**ORIGINAL ARTICLE**

**UGT1A1 polymorphisms in rectal cancer associated with the efficacy and toxicity of preoperative chemoradiotherapy using irinotecan**

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The purpose of the present study was to assess the efficacy and toxicity of preoperative chemoradiotherapy using irinotecan against locally advanced lower rectal cancer according to UDP-glucuronosyltransferase 1A1 (UGT1A1) polymorphisms. Between 2009 and 2016, 46 patients with resectable rectal cancer (T3-T4, N0-N2, M0) received preoperative chemoradiotherapy consisting of 80 mg/m² per day tegafur/gimeracil/oteracil (S-1; days 1-5, 8-12, 22-26, and 29-33), 60 mg/m² per day irinotecan (days 1, 8, 22, and 29), and 45 Gy radiation (1.8 Gy/day, 5 days per week for 5 weeks). Six to eight weeks after completing chemoradiotherapy, total mesorectal excision was carried out. Patients with UGT1A1 polymorphisms were divided into WT (n = 26), heterozygous (n = 15), and homozygous (n = 5) groups, the latter including double heterozygosities. We evaluated associations between clinical characteristics, including UGT1A1 polymorphisms, and chemoradiotherapy efficacy and toxicity. Incidence rates of grade 3+ neutropenia and diarrhea were 17.0% and 30.4%, respectively. Relative dose intensity was 89.3%. Pathological complete response rate (grade 3) was 26.1%, and the good response (grade 2/3) rate was 84.8%. UGT1A1 polymorphisms were significantly associated with neutropenia and pathological good responses, but not with diarrhea. UGT1A1 polymorphism was the only predictive factor for pathological good responses. Our results indicate that UGT1A1 polymorphism is a predictive factor to determine the clinical efficacy of preoperative chemoradiotherapy and hematological toxicity induced by chemoradiotherapy using irinotecan in locally advanced rectal cancer patients.

**KEYWORDS**
clinical efficacy, irinotecan, rectal cancer, toxicity, UGT1A1 polymorphism

**Abbreviations:** APR, abdominopereineal resection; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CT, computed tomography; mGPS, modified Glasgow prognostic score; pCR, pathological complete response; 5-FU, tegafur/gimeracil/oteracil; TME, total mesorectal excision; UGT1A1, UDP-glucuronosyltransferase 1A1; ypCR, grade 3 pathological complete response (from preoperative treatment).
1 | INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies, and the number of CRC patients has been increasing annually worldwide.\(^1\) Surgical procedures for lower rectal cancer have a relatively high risk of positive circumferential resection margin because the mesorectum is thin or absent.\(^2\) Therefore, this patient population suffers from local recurrence more often than other colon cancer patients. To reduce local recurrence, the National Comprehensive Cancer Network and European Society for Medical Oncology consensus guidelines recommend preoperative chemoradiotherapy for lower rectal cancer consisting of 45 Gy radiotherapy concomitant with 5-fluorouracil (5-FU)-based drugs before surgery.\(^3,4\) However, grade 3 pathological complete response from preoperative treatment (ppCR) after preoperative 5-FU-based chemoradiotherapy alone were only 10%-17%.\(^5,6\)

Adding oxaliplatin or irinotecan to 5-FU-based preoperative chemoradiotherapy was shown to improve pCR rates in several clinical trials.\(^7-15\) Five phase III clinical trials using oxaliplatin in addition to 5-FU-based preoperative chemoradiotherapy have been reported; however, most results have shown that the number of adverse events increased without achieving clinical benefits.\(^7,11\) No phase III clinical trials using irinotecan with 5-FU-based preoperative chemoradiotherapy have been documented, but several phase II studies have shown clinical benefits without increasing adverse events.\(^12-16\) Among these, Sato et al\(^12\) reported a pCR of 34.7% and 9% grade 3+ toxicities with preoperative chemoradiotherapy consisting of tegafur/gimeracil/oteracil (S-1) plus irinotecan.

