Relevance of Pharmacogenetic Polymorphisms With Response to Docetaxel, Cisplatin, and 5-Fluorouracil Chemotherapy in Esophageal Cancer.

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Abstract

Purpose: Docetaxel, cisplatin, and 5-fluorouracil (DCF) have high response rates, but severe neutropenia is frequently observed. The occurrence of neutropenia is associated with high histological response in solid tumors, and it might be associated with tumor shrinkage after DCF therapy. This study aimed to determine the genetic polymorphisms involved in the clinical response to preoperative DCF therapy in esophageal cancer patients.

Methods: We included 56 patients with measurable lesions who received preoperative DCF therapy for esophageal cancer. Twenty-one genetic polymorphisms were analyzed, and univariate logistic regression analysis was used to evaluate the association between genetic polymorphisms and tumor shrinkage. A multivariate logistic regression analysis adjusted for T category and tumor location and a univariate analysis for potential genetic factors with *P* values < 0.05 were performed to explore the predictive factors and to estimate odds ratios and their 95% confidence intervals.

Results: No patient achieved a complete response, whereas 20 patients achieved a partial response, 31 patients had stable disease, and 5 patients had progressive disease. Although no association was found between pharmacokinetic-related gene polymorphisms, *XRCC3* rs17997944 was extracted as the only genetic factor that affected tumor shrinkage (*P* = 0.033) by univariate analysis. The multivariate analysis adjusted for T category and tumor site also showed that *XRCC3* rs1799794: AA was a predictive factor that affected tumor shrinkage (odds ratio, 0.243; 95% confidence interval, 0.065–0.914; *P* = 0.036).

Conclusion: *XRCC3* rs1799794, which is involved in homologous recombination, is a genetic factor that affects clinical responses to DCF therapy.

Introduction

Esophageal cancer is a highly lethal malignancy that is typically diagnosed at an advanced stage [1]. Surgery is the standard treatment for potentially resectable esophageal cancer, and neoadjuvant chemotherapy is given prior to surgery if it is believed that a reduction of the tumor mass is necessary for optimal surgery [2,3]. In patients with esophageal cancer, neoadjuvant chemotherapy followed by surgery has been shown to improve survival [4]. Neoadjuvant chemotherapy in combination with cisplatin and 5-fluorouracil (CF) is a commonly used standard regimen based on the results of phase III trials that have compared preoperative and postoperative chemotherapy [5]. However, to date, the survival rate with this regimen is not satisfactory. Therefore, more effective neoadjuvant regimens are currently under development. Specifically, a phase I/II study, which was conducted to assess the feasibility of adding docetaxel to CF as a neoadjuvant chemotherapy (DCF) in patients with esophageal cancer, demonstrated promising results [6]. Additionally, a phase III trial (JCOG1109) comparing preoperative CF with DCF in patients with locally advanced esophageal cancer is currently underway [7]. Although a high response rate with the DCF regimen was observed in a phase II study in Japan, a high frequency of adverse reactions, such as severe neutropenia and febrile neutropenia, was observed.

Chemotherapy-induced neutropenia is an important dose-limiting toxicity of anticancer agents, and an association between chemotherapy-induced neutropenia and good clinical response has been reported in several solid tumor types [8-14]. It has also been reported that the occurrence of neoadjuvant chemotherapy-induced severe neutropenia is correlated with a high histological response in patients with esophageal squamous cell carcinoma [15].

