric carcinoma.

The aim of the present study was to investigate whether the ERCC1 and XRCC1 polymorphisms exhibit a resistant or sensitive role in advanced gastric cancer patients receiving oxaliplatin-based chemotherapy.

Patients and methods

Patients

Between September 2009 and September 2011, 115 patients with histologically confirmed gastric cancer were enrolled in the present study at the Cancer Treatment Center of the Affiliated Hospital of Qingdao University Medical College (Qingdao, China). All patients agreed to genotype analyses, and written informed consent from patients was obtained prior to the commencement of the study, which was approved by the ethic committee of Medical College of Qingdao University.

The inclusion criteria for the present study were as follows: i) All patients exhibited stage IV disease; ii) performance status of patients was classified according to the Eastern Cooperative Oncology Group (ECOG) criteria [11], and each patient's ECOG status did not exceed a score of two; iii) patients had not previously been treated with chemotherapy; iv) adequate bone marrow function (as defined by an absolute granulocyte count of more than 1,500/μL and platelet count of more than 100,000/μL), renal function (serum creatinine, ≤1.5 mg/dl; or Cockroft formula-calculated creatinine clearance, ≥50 ml/min) and hepatic function (aspartate aminotransferase <40 U/L and alanine aminotransferase <45 U/L; total bilirubin <17.1 μmol/L); and v) classification of function capacity was determined as >II degrees, as previously defined by the New York Heart Association [12]. According to the aforementioned criteria, 89 patients were identified as eligible and included in this study.

Chemotherapy regimen

Patients were administered with the following modified FOLFOX4 regimen as first-line treatment once every three weeks: Oxaliplatin, 130 mg/m^2 on day 1 (Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China); calcium folinate, 130 mg/m^2 on days 1-5 (Jiangsu Hengrui Medicine Co., Ltd.) combined with 5-fluorouracil (5-FU), 300 mg/m^2 on days 1-5 (Tianjin Jinyao Amino Acids Co., Ltd., Tianjin, China). This regimen was administered until disease progression was controlled, unacceptable levels of toxicity occurred or patient refusal.

Clinical evaluation

All patients completed a minimum of two cycles of chemotherapy and underwent bidimensionally measurable computed tomography (CT) or magnetic resonance imaging of the lesion prior to treatment. Subsequently, CT imaging was performed every six weeks. The disease control rate [DCR: Complete response (CR) + partial response (PR) + stable disease (SD)] was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [13], which is defined as follows: CR, a sustained decrease in the maximum tumor diameter by ≥50% for ≥4 weeks; PR, a reduction in tumor progression between the rates for CR and SD; SD, a <50% reduction or <25% shrinkage in the maximal tumor diameter; and progressive disease (PD), an increase in the maximum tumor diameter by ≥25% (compared with the smallest measurement) or the appearance of new lesions. Furthermore, overall survival (OS) was defined as the time interval between the initial commencement of treatment and the date of mortality or last follow-up.

Genotyping

Prior to chemotherapy administration, a Blood Genomic DNA Isolation kit (TransGene Biotech Company, Beijing, China) was used to extract DNA from 2-ml peripheral blood samples, and the Roter gene real time 36-well polymerase chain reaction (PCR) system (Gene Company Ltd., Hong Kong, China) was used to analyze polymorphisms in ERCC1 and XRCC1 with TaqMan genotyping assays. The TaqMan assay was performed in a 25-μL reaction solution containing: 1.25 μL probe (Life Technology, Grand Island, NY, USA), 12.5 μL PCR mixture reagent (Gene Company Ltd) and 20 ng genomic DNA. The PCR conditions included an initial step at 95°C for 10 min, followed by 48 cycles of denaturing at 92°C for 15 sec and annealing

Table 1. Patient characteristics

Patient characteristics		Number
Gender	Male	60
	Female	29
Age (years)	≤44	9
	45-59	61
	≥60	19
Site of tumor	Fundus	11
	Body	25
	Sinus	42
	Other	11
Differentiation	Well/moderate	30
	Poor	59
Number of metastasis	1	32
	2	21
	≥3	36
ECOG score	≤1	66
	=2	23

Table 2. Association between ERCC1 gene polymorphisms and disease control rate

ERCC1 genotype	Cases [n]		Test value	*P*-value
	CR + PR + SD (n=58)	PD (n=31)		
C/C	33	10	4.911[a]	0.044
C/T + T/T	25	21	0.035[b]	0.852

[a]The C/C genotype was evaluated using the χ^2 test to provide a χ^2 test value. [b]The C/T + T/T genotype was evaluated by logistic regression analysis to provide an odds ratio test value. ERCC1, excision repair cross-complementing protein 1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

at 60°C for 1 min. To obtain reliable results, 30 randomly selected DNA samples were genotyped a minimum of two times each.