Irinotecan causes a range of toxicities including diarrhea and neutropenia. UDP-glucuronosyltransferase (UGT) plays an important role in irinotecan metabolism.\(^17\) A previous study showed that the UGT1A1*6/*28 gene polymorphisms increase the risk of neutropenia and diarrhea in lung cancer and CRC patients during chemoradiotherapy.\(^18\) UGT1A1 homozgyosity (UGT1A1*28/*28, UGT1A1*6/*6) and double heterozygosities (UGT1A1*6/*28) significantly increase the incidence of neutropenia and diarrhea during chemoradiotherapy;\(^19\) therefore, dose reduction is recommended for such patients.\(^20\) However, no study has assessed the association between UGT1A1 polymorphisms and chemoradiotherapy because patients with homozgyosity or double heterozygosities were excluded from previous clinical trials.\(^12,13,21\)

In the present study, we assessed the associations between preoperative S-1 plus irinotecan chemoradiotherapy for lower rectal cancer and UGT1A1 polymorphisms including homozgyosity and double heterozygosities. We included patients with these mutations because other studies found that the risk of severe toxicity was not higher in these patients than in WT patients when <150 mg/m\(^2\) irinotecan was used.\(^22,23\) We further evaluated clinical features in association with pathological response to preoperative chemoradiotherapy. Clinical features included clinical T stage, N stage, low CEA levels, low grade in mGPS before chemoradiotherapy, and well-differentiated tumors.\(^24,25\)

2 | MATERIALS AND METHODS

2.1 | Patients and the preoperative chemoradiotherapy protocol

Between 2009 and 2016, 82 patients with untreated resectable rectal cancer (T3-T4, NO-N2, M0) received preoperative S-1 plus irinotecan chemoradiotherapy before radical surgery. Among these patients, 46 patients agreed to undergo assessment of UGT1A1 polymorphisms. We retrospectively collected the clinical data of these 46 patients. These patients had histologically confirmed adenocarcinoma and an ECOG performance status of 0-2. Disease was staged according to the UICC staging system. We used physical examinations, barium enemas, magnetic resonance imaging (MRI), and CT to evaluate the patients according to the TNM staging system. We defined lower rectal cancer as tumors located below or including the peritoneal reflection. Preoperative chemoradiotherapy consisted of 80 mg/m\(^2\) per day S-1 (days 1-5, 8-12, 22-26, and 29-33), 60 mg/m\(^2\) per day irinotecan (days 1, 8, 22, and 29), and 45 Gy radiation (1.8 Gy/day, 5 days per week for 5 weeks). Dose reductions were not applied to the group of homozygous patients. Six to eight weeks after completing chemoradiotherapy, the patients were scheduled for total mesorectal excision.

These protocols were based on the S-1 combined preoperative neoadjuvant multimodality therapy with radiation and irinotecan for locally advanced rectal cancer (SAMRAI-1) trial\(^26\) and were approved by the institutional review board at Hyogo College of Medicine (No. 2756).

2.2 | Classification of UGT1A1 polymorphisms

UGT1A1 polymorphisms were assessed after consulting with a specialist of hereditary diseases. Blood samples were obtained from patients scheduled to undergo irinotecan treatment, and UGT1A1*28 and UGT1A1*6 were analyzed using the Invader assay (SRL Inc., Kobe, Japan). Polymorphisms were classified into three groups: WT (*1/*1), heterozygous (*28/*1, *6/*1), and homozygous (*28/*28, *6/*6, *28/*6). Double heterozygosities (*28/*6) were classified in the homozygous group because of the reported possible serious toxicities associated with double heterozygosities.\(^27\)

2.3 | Surgical procedure

All patients underwent total mesorectal excision, which included low anterior resection followed by double-stapling technique for reconstruction, intersphincteric resection, and APR. Diverting ileostomy was routinely constructed for all cases, except those with APR. If the involvement of adjacent organs was diagnosed before preoperative chemoradiotherapy, en bloc resection of primary tumors was carried out. Lateral lymph node (LLN) dissection was carried out when lateral lymph nodes were >7 mm determined by MRI before preoperative chemoradiotherapy.