Recently, several studies have reported an association between genetic polymorphisms related to the pharmacokinetics and pharmacodynamics of anticancer agents and chemotherapy-induced neutropenia. In a previous study where we used National Cancer Center (NCC) Biobank Registry samples, we examined the association between the development of severe neutropenia and genetic polymorphisms related to docetaxel pharmacokinetics in patients with locally advanced esophageal cancer who received preoperative DCF therapy. As a result, we found that two pharmacokinetic-related gene polymorphisms, namely, *ABCB1* rs1045642 and *ABCC2* rs12762549, were associated with severe neutropenia [16]. Therefore, it is possible that these pharmacokinetic-related genetic polymorphisms associated with the development of severe neutropenia will affect the response to DCF therapy. Furthermore, in addition to pharmacokinetic factors, pharmacodynamic genetic factors might be involved in the response to anticancer agents. In particular, it is well known that platinum-based anticancer drugs, such as cisplatin, inhibit DNA synthesis by binding to DNA and by forming intrastrand and interstrand crosslinks. In addition to nucleotide excision repair (NER) and base excision repair (BER), which occur as a result of DNA damage, homologous recombination (HR) has been suggested to be involved in the repair of double-strand breaks formed during DNA replication. Therefore, multiple DNA repair mechanisms are likely involved [17]. Genes encoding enzymes involved in these repair pathways are known to contain genetic polymorphisms, and a systematic review of clinical studies in patients with non-small cell lung cancer treated with platinum-based chemotherapy reported an association between these genetic polymorphisms and survival [18].

However, to the best of our knowledge, the association between genetic polymorphisms involved in the pharmacokinetics and pharmacodynamics of anticancer agents and clinical response has not been reported in esophageal cancer patients treated with DCF chemotherapy. Therefore, we performed this study to explore the genetic polymorphisms involved in the clinical response of patients with locally advanced esophageal cancer to preoperative DCF chemotherapy.

Patients And Methods

Patients

The medical data of individual patients who were diagnosed with esophageal cancer and who received neoadjuvant DCF chemotherapy at the NCC Hospital East in Japan between August 2011 and December 2016 were extracted from the electronic medical records system.

The DCF regimen consisted of a 1-h intravenous (i.v.) infusion of docetaxel at 70 mg/m^2, a 2-h infusion of cisplatin at 70 mg/m^2 on day 1, and a continuous i.v. infusion of 5-fluorouracil at 750 mg/m^2/day on days 1–5 every 3 weeks. All patients received DCF without any dose reductions during the first cycle. The tumor objective response rate was evaluated by computerized tomography until the next cycle of DCF chemotherapy was initiated. Only patients with measurable lesions were included in this study.

We conducted a retrospective study using DNA samples from the NCC Biobank Registry to explore the genetic predictors of tumor responses in patients with esophageal cancer who received DCF chemotherapy. The Institutional Review Board of the NCC approved this study (2016-384), which was conducted in accordance with the Declaration of Helsinki and Japanese national regulations, as well as with the Ethical Guidelines for Medical and Health Research Involving Human Subjects (available: https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf). All patients provided their written informed consent to allow the use of their clinical information and DNA samples, which are available in the NCC Biobank Registry.

Response evaluation

Tumor response was evaluated in measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [19]. On the basis of the RECIST criteria, the treatment outcomes were divided into the following four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Patients who achieved an objective response (CR or PR) were defined as clinical responders, whereas patients with SD or PD were considered nonclinical responders.

Pharmacogenetic analysis

In this study, we investigated the effect of polymorphisms in pharmacokinetic and pharmacodynamic genes on DCF chemotherapy.

The purpose of the current exploratory study was to comprehensively investigate the pharmacogenomic polymorphisms in drug transporters (*SLCO1B3*, *ABCB1*, *ABCC2*, and *ABCG2*), drug metabolism enzymes (*CYP3A5* and *GST*), and enzymes involved in DNA repair mechanisms, including NER (*ERCC1*, *ERCC2*, *XRCC1*, and *XRCC3*), and their influence on the tumor objective response to neoadjuvant DCF chemotherapy. We selected the following representative 21 polymorphisms with the following criteria of minor allele frequency > 0.05, as reported in Hap-Map data of the Japanese population: *SLCO1B3* rs11045585 (A>G); *ABCB1* rs1128503 (C>T), rs2032582 (G>T/A), and rs1045642 (C>T); *ABCC2* rs12762549 (C>G); *ABCG2* rs2231137 (G>A) and rs2231142 (C>A); *CYP3A5* rs776746 (A>G); *GSTP1* rs1695 (A>G) and *M1/T1* null; *ERCC1* rs11615 (C>T) and rs3212986 (C>A); *ERCC2* rs13181 (T>G) and rs238406 (T>G); *XRCC1* rs25487 (G>A), rs25489 (G>A), and rs1799782 (C>T); and *XRCC3* rs861530 (A>G), rs861539 (C>T), and rs1799794 (G>A). All polymorphisms, excluding *ABCG2* 421C>A and *GST M1/T1* null, were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. The polymorphism *ABCG2* 421C>A was determined by allele-specific PCR, and *GST*

M1/T1 genotyping was performed using multiplex PCR. In addition, for further confirmation, the representative samples were sequenced by direct sequencing using the ABI 310 genetic analyzer (Applied Biosystems). All laboratory staff were blinded to the clinical data collection.