Statistical analysis

Genotype distribution was analyzed by performing the χ^2 test and using the Hardy-Weinberg equilibrium. The Kaplan-Meier method was adopted to estimate survival curves, and the log-rank test was used to assess the patient survival time and gene polymorphism status. Additionally, the Cox proportion hazards regression model was used to obtain hazard ratio (HR) and 95% confidence interval (CI) values; all analyses were adjusted for age, gender, performance status, histology, site of tumor and number of metastases. Odds ratios (OR) and 95% CIs were calculated concurrently. Furthermore, all reported *P*-values were two-sided and P≤0.05 was considered to indicate a statistically significant difference. All analyses were performed using SPSS software (version 17; SPSS, Inc., Chicago, IL, USA).

Results

Patient responses to chemotherapy

Between September 2009 and September 2011, 89 gastric cancer patients were followed-up, with a median follow-up period of 12 months (range, 4-16 months). The 89 patients consisted of 29 females (32.58%) and 60 males (67.42%), with a median age of 53 years (range, 32-70 years). Additional characteristics of the patients are listed in **Table 1**. The response of the patients to the chemotherapy regimen was as follows: CR, two; PR, 18; SD, 38; and PD, 31; and the median OS (mOS) time was eight months (95% CI, 6.739-9.261 months).

Genotype frequencies of ERCC1 and XRCC1 polymorphisms

PCR was conducted on blood samples from all patients to identify ERCC1 codon 118 polymorphisms; it was determined that 43 patients (48.31%) were homozygous for the C/C genotype, nine (10.11%) were homozygous for the T/T genotype and 37 (41.58%) were heterozygous for the C/T genotype. Thus, the frequencies of the T and C alleles of codon 118 were 69.1 and 30.9%, respectively. Furthermore, analysis of XRCC1 codon 399 polymorphisms identified that 45 patients (50.56%) were homozygous for the G/G genotype, eight (8.99%) were homozygous for the A/A genotype and 36 (40.45%) were heterozygous for G/A genotype. Therefore, the frequencies of the G and A alleles of codon 399 were 70.79 and 29.21%, respectively. Additionally, the genotype frequencies for ERCC1 (χ^2, 0.062; P=0.803) and XRCC1 (χ^2, 0.043; P=0.836) genes were identified to be in Hardy-Weinberg equilibrium.

Association between the ERCC1 C118T polymorphism and treatment outcome

A significant association was identified between ERCC1 genotypes and DCR (P=0.044), howev-

Table 3. Association between ERCC1 gene polymorphisms and mOS

ERCC1 genotype	mOS (months, 95% CI)	Test value (95% CI)	*P*-value
C/C	9.5 (9.155-9.845)	10.917[a]	0.001
C/T + T/T	7 (5.764-8.236)	1.014 (0.586-1.756)[b]	0.959

[a]The C/C genotype was evaluated using the logrank test to provide a χ^2 test value. [b]The C/T + T/T genotype was evaluated by Cox regression analysis to provide a hazard rate test value. ERCC1, excision repair cross-complementing protein 1; mOS, median overall survival; CI, confidence interval.