2.4 | Association between UGT1A1 polymorphisms and clinicopathological features

The investigated clinical features included age, gender, tumor location, tumor size, pretreatment clinical T stage, N stage and UICC
stage, operation type, CEA level, and mGPS. Pathological features included ypT stage, ypN stage, ypUICC stage, histology, circumferential resection margin, downstage, and tumor regression grade. Tumor regression grade by chemoradiotherapy was evaluated according to the 8th edition of the Japanese classification of colorectal carcinoma by the Japanese Society for Cancer of the Colon and Rectum. Briefly, grade 0 was defined as no evidence of effect; grade 1 was defined as viable tumor cells remaining in more than one-third of the tumor area; grade 2 was defined as viable tumor cells remaining in less than one-third of the tumor area; and grade 3 (ypCR) was defined as no viable tumor cells remaining. We defined a good response as grades 2 or 3 and a poor response as grades 0 or 1.

2.5 | Association between UGT1A1 polymorphisms and toxicity or relative dose intensity

Hematological and non-hematological toxicities from preoperative chemoradiotherapy were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. Relative dose intensity (RDI) was calculated as the ratio of the actual dose to the scheduled dose: S-1 (1600 mg/m²), irinotecan (240 mg/m²), and irradiation (45 Gy).

2.6 | Associations with pathological response

We further analyzed predictors of pathological good response by selecting six candidate factors including pretreatment clinical T stage, pretreatment clinical N stage, histology, CEA before chemoradiotherapy, mGPS before chemoradiotherapy, and UGT1A1 polymorphisms. mGPS was classified using C-reactive protein levels (CRP: >0.5 mg/dL) and serum albumin levels (<3.5 mg/day).

2.7 | Statistical analysis

Subjects with UGT1A1 polymorphisms are presented as a frequency distribution. Patient characteristics and pathological outcomes are presented as the median and range for continuous variables and by frequency distribution for categorical variables. For comparisons of patient characteristics and outcomes between the UGT1A1 groups, analysis of variance models for continuous variables and Fisher’s exact test for categorical variables were used. RDI for each preoperative chemoradiotherapy are presented as median and quartiles and were compared between the UGT1A1 groups using analysis of variance models. Occurrence of grade 1-4 (any grade) toxicity and grade 3-4 is presented as frequency distributions for each UGT1A1 group. Associations between grade 3-4 toxicity and the UGT1A1 groups were evaluated using Fisher’s exact test. The frequency distributions of the pathological response (good or poor) for each patient characteristic are shown. Associations between pathological responses and patient characteristics were evaluated using odds ratio and Fisher’s exact tests, where the categories “heterozygous” and “homozygous” in the UGT1A1 groups were combined. Allele frequencies of UGT1A1 *6 and *28 were evaluated by an exact test for Hardy-Weinberg equilibrium. A two-sided P-value < .05 was considered statistically significant without adjusting for multiplicity for exploratory analysis. All statistical analyses were carried out using SAS software (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | UGT1A1 polymorphisms

We examined UGT1A1 polymorphisms in the 46 patients in the present study. The distribution of UGT1A1*6 and UGT1A1*28 polymorphisms is shown in Table 1. Twenty-six patients (56.5%), 15 patients (32.6%), and five patients (10.9%) were classified into the WT, heterozygous (*1/*6 and *1/*28), and homozygous groups, respectively. The allele frequencies of UGT1A1 *6 and *28 were calculated as 15.3% and 12.0%, respectively. Genotype frequencies did not significantly deviate from the Hardy-Weinberg equilibrium (P = 0.38).

3.2 | Associations between clinicopathological features and UGT1A1 polymorphisms

Clinical features are listed in Table 2. There were no significant differences in clinical features between the UGT1A1 polymorphism groups.

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TABLE 1 | Distribution of UGT1A1 polymorphisms in patients with resectable rectal cancer

| UGT1A1 polymorphism | Classification of UGT1A1 polymorphisms, n (%) |
|----------------------|-----------------------------------------------|
|                      | WT | Heterozygous | Homozygous |
| *1/*1                | 26 (56.5) |           |            |
| *1/*6                | 9 (19.6) |           |            |
| *1/*28               | 6 (13.0) |           |            |
| *6/*6                |     | 1 (2.2)     |            |
| *28/*28              |     | 1 (2.2)     |            |
| *6/*28               |     | 3 (6.5)     |            |
|                      | 26 (56.5) | 15 (32.6) | 5 (10.9)   |

UGT1A1, UDP-glucuronosyltransferase 1A1.
groups, except for mGPS. Pathological features are listed in Table 3. Among the patients treated with preoperative chemoradiotherapy, 71.7% were downstaged according to the UICC criteria. Five patients (10.9%) were grade 1a (all in the WT group), two (4.3%) were grade 1b (all in the WT group), 27 (58.7%) were grade 2 (13 in the WT group, 11 in the heterozygous group, and three in the homozygous group), and 12 (26.1%) were grade 3 (six in the WT group, four in the heterozygous group, and two in the homozygous group). There were no significant differences in pathological features between the UGT1A1 polymorphism groups.