Statistical analysis

Continuous data were summarized as medians (ranges), and categorical data were presented as frequencies (percentages) and were compared using Fisher's exact test. The Mann–Whitney *U* test was used to compare nonnormally distributed variables between groups. A univariate analysis was performed to identify the genetic predictive factors of the clinical response after the first cycle of DCF chemotherapy. Twenty-one genetic polymorphisms were genotyped, and the association of these genotypes with a clinical response was then analyzed using both dominant and recessive models. In a previous study, the clinical T category and the tumor location were reported to be predictive factors in patients with esophageal cancer treated with neoadjuvant chemoradiotherapy [20]. The potential genetic factors for which $P < 0.05$ in the univariate analysis, the node factor, and the tumor location were included as independent variables via the forced entry method, and multivariate logistic regression analysis was performed to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) for associations between each gene polymorphism and the clinical response of patients with esophageal cancer to DCF chemotherapy. This is an exploratory study because it is the first study to examine the effect of genetic polymorphisms and DCF chemotherapy on esophageal cancer. Thus, no correction for multiple comparisons was done due to exploratory nature of this study. P values <0.05 were considered significant and were two-sided without adjustment for multiple testing. The statistical analyses were performed using SPSS software version 22.0 (IBM Japan Ltd., Tokyo, Japan).

Results

Patient disposition and patient characteristics

In all, 211 patients received DCF chemotherapy during the data extraction period, and after the exclusion criteria were considered, 158 patients were eligible for our previous study, which aimed to investigate the relationship between severe neutropenia and pharmacogenetic polymorphisms related to docetaxel. Of these, 102 patients did not have measurable lesions, and thus, 56 patients were eligible for this study. Table 1 summarizes the baseline characteristics of all eligible patients, who were classified as either clinical responders or nonclinical responders. Most patients were male (91.1%). Their median age (range) was 64 (41–75) years, and all patients demonstrated a performance status of 0–1. Histologically, squamous cell carcinoma was the most common diagnosis as only eight (14.3%) patients were diagnosed with adenocarcinoma. None of the patients had abnormal values in the baseline biochemical and hematological data. No significant difference was observed between the two groups.

Association between patient gene polymorphisms and efficacy by univariate and multivariate analyses

To explore the genetic factors involved in the clinical efficacy of preoperative DCF therapy, we analyzed genetic polymorphisms related to the pharmacokinetics and pharmacodynamics of docetaxel and cisplatin. The observed genotype distributions were in agreement with Hardy–Weinberg equilibrium (P > 0.05 for all variants).

We classified the genotypes of these patients into two groups: (1) homozygous wild-type genotype and variant allele-carrying genotypes (dominant model) or (2) homozygous wild-type and heterozygous genotypes or homozygous variant genotype (recessive model). Table 2 shows the results of the univariate analysis for the dominant and recessive models and the proportions of patients who achieved a clinical response according to each genotype group. Among the 21 candidate polymorphisms, a significant association with the clinical response was observed only for *XRCC3* rs1799794 in the dominant model (OR, 0.242; 95% CI, 0.066–0.889; P = 0.033).

Table 3 shows the result of the multivariate analysis for predictive factors of a clinical response to DCF therapy. The multivariate analysis adjusted for these potential factors revealed that *XRCC3* rs1799794 (OR, 0.243; 95% CI, 0.065–0.914; P = 0.036) was retained as a significant predictor of the clinical response to preoperative DCF chemotherapy in patients with esophageal cancer.

