Small intestinal mucosal injury in patients with gastrointestinal cancer who develop complicated fluoropyrimidine-induced diarrhea

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Abstract
Background: Diarrhea is a common adverse event of fluoropyrimidine-based chemotherapy. However, no treatment with promising evidence has been established for chemotherapy-induced diarrhea (CID); limited data are available on the frequency of complicated CID and small intestinal mucosal damage. In this current study, we aimed to determine the incidence of complicated CID and mucosal injury among patients with complicated CID receiving fluoropyrimidine via small bowel capsule endoscopy (CE).

Methods: In total, 536 patients with advanced or recurrent gastrointestinal cancer who received fluoropyrimidine-based chemotherapy were retrospectively analyzed. Diarrhea was evaluated using the Common Terminology Criteria for Adverse Events version 4. Complicated CID was defined according to the American Society of Clinical Oncology guidelines. To evaluate small intestinal mucosal injury in patients with complicated CID, CE was performed. Multivariate analysis was performed to identify risk factors for complicated CID.

Results: In total, 32 (6%) patients developed complicated CID. Complicating symptoms were noted in 24 (75%) patients, with cramping, vomiting, and sepsis being observed in 15 (63%), 8 (33%), and 2 (8%) patients, respectively. Among the 12 patients who underwent CE, 10 (83%) exhibited abnormal findings. Multivariate analysis showed that oral fluoropyrimidine administration was a risk factor for complicated CID (odds ratio, 2.95; 95% confidence interval, 1.06–8.19).

Conclusions: Despite the relatively low incidence of complicated CID, most patients with complicated CID exhibited small intestinal mucosal injury, with some developing fever or sepsis as complications. Thus, bacterial translocation secondary to small intestinal mucosal injury should be considered in the management of patients with complicated fluoropyrimidine-induced diarrhea.

Background
Prospective clinical trials and meta-analyses in the 1990s demonstrated that chemotherapy had greater survival benefit than that of the best supportive care. Cytotoxic chemotherapy, especially that involving use of fluoropyrimidines, prolongs survival and has been widely used in patients with various malignancies, including gastrointestinal, breast, and head and neck cancers. Recently, oral
chemotherapy involving the use of fluoropyrimidines (capecitabine and S-1) has provided new perspectives for the treatment of gastrointestinal cancer owing to its greater simplicity and convenience than conventional chemotherapy involving 5-fluorouracil (5-FU) 2. Nonetheless, cytotoxic side effects are serious issues hindering the clinical application of beneficial therapies. Common clinical toxicities of fluoropyrimidines result from the inhibition of rapidly dividing cells, such as bone marrow hematopoietic and gastrointestinal epithelial cells, causing cytopenia and diarrhea, respectively. Studies have shown that chemotherapy-induced diarrhea (CID), a common non-hematological toxicity, can be predicted based on dose, schedule, and administration route 3, 4. Severe diarrhea has been noted in 8%-37% of patients receiving fluoropyrimidines owing to lower gastrointestinal tract toxicity; diarrhea tolerance among patients within and outside the United States (US) has been found to differ 5. Particularly, the incidence of CID among Japanese patients has been considered to be low, with studies reporting a frequency of 1%-8% of grade 3-4 diarrhea 6, 7. However, it can be severe in some patients, especially when sepsis occurs 8, 9. Appropriate treatment for CID is important considering that it would allow patients to continue chemotherapy for cancer, leading to a better prognosis. Accordingly, only loperamide, octreotide, and opium tincture have been recommended in the updated treatment guidelines by the consensus conference on the management of CID 10. From the perspective of treating CID, diarrhea can be classified as either uncomplicated or complicated 10. Loperamide, which functions by decreasing intestinal motility, has been widely used as the primary treatment for CID, with additional aggressive management, including administration of antibiotics or octreotide, being recommended for complicated CID. However, details regarding aggressive management and its impact on patients have been limited. Furthermore, while evaluation of intestinal mucosal injury among patients with CID might be important for determining the treatment strategy, only a few reports have investigated the incidence or severity of small intestinal mucosal injury and the incidence of CID accompanied by complications.

The present study aimed to determine the incidence of complicated CID and mucosal injury among
patients receiving fluoropyrimidine using small bowel capsule endoscopy (CE).

Methods

Patients

Patients with advanced or recurrent gastrointestinal cancer who underwent fluoropyrimidine-based chemotherapy at Toyama University hospital between April 2006 and June 2017 were retrospectively analyzed. Clinical assessments were repeated every 2 or 3 weeks during chemotherapy, while information was retrospectively collected from medical records. This study was approved by the Institutional Review Board (No. 26-136), and all patients signed an informed consent form prior to participation.