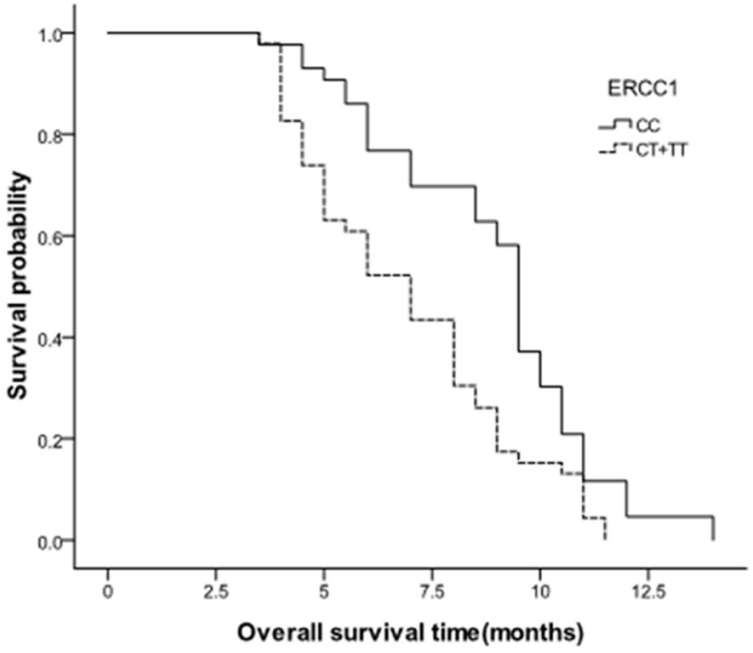

Figure 1. Kaplan-Meier curves representing the median overall survival time of patients with ERCC1 CT and TT genotypes compared with a ERCC1 CC genotype. ERCC1, excision repair cross-complementing protein 1.

Table 4. Association between XRCC1 gene polymorphisms and disease control rate

XRCC1 genotype	Cases [n]		Test value	*P*-value
	CR + PR + SD (n=58)	PD (n=31)		
G/G	35	10	6.376[a]	0.015
G/A + A/A	25	21	3.532[b]	0.060

[a]The G/G genotype was evaluated using the χ^2 test to provide a χ^2 test value. [b]The G/A + A/A genotype was evaluated by logistic regression analysis to provide an odds ratio test value. XRCC1, X-ray repair cross-complementing protein 1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

er, this statistical significance was lost following adjustment by the logistic regression analysis (P=0.852), as indicated in **Table 2**. It might indicate that ERCC1 would not be able to predict DCR. Patients with one or two T alleles exhibited a reduced mOS. For example, the mOS for patients with ERCC1 CT and TT genotypes was 7.0 months, whereas the mOS for patients with the ERCC1 CC genotype was 9.5 months. Furthermore, performing a log-rank test demonstrated that mOR and the ERCC1 CC genotype were significantly associated (P=0.001; **Table 3**). Kaplan-Meier curves of the two groups are shown in **Figure 1**.

Association between the XRCC1 A399G polymorphism and treatment outcome

A significant association between XRCC1 genotypes and DCR was identified (P=0.015), however, this statistical significance was lost following adjustment by the logistic regression analysis (P=0.060; **Table 4**). It might indicate that XRCC1 would not able predict DCR. Patients with one or two G alleles exhibited a significantly inferior mOS (7.0 months for G/A and A/A genotypes compared with 9.5 months for patients with the G/G genotype, P=0.001). The log-rank test identified a significant association between mOS and the two types of gene polymorphism investigated (P=0.001). Kaplan-Meier curves of the two groups are shown in **Figure 2** and additional analysis of this association was investigated using Cox regression analysis (**Table 5**).

Association between combined ERCC1 C118T and XRCC1 G399A polymorphisms, and treatment outcome

In consideration of the aforementioned observations, the present study investigated whether a pattern of favorable genotypes could be used to evaluate differences in the clinical outcome of gastric cancer patients. ERCC1 C/C and