### 3.3 Association between toxicity and UGT1A1 polymorphisms

Toxicities are listed in Table 4. We observed a significant difference in the incidence of leukopenia and neutropenia in the UGT1A1 polymorphism groups. Grade 3-4 leukopenia and neutropenia did not occur in WT patients. Patients in the heterozygous and homozygous groups had more grade 3-4 neutropenia and leukopenia than those in the WT patient group ($P < .05$). However, there was no significant difference in the incidence of other factors, including diarrhea, liver function, and renal function, among the three groups.
3.4 | Association between RDI and UGT1A1 polymorphisms

Relative dose intensities are listed in Table 4. Each UGT1A1 group showed >90% RDI in those receiving S-1, 88% in those receiving irinotecan, and 99% in those receiving radiation therapy. There was no significant difference in RDI according to UGT1A1 polymorphism despite the significant differences observed in hematological toxicities.

3.5 | Associations with pathological responses

Associations between representative candidate factors and pathological responses are listed in Table 5. Only UGT1A1 polymorphisms were significantly associated with good tumor response by preoperative chemoradiotherapy (P = .014) (Table 5). All patients in the heterozygous and homozygous groups showed a good response (grade 2/3) following preoperative chemoradiotherapy.

4 | DISCUSSION

In the present study, we showed that UGT1A1 polymorphisms were the only factor for predicting a good pathological response to preoperative chemoradiotherapy using irinotecan in patients with locally advanced rectal cancer. To our knowledge, this is the first study to evaluate the efficacy and toxicity of preoperative chemoradiotherapy using irinotecan according to UGT1A1 polymorphisms.
Our study showed that the allele frequencies of UGT1A1 *6 and *28 were 15.3% and 12.0%, respectively. Genotype frequencies did not deviate significantly from Hardy-Weinberg equilibrium. Miyata et al.20 reported that the allele frequencies of UGT1A1 *6 and *28 were 16.7% and 12.6%, respectively, in 795 Japanese prospective studies. Thus, the frequencies of UGT1A1 *6 and *28 in our report were comparable to the data previously reported in Japanese patients.

Our preoperative chemoradiotherapy using S-1 plus irinotecan was designed to increase the ypCR rate compared with conventional preoperative chemoradiotherapy using 5-FU-based chemotherapy26 because the usefulness of adding irinotecan to preoperative chemoradiotherapy has not been established in clinical trials. The ypCR rate in the present study was 26.1%, which was similar to the 21% observed by Shin et al.13 who used chemotherapy consisting of 70 mg/m² S-1 and 40 mg/m² irinotecan, the 25% reported by Jung et al.14 (35 mg/m² S-1 and 40 mg/m² irinotecan), and the 25% reported by Jung et al.14 (35 mg/m² S-1 and 40 mg/m² irinotecan). In a phase I study, Kawai et al.31 reported that the proportion of good responders increased linearly with the increased dose of irinotecan. Importantly, the presence of UGT1A1 polymorphisms was not assessed in these reports.12-15 Therefore, our study is the first to report on preoperative irinotecan-based chemoradiotherapy while also grouping the patients by UGT1A1 polymorphisms without excluding any patient groups.

In Western countries, UGT1A1 polymorphisms have been confirmed to be a predictor of toxicity to irinotecan.23 Indeed, patients with double heterozygosities or homozygosity are recommended to reduce the amount of irinotecan in cases of high-dose chemotherapy.