Treatment regimens and schedule

Chemotherapy regimens in clinical practice or within the context of a clinical trial were selected individually. The dosage and schedules of most chemotherapy regimens were based on previously reported recommendations. Treatment was continued until disease progression, occurrence of unacceptable toxicity, or patient refusal to continue therapy despite appropriate dose reduction.

Evaluation and management of diarrhea

Diarrhea severity was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. Complicated diarrhea was defined according to the following American Society of Clinical Oncology guidelines: CTCAE grade 3 or 4 diarrhea or grade 1 or 2 diarrhea with one or more additional signs or symptoms, including cramping, nausea/vomiting (grade 2 or more), decreased performance status, fever, sepsis, neutropenia, frank bleeding, and dehydration. Uncomplicated diarrhea was defined as grade 1 or 2 diarrhea with no complicating symptoms.

All patients diagnosed with complicated diarrhea were admitted to the hospital, and their chemotherapy was discontinued. To distinguish between infectious and CID diarrhea, stool cultures (for Clostridium difficile, Escherichia coli, and other infectious agents that cause colitis), complete blood count, electrolyte panel, and computed tomography scans were performed in patients who developed complicated diarrhea. Intravenous fluid and antibiotics were administered until all symptoms had resolved.
Small bowel CE procedure and evaluation

Patients with complicated CID underwent CE when their condition improved to CTCAE grade 1. All patients who underwent CE satisfied the following criteria: (1) no massive ascites or severe peritoneal dissemination; (2) a condition that permitted continued chemotherapy; and (3) oral intake capability. Depending on each patient’s condition, a patency capsule was used to confirm intestinal patency according to the operator’s discretion. Each patient was instructed not to consume solid food after 8 PM on the day before the procedure. CE studies were performed using the Pillcam™ SB2, SB3 system (Medtronic, Dublin, Ireland) or Endo Capsule™ system (Olympus, Tokyo, Japan). The monitoring period was approximately 10 h, corresponding to the battery life of the device. Two operators classified abnormalities observed in the video as red spots, erosions, and ulcers. Red spots were predominantly distinguished from angiectasia based on size. Mucosal erosions and ulcers were classified according to the size of the small bowel mucosal breaks considering that ulcers, by definition, require a degree of penetration and that evaluating lesion depth based on the angle of the image taken by the capsule was often impossible.

Statistical analysis

The incidence of diarrhea and the number of days from initiation of fluoropyrimidine-based chemotherapy to the onset of complicated CID were investigated. Additionally, time-to-event curves were calculated using the Kaplan–Meier method and compared using the log-rank test. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to identify which clinical factors influenced complicated CID. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. A p value of <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

The present study included 536 patients (256 with gastric cancer and 280 with colorectal cancer), the
clinical characteristics of whom are presented in Table 1. The most common types of
fluoropyrimidines administered were S-1 (70%) for gastric cancer and 5-FU (72%) for colorectal
cancer. Both groups had low frequency of capecitabine use. The chemotherapy regimen consisted of
fluoropyrimidine alone and combination chemotherapy in 77 (14%) and 459 (86%) patients,
respectively, while molecular-targeted drug therapy consisted of fluoropyrimidine and cisplatin plus
tрастузумаб in 35 patients with HER2-positive gastric cancer. Patients with colorectal cancer received
molecular-targeted drugs in combination with fluoropyrimidine and oxaliplatin or irinotecan.
Bevacizumab and cetuximab/panitumumab were administered in 25 and 116 patients, respectively.

**Complicated diarrhea**

A total of 32 (6%) patients developed complicated CID, among whom 22 (8.6%) and 10 (3.6%) had
gastric and colorectal cancer, respectively. Most of the patients developed the condition within a
month (Figs. 1 and 2). Diarrhea grades 2 and 3 were most frequently observed, with 12 (38%)
patients having each grade. Complicating symptoms were noted in 24 (75%) patients. Accordingly,
cramping, vomiting, sepsis, and fever were observed in 15 (63%), 8 (33%), 2 (8%), and 1 (4%)
patients, respectively. Complicated CID developed in 22% 56%, and 6% of the patients receiving
chemotherapy involving 5-FU, S-1, and capecitabine, respectively.

Among the 32 patients with complicated CID, 2 (6%) and 30 (94%) developed the condition after
receiving single-agent chemotherapy involving S-1 and combination chemotherapy, respectively. All
patients, except one who died after developing grade 4 neutropenia and sepsis, recovered from
complicated CID through infusion and antibiotic therapy. The median time to recovery from
complicated CID to grade 1 diarrhea was 6 days (range, 1–59 days).