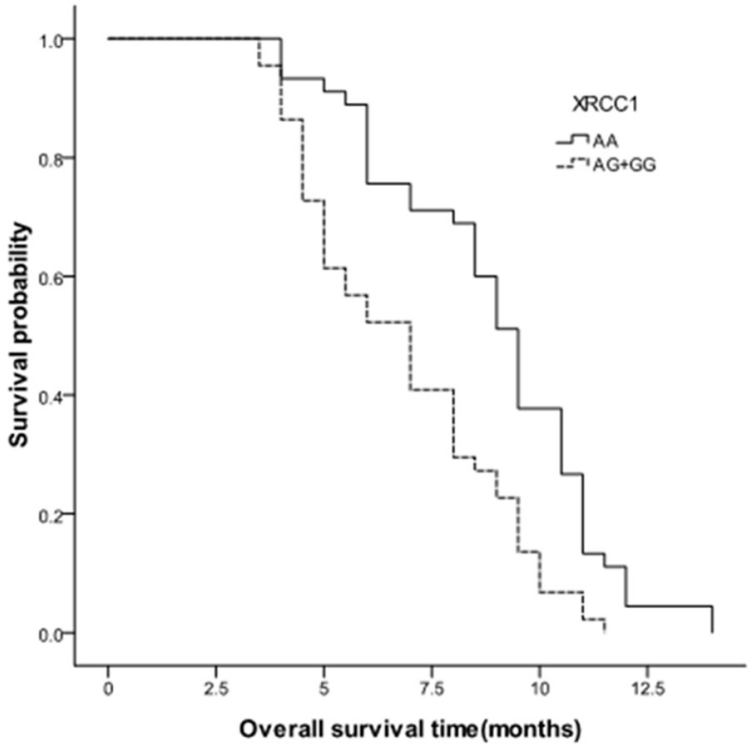

Figure 2. Kaplan-Meier curves of the median overall survival time of patients with XRCC1 G/A and A/A genotypes compared with a XRCC1 G/G genotype. XRCC1, X-ray repair cross-complementing protein 1.

Table 5. Association between XRCC1 gene polymorphisms and mOS

XRCC1 genotype	mOS (months, 95% CI)	Test value (95% CI)	*P*-value
G/G	9.5 (8.863-10.137)	14.864[a]	0.001
G/A + A/A	7 (5.630-8.370)	3.558 (2.011-6.295)[b]	0.001

[a]The G/G genotype was evaluated using the log-rank test to provide a χ^2 test value. [b]The G/A + A/A genotype was evaluated by Cox regression analysis to provide a hazard rate test value. XRCC1, X-ray repair cross-complementing protein 1; mOS, median overall survival; CI, confidence interval.

XRCC1 G/G were defined as favorable genotypes. A favorable genotype was identified and compared with the group of patients exhibiting the remaining two unfavorable genotypes. In all, 24 patients had two favorable genotypes (group one), 50 patients had one favorable genotype (group two), and 25 patients had no favorable genotypes (group three). The DCR was significantly associated the genotype group (P=0.001, **Table 6**). In the current analysis, patients who possessed one or two favorable genotypes survived for a median of 8.5 and 9.5 months, respectively, while patients exhibiting no favorable genotypes had a median survival of only 5.0 months. Compared to the reference group of patients with two favorable polymorphisms, the relative risk of mortality was 2.498 (95% CI, 1.298-4.807) and 3.102 (95% CI, 1.451-6.632) for patients with one (group two) or zero (group three) favorable polymorphisms, respectively (**Table 6**; **Figure 3**). Kaplan-Meier curves of the three groups are shown in **Figure 3** and the significance was analyzed by Cox regression. In addition, patient performance status and the number of metastases demonstrated an association with mOS, as determined by the ECOG scale (95% CI, 3.704-11.185; P< 0.001) and number of metastatic lesions (95% CI, 1.001-1.816; P=0.049). By contrast, gender, age, site of the tumor and tumor differentiation were not significantly associated with mOS.

Discussion

The present study conducted an investigation into the associations between ERCC1 and XRCC1 gene polymorphisms, and the DCR and mOS of advanced gastric cancer patients receiving 5-FU/oxaliplatin chemotherapy, individually as well as in combination. The presence of the two gene polymorphisms, independently and in combination, failed to demonstrate an association with DCR. However, to the best of our knowledge, the present study is the first to demonstrate that the XRCC1 gene at codon 399 is associated with mOS in gastric cancer, independently or combined with ERCC1 polymorphisms.

It has previously been reported that the ERCC1 118 polymorphism may affect the mRNA and protein expression levels of various proteins, therefore, resulting in differential cisplatin sen-

Table 6. Influence of ERCC1 and XRCC1 polymorphism on mOS

Genotype group	mOS (months) (95% CI)	Log-rank test		Cox regression analysis	
		χ^2	*P*-value	HR (95% CI)	*P*-value
One[a]	9.5 (8.540-10.460)				0.007
Two[b]	8.5 (6.187-10.813)	23.749	0.001	2.498 (1.298-4.807)	0.006
Three[c]	5.0 (4.021-5.979)			3.102 (1.451-6.632)	0.004

[a]Two favorable genotypes; [b]one favorable genotype; [c]no favorable genotypes. ERCC1, excision repair cross-complementing protein 1; XRCC1, X-ray repair cross-complementing protein 1; mOS, median overall survival. CI, confidence interval; HR, hazard ratio.