### Table 4

| Toxicity, n (%) | WT (n = 26) | Heterozygous (n = 15) | Homozygous (n = 5) | P-value |
|----------------|-------------|----------------------|-------------------|---------|
| Hematological toxicity | | | | |
| Leukopenia | Any grade | Grade 3-4 | Any grade | Grade 3-4 | Any grade | Grade 3-4 | P-value |
| | 16 (61.5) | 0 | 10 (66.7) | 5 (33.3) | 5 (100) | 5 (100) | <.001 |
| | 16 (61.5) | 0 | 11 (73.3) | 3 (20.0) | 5 (100) | 5 (100) | <.001 |
| Neutropenia | 0 | 0 | 0 | 0 | 1 (20.0) | 1 (20.0) | .109 |
| Febrile neutropenia | 14 (53.8) | 0 | 11 (73.3) | 0 | 4 (80.0) | 0 | - |
| Anemia | 7 (26.9) | 0 | 2 (13.3) | 0 | 2 (40.0) | 0 | - |
| Thrombocytopenia | 0 | 0 | 1 (6.7) | 1 (6.7) | 3 (60.0) | 0 | .435 |
| Increased blood bilirubin | 2 (7.7) | 0 | 2 (13.3) | 0 | 0 | 0 | - |
| Increased AST | 7 (26.9) | 0 | 3 (20.0) | 0 | 1 (20.0) | 0 | - |
| Increased ALT | 0 | 0 | 0 | 0 | 1 (20.0) | 0 | - |
| Increased creatinine | | | | | | | |
| Non-hematological toxicity | | | | |
| Diarrhea | 23 (88.5) | 9 (34.6) | 9 (60.0) | 4 (26.7) | 3 (60.0) | 2 (40.0) | .817 |
| Anorexia | 14 (53.8) | 1 (3.8) | 6 (40.0) | 1 (6.7) | 3 (60.0) | 0 | 1.000 |
| Nausea | 6 (23.1) | 0 | 6 (40.0) | 0 | 2 (40.0) | 0 | - |
| Fatigue | 6 (23.1) | 0 | 7 (46.7) | 0 | 4 (80.0) | 0 | - |
| Dermatitis | 1 (3.8) | 0 | 2 (13.3) | 0 | 1 (20.0) | 0 | - |
| Vomiting | 1 (3.8) | 0 | 3 (20.0) | 0 | 0 | 0 | - |
| Stomatitis | 1 (3.8) | 0 | 1 (6.7) | 0 | 0 | 0 | - |
| Anal pain | 6 (23.1) | 0 | 1 (6.7) | 0 | 3 (60.0) | 0 | - |
| Hiccoughs | 0 | 0 | 1 (6.7) | 0 | 0 | 0 | - |
| Alopecia | 0 | 0 | 0 | 0 | 1 (20.0) | 0 | - |
| RDI (%) | | | | |
| S-1 | Mean (range) | 91.2 (25-100) | 90.5 (50-100) | 100 (100-100) | .558 |
| Irinotecan | Mean (range) | 88.5 (25-100) | 89.3 (25-100) | 93.4 (67-100) | .898 |
| RT | Mean (range) | 99.5 (87-100) | 99.1 (87-100) | 100 (100-100) | .815 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; RDI, relative dose intensity; RT, radiation therapy; UGT1A1, UDP-glucuronosyltransferase 1A1. The factor showing the significant difference is bold value.

*P*-values were calculated for grade 3-4 toxicity using Fisher’s exact test when present in at least one patient from any UGT1A1 group; otherwise, *P*-values were calculated using an analysis of variance model. End-dash in the column of the "P-value" indicates that no grade 3-4 toxicity occurred in any UGT1A1 polymorphisms.
because of severe hematological toxicity and diarrhea.\(^{32}\) In Japan, increased cases of neutropenia were reported in patients who received FOLFIRI for CRC or combination chemotherapy of irinotecan and cisplatin for lung cancer and gastric cancer.\(^{20,33,34}\) The influence of \(UGT1A1\) polymorphisms on the therapeutic effect of irinotecan has been investigated much less than toxicity, although Xu et al and Toffoli et al\(^{35,36}\) reported differences in the clinical responses to irinotecan-based chemotherapy in advanced CRC patients with \(UGT1A1^{*}28\) genotype mutations. In addition, Han et al\(^{37}\) showed that patients with homozygous \(UGT1A1^{*}6\) were associated with tumor response rates. However, the usefulness of \(UGT1A1\) polymorphisms in predicting response to chemoradiotherapy has not been well investigated.