**Small bowel CE findings**

Among the 32 patients with complicated CID, 12 (38%) underwent CE (Fig. 1). The remaining 20
patients with complicated CID did not undergo CE given their failure to satisfy the aforementioned CE
criteria or provide consent. A patency capsule was used in 6 patients, all of whom were confirmed to
have intestinal patency. The mean duration between the onset of complicated CID and small bowel CE
was 9 days (range, 2–21 days). Among the 12 patients who underwent CE, 9 (75%) had the capsule
pass through their small intestine within the scheduled timeframe. Capsule excretion was ultimately confirmed in all 12 patients, with no adverse events, including capsule retention, having occurred. Among the 12 patients who underwent CE, 10 (83%) showed abnormal findings. Accordingly, red spots, erosions, and ulcers were noted in 10 (91%), 7 (58%), and 3 (25%) patients, respectively (Fig. 3). Table 2 summarizes the characteristics of patients with complicated CID who underwent CE.

**Clinical factors associated with the incidence of complicated CID**

Univariate and multivariate analyses were performed to identify clinical or treatment factors associated with the incidence of complicated CID (Table 3) given that small intestinal mucosal injury was observed in most of the patients with complicated CID. Univariate analysis involving the entire patient cohort indicated that gastric cancer ($p = 0.01$) and oral fluoropyrimidine ($p = 0.003$) were significantly associated with the incidence of complicated CID, whereas sex, age, performance status, primary site resection, peritoneal metastasis, number of metastatic sites, and chemotherapy regimen were not. Multivariate analysis revealed that oral fluoropyrimidine (OR 2.95; 95% CI 1.06–8.19) was independently associated with the incidence of complicated CID.

**Discussion**

The present study carefully evaluated the small intestinal mucosa of patients with gastrointestinal cancer who developed complicated CID using CE. After chemotherapy discontinuation, almost all patients recovered from the condition, which had developed within a month. CE revealed that most patients with complicated CID developed multiple mucosal injuries even after the improvement to CTCAE grade 1 diarrhea. To our knowledge, this has been the first study to evaluate the entire small intestine of patients with complicated CID using CE.

Although consensus guidelines suggest the need for aggressive treatment, including intravenous fluid administration and antibiotic therapy, among patients with complicated CID $^{10, 14}$, they do not provide sufficient evidence for such. Most of the patients with complicated CID included herein had small intestinal mucosal injury, with 3 of 11 patients developing fever or sepsis as complicating symptoms that can be attributed to bacterial translocation secondary to small intestinal mucosal injury. In fact, one patient who developed severe neutropenia and diarrhea died without recovering from sepsis.
Thus, considering that patients with complicated CID are potentially at risk of infection, aggressive treatment, including antibiotic therapy and octreotide therapy, in addition to loperamide therapy is necessary. Indeed, a randomized controlled trial comparing octreotide with loperamide in 41 patients with 5-FU-induced diarrhea showed that the octreotide group had a higher diarrhea control rate than the loperamide group [90.4%, (19/21) vs. 15.0% (3/20); \( p < 0.05 \)].

While earlier studies conducted in mice models have established the microscopic features of gastrointestinal mucositis in 5-FU toxicity, recent reports have shown NF-kB and IL-4 to be critical mediators in this process. In fact, ileal biopsy with colonoscopy in patients with 5-FU-induced diarrhea revealed marked acute and chronic inflammation, which might correspond with the pathophysiology of fluoropyrimidine in rodent models. However, the extent and severity of this damage has yet to be studied in detail given that a considerable portion of the small intestine is beyond the reach of a colonoscope. Two recent studies evaluated the small intestinal mucosa of patients receiving chemotherapy. Accordingly, after performing CE in only those with diarrhea grades 0 to 2, both studies revealed that diarrhea grade was significantly correlated with the percentage of patients with intestinal mucosal injury. In contrast, the present study found a high rate of mucosal injury regardless of diarrhea severity, perhaps because our endoscopic study targeted patients with complicated diarrhea, which includes both diarrhea severity and clinical factors. This finding suggests that complicating symptoms reflect chronic inflammation induced by fluoropyrimidine even among patients with grade 1 diarrhea. Therefore, assessing symptoms, such as fever, sepsis, and cramping, are important for the management CID based on our endoscopic findings.