Antitumor activity

Figure 1 shows a waterfall plot of the percent change in the target tumor diameter from baseline after the first cycle of DCF chemotherapy. Of the 56 patients with a postbaseline tumor assessment, 47 (84%) exhibited tumor shrinkage of the measurable lesions relative to baseline. Furthermore, of 13 patients with *XRCC3* rs1799794 AA, 12 (92.3%) exhibited tumor shrinkage of the measurable lesions relative to baseline.

Discussion

This is the first study to examine the effect of germline genetic polymorphisms on the clinical response of patients with esophageal cancer to preoperative DCF chemotherapy.

In our previous study, we reported that genetic polymorphisms involved in docetaxel pharmacokinetics affect the development of grade 3 or higher neutropenia[21]. In addition, a study of preoperative chemotherapy for esophageal cancer reported that grade 3 or higher neutropenia was correlated with a high histological response [15]. The incidence of docetaxel-induced neutropenia is particularly high in Asians [22], and neutropenia is considered a major concern because it is a dose-limiting toxicity of docetaxel. Therefore, we performed this pharmacogenomic study with the hypothesis that genetic polymorphisms that affect docetaxel pharmacokinetics may influence the response to DCF chemotherapy. However, contrary to expectations, the two ABC transporter gene polymorphisms (*ABCB1* rs1045642 and *ABCC2* rs12762549), which were shown to be associated with grade 3 or higher neutropenia in a previous study, did not affect the clinical response to DCF. No pharmacokinetic-related

genetic polymorphisms, including those in other drug transporters and metabolic enzymes, had any impact on the clinical efficacy of DCF therapy.

Polymorphisms in genes related to DNA repair processes, such as NER, are also known to affect the response to chemotherapy. Some reports suggest that polymorphisms in the *ERCC* and *XRCC* genes, which are involved in DNA repair mechanisms, may affect the response to platinum-based chemotherapy and chemoradiotherapy [23,24].

In this study, no association was observed between polymorphisms located in NER and BER pathway genes and DCF response rate, which indicates that the *XRCC3* rs17997944 polymorphism in the *XRCC3* gene, which is involved in HR, might be the only genetic factor that affects tumor objective response. *XRCC3* facilitates the binding of RAD51 to DNA, which has been implicated in the recognition and repair of DNA interstrand crosslinks [25]. Functional analysis has also shown that *XRCC3* overexpression is associated with increased Rad51C protein levels [26] and is strongly correlated with DNA damage resistance [27]. *XRCC3* rs1799794, which was shown to be associated with tumor reduction in this study, is located in the 5'-UTR region, 316 bp upstream of the ATG start codon of the *XRCC3* gene. According to an *in silico* analysis of regulatory RNA motifs, this genetic polymorphism is assumed to cause the loss of upstream open reading frames (uORFs), and because it is involved in translational regulation by controlling uORF expression, this polymorphism may affect gene expression [28].

To the best of our knowledge, no studies have reported an association between *XRCC3* gene polymorphisms and tumor shrinkage in esophageal cancer patients treated with DCF chemotherapy. Although the clinical importance of *XRCC3* rs17997944, which was shown to be significantly associated with the response to DCF chemotherapy, is still unclear, several clinical studies support the results of this study. A study of patients with localized prostate adenocarcinoma who were treated with radiation therapy revealed no relationship between *XRCC3* rs1799794 and the response to radiation therapy, but an association between this genotype and the development of common late radiation injury was found [29]. Furthermore, in a recent study of patients with glioblastoma treated with chemoradiotherapy consisting of temozolomide, a statistically significant association was found between progression-free survival and overall survival and *XRCC3* rs1799794 [30].

The development of clinically useful biomarkers that can predict sensitivity to preoperative chemotherapy is an important issue. The tumor response to chemotherapy is believed to be affected by both somatic and germline gene mutations. The results of a systematic review and meta-analysis of studies that evaluated the impact of somatic and germline polymorphisms on tumor response to preoperative treatment in rectal and esophageal cancers were reported in 2015 [31]. In the present study, a germline *XRCC3* polymorphism was shown to be a predictive factor of a good clinical response to preoperative DCF chemotherapy, but in the abovementioned meta-analysis, which focused on esophageal cancer, only wild-type *TP53* predicted better efficacy of preoperative treatment. On the contrary, few articles have reported germline mutations suitable for incorporation into a meta-analysis, and thus, a meta-analysis

could not be conducted because of lack of data. Therefore, it is desirable to develop pharmacogenetic biomarkers for clinical application.