In the present study, patients with \(UGT1A1\) mutations showed a significantly better response to chemoradiotherapy (including irinotecan) than those without these mutations. Moreover, univariate analysis using CEA and mGPS, which were reported as biomarkers for chemoradiotherapy,\(^{25,38-40}\) identified that only \(UGT1A1\) polymorphisms were a predictive factor for pathologically good response.

In terms of toxicity, in the present study, only the incidence of neutropenia was significantly affected by \(UGT1A1\) polymorphisms. Indeed, the incidence of diarrhea, a critical symptom of toxicity that is significantly worsened by \(UGT1A1\) mutations in chemotherapy regimens,\(^{35}\) was not affected. The incidence of grade 3+ diarrhea was 29.3% in this study, which was higher than the 4.5% reported by Sato et al,\(^{12}\) the 5.7% seen by Jung et al,\(^{14}\) and the 11.1% observed in the SAMRAI-1 trial.\(^{26}\)

There were several limitations to the present study; first, it was a retrospective study in which \(UGT1A1\) polymorphism analysis was done retrospectively.

| Factors, n (%) | Good response (n = 39) | Poor response (n = 7) | Odds ratio (CI) | P-value\(^{a}\) |
|---------------|------------------------|-----------------------|----------------|-------------|
| CEA levels before CRT\(^{b}\) | | | | |
| Normal CEA | 23 (59.0) | 3 (42.9) | 2.04 (0.400-10.457) | .433 |
| Elevated CEA | 15 (38.5) | 4 (57.1) | | |
| cT stage | | | | |
| T3 | 28 (71.8) | 4 (57.1) | 1.91 (0.366-9.955) | .658 |
| T4 | 11 (28.2) | 3 (42.9) | | |
| cN stage | | | | |
| N− | 18 (46.2) | 1 (14.3) | 5.14 (0.565-46.817) | .213 |
| N+ | 21 (53.8) | 6 (85.7) | | |
| Histology | | | | |
| Well/ moderately | 33 (84.6) | 6 (85.7) | 0.92 (0.093-9.041) | 1.000 |
| Poorly/ mucinous/ signet | 6 (15.4) | 1 (14.3) | | |
| mGPS score | | | | |
| 0 | 28 (71.8) | 6 (85.7) | 0.42 (0.046-3.941) | .657 |
| 1/2 | 11 (28.2) | 1 (14.3) | | |
| UGT1A1 polymorphisms | | | | |
| Wild-type | 19 (48.7) | 7 (100) | | .014 |
| Heterozygous/ homozygous | 20 (51.3) | 0 | | |

Analysis for trivial factors such as age, gender, distance from anal verge, tumor size, clinical UICC stage, and type of operation was carried out in the same way (data not shown). Cut-off values for continuous variables were set as their respective medians. Type of operation was categorized into APR and Other. Minimum P-value among these factors was .096, which was derived from the analysis of age (<62.5 vs ≥62.5 y odds ratio: 0.13, CI: 0.014-1.174). The second smallest P-value was .213, which was derived from the analysis of clinical UICC stage (Stage II vs Stage III odds ratio: 5.14, CI: 0.565-46.817. CEA, carcinoembryonic antigen; CI, confidence interval; CRT, chemoradiotherapy; mGPS, modified Glasgow prognostic score; \(UGT1A1\), UDP-glucuronosyltransferase 1A1. The factor showing the significant difference is bold value.

\(^{a}\)P-values were calculated using Fisher’s exact test.

\(^{b}\)One subject with missing CEA data was excluded from the analysis.

\(^{c}\)Odds ratios and CI could not be calculated because there was a zero count.
not carried out for all patients receiving preoperative chemoradiotherapy (including irinotecan). Second, it was a relatively small study carried out in a single institute with no adjustment for clinical background. Finally, the follow-up time was not sufficient to evaluate long-term efficacy according to UGT1A1 polymorphisms.

Our results indicate that UGT1A1 polymorphism is a predictive factor to determine the clinical efficacy of preoperative chemoradiotherapy and hematological toxicity induced by chemoradiotherapy using irinotecan in locally advanced rectal cancer patients. A randomized multicenter study could elucidate the influence of dose setting by UGT1A1 polymorphism on efficacy and toxicity of preoperative chemoradiotherapy using irinotecan for rectal cancer patients.

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CONFLICTS OF INTEREST

Authors declare no conflicts of interest for this article.

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