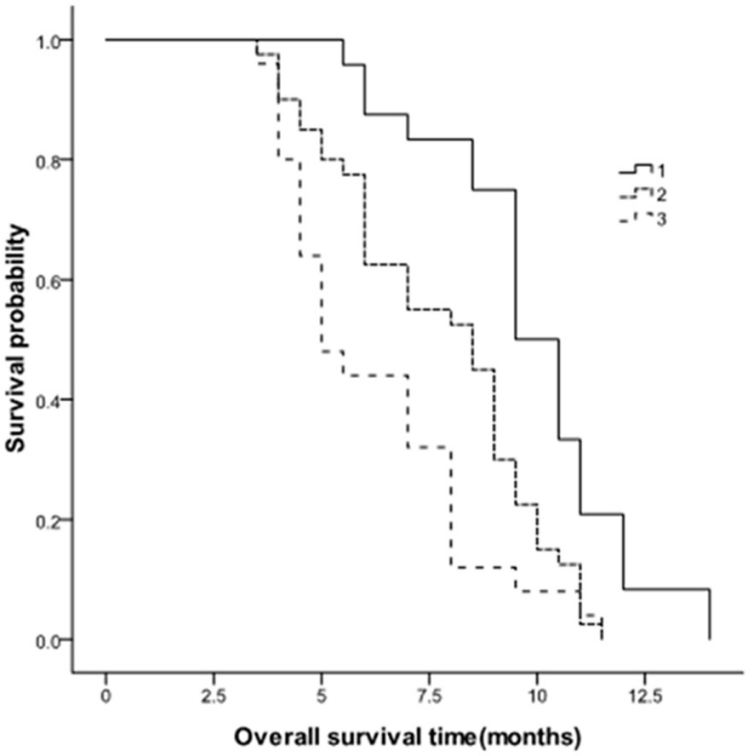

Figure 3. Kaplan-Meier curves of the median overall survival time of patients with one or more favorable genotypes (groups 1 and 2) compared to patients with no favorable genotypes (group 3).

sitivity [14]. A favorable therapeutic response and survival rate were previously identified in advanced gastric cancer patients treated with 5-FU and oxaliplatin who did not demonstrate ERCC1 protein expression [15]. Furthermore, various studies demonstrated that low ERCC1 mRNA expression was associated with favorable clinical outcomes following treatment with platinum-based chemotherapy in lung [16, 17], colorectal [18], gastric [19-21], ovarian [22], bladder [23], and head and neck [24] cancer. However, the clinical data regarding the assumed association between the ERCC1 codon 118 polymorphism and platinum sensitivity remains controversial [25].

The findings of the present study demonstrate that patients with ERCC1 118 C/T or T/T genotypes typically exhibit a lower probability of response to platinum-based treatment and shorter mOS, compared to patients with C/C polymorphisms. However, this difference was not statistically significant, which was consistent with the results of previous reports in advanced gastric cancer [26, 27].

XRCC1 is important for repairing DNA damage in BER. The present study demonstrated that patients with the XRCC1 399 G/G polymorphism exhibited a significantly shorter survival rate than patients with the alternative two genotypes, in agreement with a previous study [10]. However, the predictive value of the polymorphism in the clinic and *in vitro* studies was not always consistent [9, 28, 29]. Additional analysis of the clinical outcomes was performed according to the number of favorable genotypes. It proposed that as the number of favorable genotypes increases, patients may experience greater benefit from oxaliplatin-based adjuvant chemotherapy. This is consistent with a previous study conducted in metastatic colorectal cancer at the Central Laboratory of the Cancer Treatment Center in the Affiliated Hospital of Medical College of Qingdao University [30].

In conclusion, the present study demonstrates that the two possible polymorphisms of XRCC1 Arg399Gln, and a combination of XRCC1 and

ERCC1 polymorphisms appeared to be independent prognostic factors in advanced gastric cancer patients treated with oxaliplatin-based first-line chemotherapy. However, the predictive role of these polymorphisms may be affected by specific clinical characteristics, such as the patient's ECOG score and number of metastatic lesions. Due to the limited number of samples, large randomized prospective control trials should be conducted to obtain more accurate data.

Disclosure of conflict of interest

None.

Address correspondence to: Xiuwen Wang, Department of Oncology, Qilu Hospital of Shandong University, Jinan 250012, China. Tel: +86 531 82169851; Fax: +86 531 86908010; E-mail: wangxiumen@yeah.net

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