The current study has some limitations. First, the sample size is relatively small. Although all patients who received DCF chemotherapy were surveyed, only 56 evaluable patients with measurable lesions were ultimately included in the analysis. This study was two-sided without adjustment for multiple testing. Therefore, it is suggested that the germline *XRCC3* rs1799794 genetic polymorphism might not be significant. Second, no patients had the homozygous variant of the minor allele in some genetic polymorphisms, which may be related to the small sample size. Third, the timing of the tumor response evaluation was limited. This study was based on a single evaluation after the first cycle, but an evaluation after three cycles of chemotherapy may be necessary. However, if the evaluation had been performed after three cycles, it would have been impossible to accurately evaluate the relationship with tumor shrinkage because of dose reduction and prolonged dosing intervals caused by adverse reactions. Therefore, tumor response was evaluated only after the first cycle. That is, we believe that this limitation is actually a strength and that the relationship between tumor response and gene polymorphisms was evaluated correctly in this study.

In conclusion, this study suggests that the germline *XRCC3* rs1799794 genetic polymorphism in the DNA repair pathway might influence the clinical response of patients treated with preoperative DCF therapy. Because this study was performed retrospectively with a small number of patients whose DNA samples in the NCC Biobank Registry were used, external validation in another cohort with a large sample is necessary to clarify the clinical significance of this *XRCC3* polymorphism in DCF therapy.

Declarations

AUTHOR DECLARATIONS

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of the NCC, Japan in March 2017 (2016-384). These patients were consented to be used the clinical information and DNA sample in the National Cancer Center (NCC) Biobank Registry. The study design is displayed on the website for the National Cancer Center Hospital East, providing the relatives of deceased patients the opportunity to decline participation in the current study.

Consent for publication

All authors agree to publish.

Availability of data and material

The datasets during and analyzed during the current study available from the corresponding author on reasonable. request.

Competing interests

Not applicable

Funding

Not applicable

Authors' contributions

Conception and design were performed by HN, DT, TaKo, HD, and SF. Acquisition of data was carried out by HN, KD, HD, and TaKo. The analysis of SNPs were DT, SU, and KI. Statistical analysis and interpretation of the data were carried out by DT and SU. Drafting of the article was carried out by NH, DT, TaKo, ToKa, and SF. All authors read and approved the final manuscript.

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COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflicts of interest

Takashi Kojima received honoraria from Ono and MSD and research funding from Ono, MSD, Taiho, Chugai, Shionogi and Palexel. Tomoaki Yano received honoraria from Olympus, Meijiseika pharma and research funding from Olympus, Fujifirm, HOYA PENTAX, Rakuten Medical, SHIMADZU and Tokyo Giken. All other authors declare no potential conflicts of interest.

Research involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

All patients provided their written informed consent to allow the use of their clinical information and DNA samples, which are available in the NCC Biobank Registry.

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Tables

Table 1 Baseline patient characteristics

	Total (*N* = 56)		Clinical Responder (*N* = 20)		Nonclinical responder (*N* = 36)		*P-value*
	N	%	*N*	%	*N*	%	
Gender							
Male	51	91.1	18	90.0	33	91.7	1.000
Female	5	8.9	2	10.0	3	8.3	
Age (years)							
Median (range)	64 (41–75)		63.5(47–74)		64(41–75)		0.421
BMI							
Median (range)	22.3 (15.5–31.0)		22.7(16.3–28.9)		22.3(15.5–31.0)		0.505
Clinical Stage							
II	2	3.6	1	5.0	1	2.8	0.626
III	24	42.9	7	35.0	17	47.2	
IV	30	53.6	12	60.0	18	50.0	
Histology							
Adenocarcinoma	8	14.3	5	25.0	3	8.3	0.118
Squamous cell carcinoma	48	85.7	15	75.0	33	91.7	
Location							
Upper	10	17.9	3	15.0	7	19.4	0.404
Middle	19	33.9	5	25.0	14	38.9	
Lower	27	48.2	12	60.0	15	41.7	
Baseline chemistry and Hematology							
ANC /mm^3 (range)	5,000 (1,760–10,370)		4,210(2,250–10,190)		5,060(1,760–10,370)		0.501
Hemoglobin g/dL (range)	13.6 (8.7–17.1)		13.6(10.1–17.1)		13.6(8.7–16.3)		0.600
Albumin g/dL (range)	4.2 (3.0–4.8)		4.25(3.3–4.8)		4.2(3.0–4.7)		0.416
AST U/L (range)	18 (11–64)		18(11–29)		18(12–64)		0.939
ALT U/L (range)	17 (6–52)		16.5(7–30)		17(6–52)		0.571

Serum creatinine (range)	0.75 (0.45–1.05)	0.745(0.49–1.05)	0.75(0.45–0.94)	0.973

Abbreviations: BMI, body mass index; ANC, absolute neutrophil count; ALT, alanine aminotransferase.

Data regarding age, BMI, ANC, hemoglobin, albumin, ALT and serum creatinine are shown as median values and ranges.

Other data in the table represent the number of patients and data in the parentheses are expressed as %

Table 2 The association between patient gene polymorphisms and the efficacy of DCF chemotherapy in patients with esophageal cancer

Polymorphisms (Reference SNP number)		Treatment outcomes (*N*)		Objective response rate (%)	OR (95% CI)	*P*-value
		PD + SD	PR + CR			
SLCO1B3 **rs11045585 (*A>G*)**					–	
Dominant	AA	32	15	31.9%	2.667 (0.625–11.377)	0.185
	non-AA	4	5	55.6%		
Recessive	GG	1	0	0.0%	NE	NE
	non-GG	35	20	36.4%		
ABCB1 **rs1128503 (C>T)**						
Dominant	CC	6	3	33.3%	1.133 (0.251–5.121)	0.871
	non-CC	30	17	36.2%		
Recessive	TT	15	9	37.5%	0.873(0.290–2.629)	0.809
	non-TT	21	11	34.4%		
ABCB1 **rs2032582 (G>T/A)**						
Dominant	GG	6	3	33.3%	1.133 (0.251–5.121)	0.871
	non-GG	30	17	36.2%		
Recessive	TT, TA, AA	9	6	40.0%	0.778 (0.23–2.629)	0.686
	other	27	14	34.1%		
ABCB1 **rs1045642 (C>T)**						
Dominant	CC	14	5	26.3%	1.909 (0.567–6.427)	0.296
	non-CC	22	15	40.5%		
Recessive	TT	5	2	28.6%	1.452 (0.255–8.267)	0.675
	non-TT	31	18	36.7%		
ABCC2 **rs12762549 (G>C)**						

Dominant	GG	15	8	34.8%	1.071 (0.352–3.262)	0.903
	non-GG	21	12	36.4%		
Recessive	CC	18	13	41.9%	0.538 (0.174–1.663)	0.282
	non-CC	18	7	28.0%		
***ABCG2* rs2231137(G>A)**						
Dominant	GG	26	12	31.6%	1.733 (0.547–5.497)	0.350
	non-GG	10	8	44.4%		
Recessive	AA	2	1	33.3%	1.118 (0.095–13.150)	0.930
	non-AA	34	19	35.8%		
***ABCG2* rs2231142 (C>A)**						
Dominant	CC	19	9	32.1%	1.366 (0.456–4.093)	0.577
	non-CC	17	11	39.3%		
Recessive	AA	1	2	66.7%	0.257 (0.022–3.031)	0.281
	non-AA	35	18	34.0%		
***CYP3A5* rs776746 (G>A)**						
Dominant	GG	23	12	34.3%	1.179 (0.383–3.629)	0.773
	non-GG	13	8	38.1%		
Recessive	AA	1	1	50.0%	0.543 (0.032–9.176)	0.672
	non-AA	35	19	35.2%		
***GST P1* rs1695 (A>G)**						
Dominant	AA	26	14	35.0%	1.114 (0.335–3.710)	0.860
	non-AA	10	6	37.5%		
Recessive	GG	0	1	100.0%	NE	NE
	non-GG	36	19	34.5%		

***GST M1, T1* null**						
Dominant	P/P	6	4	40.0%	0.800 (0.197–3.254)	0.755
	other	30	16	34.8%		
Recessive	N/N	27	17	38.6%	0.529 (0.125–2.236)	0.387
	other	9	3	25.0%		
***ERCC1* rs3212986 (C>A)**						
Dominant	CC	21	11	34.4%	1.145 (0.380–3.449)	0.809
	non-CC	15	9	37.5%		
Recessive	AA	2	1	33.3%	1.118 (0.095–13.150)	0.930
	non-AA	34	19	35.8%		
***ERCC1* rs11615 (C>T)**						
Dominant	CC	18	12	40.0%	0.667 (0.220–2.018)	0.473
	non-CC	18	8	30.8%		
Recessive	TT	3	2	40.0%	0.818 (0.125–5.357)	0.834
	non-TT	33	18	35.3%		
***ERCC2* rs13181 (T>G)**						
Dominant	TT	35	19	35.2%	1.842 (0.109–31.138)	0.672
	non-TT	1	1	50.0%		
Recessive	GG	0	0	0.0%	NE	NE
	non-GG	36	20	35.7%		
***ERCC2* rs238406 (G>T)**						
Dominant	GG	8	5	38.5%	0.857 (0.238–3.087)	0.814
	non-GG	28	15	34.9%		
Recessive	TT	13	8	38.1%	0.848 (0.276–2.608)	0.773
	non-TT	23	12	34.3%		

ERCC2 **rs1799793 (G>A)**						
Dominant	GG	36	19	34.5%	NE	NE
	non-GG	0	1	100%		
Recessive	AA	0	0	0%	NE	NE
	non-AA	36	20	35.7%		
XRCC1 **rs25487 (G>A)**						
Dominant	GG	17	11	39.3%	0.732 (0.244–2.193)	0.577
	non-GG	19	9	32.1%		
Recessive	AA	5	0	0.0%	NE	NE
	non-AA	31	20	39.2%		
XRCC1 **rs25489 (G>A)**						
Dominant	GG	25	18	41.9%	0.253 (0.500–1.281)	0.097
	non-GG	11	2	15.4%		
Recessive	AA	0	0	0.0%	NE	NE
	non-AA	36	20	35.7%		
XRCC1 **rs1799782 (C>T)**						
Dominant	CC	18	10	35.7%	1.000 (0.335–2.984)	1.000
	non-CC	18	10	35.7%		
Recessive	TT	2	2	50.0%	0.529 (0.069–4.078)	0.541
	non-TT	34	18	34.6%		
XRCC3 **rs861530 (G>A)**						
Dominant	GG	8	6	42.9%	0.667 (0.193–2.299)	0.521
	non-GG	28	14	33.3%		
Recessive	AA	10	6	37.5%	0.897 (0.270–2.988)	0.860
	non-AA	26	14	35.0%		
XRCC3 **rs861539 (C>T)**						

Dominant	CC	32	18	36.0%	0.889 (0.148–5.340)	0.898
	non-CC	4	2	33.3%		
Recessive	TT	0	0	0.0%	NE	NE
	non-TT	36	20	35.7%		
***XRCC3* rs1799794 (A>G)**						
Dominant	AA	5	8	61.5%	0.242 (0.066–0.889)	**0.033**
	non-AA	31	12	27.9%		
Recessive	GG	10	8	44.4%	0.577 (0.182–1.830)	0.350
	non-GG	26	12	31.6%		

Abbreviations: PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response. OR, odds ratio; CI, confidence interval; NE, not estimable. The *P* values < 0.05 are in bold.

Table 3 Multivariate analysis of associations between clinical response and clinical variables

	OR	95% CI	*P*-value
Clinical T category (T1-T2/T3)	2.417	0.229–25.469	0.463
Tumor location (Upper/Middle or Low)	1.077	0.229–5.068	0.925
***XRCC3* rs1799794 (AA/GA or GG)**	0.243	0.065–0.914	0.036

Abbreviations: OR, odds ratio; CI, confidence interval; The *P*-values < 0.05 are in bold

Figures

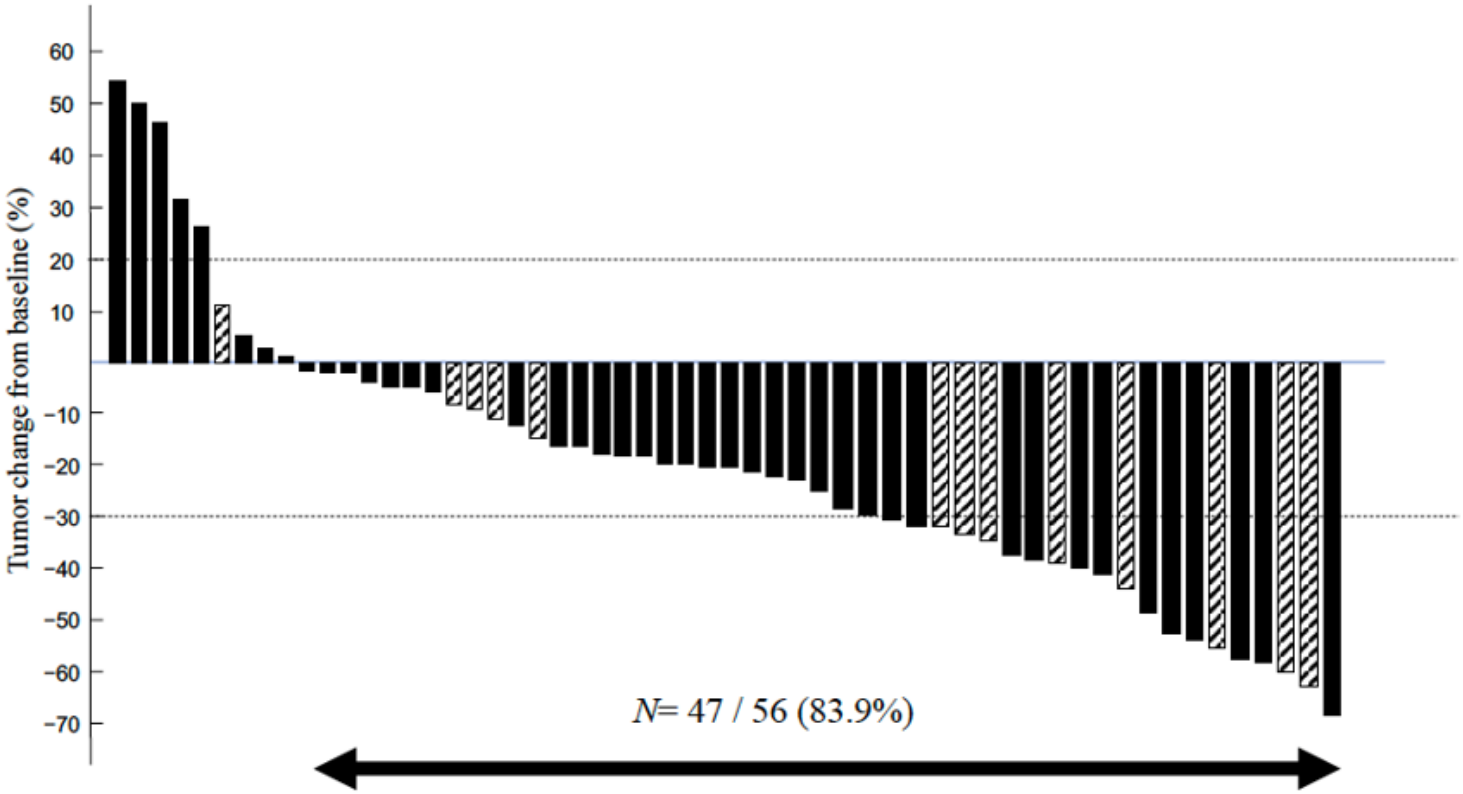

Figure 1

Waterfall plot The reduction in tumor size after the first course of chemotherapy. Of the 56 patients who received a postbaseline tumor assessment, 47 patients (83.9%) exhibited tumor shrinkage of measurable lesions relative to baseline. XRCC3 4541G>A; AA shows the hatched bar.