Recent studies have found that female sex, older age, and a normal body mass index were clinical factors predictive of fluoropyrimidine-induced diarrhea; however, none of them have been definitively established. The present study showed that the aforementioned factors were not predictive of complicated CID. On the other hand, those receiving oral fluoropyrimidine chemotherapy had higher risk for CID compared to those receiving infusional 5-FU chemotherapy. A meta-analysis including 26
Phase II and III trials on solid tumors revealed that S-1 had an OR of 2.52 (95% CI 1.80–3.52) for high-grade diarrhea for compared with infusional 5-FU, while another network meta-analysis showed that the toxicity profiles of stomatitis and diarrhea did not differ between S-1 and capecitabine. Genetics might also contribute to drug-specific toxic effects, with one study showing that dihydropyrimidine dehydrogenase (DPD) deficiency was associated with reduced clearance of fluoropyrimidines and prolonged exposure. However, the most common genetic mutations are absent among Asians, while DPD testing has not been routinely recommended. Indeed, the present study found that genetics did not appear to have an effect on the incidence of fluoropyrimidine-induced diarrhea.

Several limitations of the present study warrant consideration. First, CE had been performed after improvement of diarrhea. Thus, although mucosal injury had been noted in 83% of the patients who underwent CE, more patients might have shown abnormal endoscopic findings had the examination been performed during the acme phase of diarrhea. Second, the study included patients who received both combination chemotherapy and fluoropyrimidines alone. In addition, patients treated with irinotecan, which has been known to induce diarrhea, had been included. Third, most patients developed complicated CID after their first cycle of each chemotherapy regimen, whereas others developed the condition after a few cycles. We believe that later-onset diarrhea could have been associated with factors other than chemotherapy, such as infection, which had not been identified by the stool culture.

Conclusion
Although the incidence of complicated fluoropyrimidine-induced diarrhea was relatively low, most of the patients with the condition had small intestinal mucosal injury, some of whom developed fever or sepsis as complicating symptoms. Bacterial translocation secondary to small intestinal mucosal injury should therefore be considered in the management of complicated fluoropyrimidine-induced diarrhea.

List Of Abbreviations
CE: Capsule endoscopy
CEST: Capsule endoscopy structured terminology
CI: Confidence intervals
CID: Chemotherapy-induced diarrhea
CTCAE: Common Terminology Criteria for Adverse Events
DPD: Dihydropyrimidine dehydrogenase
OR: Odds ratios
US: United States

Declarations

Ethics approval and consent to participate
This retrospective study included a waiver of the need for written informed consent, which was approved by the Institutional Board Review (Toyama University Hospital Review Committee: 27-74).

Consent for publication
Not applicable.

Availability of data and materials
The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
TA and AH designed the study; MS, IM, HM, AU, SK, SN, HF, KO acquired data; MS wrote the paper; and TA, IY edited and revised the manuscript. All authors read and approved the manuscript.

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Tables

Table 1. Patient characteristics

|                               | Gastric cancer (n = 256) | Colorectal cancer (n = 280) |
|-------------------------------|--------------------------|-----------------------------|
| Sex                           |                          |                             |
| Male/female                   | 189/67                   | 168/112                     |
| Age                           |                          |                             |
| Median (range)                | 66 (22–87)               | 66 (11–86)                  |
| ECOG PS 0-1/≥2                | 204/52                   | 246/34                      |
| Stage                         |                          |                             |
| Advanced                      | 225 (88%)                | 208 (74%)                   |
| Postoperative recurrence      | 31 (12%)                 | 72 (26%)                    |
| Metastatic sites              |                          |                             |
| Lymph node                    | 184 (72%)                | 95 (34%)                    |
| Liver                         | 97 (38%)                 | 156 (56%)                   |
| Peritoneum                    | 101 (39%)                | 60 (21%)                    |
| Number of metastatic sites    | 0-1/≥2                   | 113/143                     |
|                               | 120/160                  |
| Fluoropyrimidine type         |                          |                             |
| 5-FU                          | 43 (17%)                 | 219 (72%)                   |
| S-1                           | 178 (70%)                | 4 (1%)                      |
| Capecitabine                  | 32 (12%)                 | 53 (19%)                    |
| Others                        | 3 (1%)                   | 4 (1%)                      |
| Molecular-targeted drugs      |                          |                             |
| Trastuzumab                   | 35                       | 0                           |
| Cetuximab/panitumumab         | 0                        | 25                          |
| Bevacizumab                   | 0                        | 116                         |
| Chemotherapy regimens         |                          |                             |
| Fluoropyrimidine alone        | 55                       | 22                          |
| Fluoropyrimidine + platinum   | 138                      | 227                         |
| Fluoropyrimidine + irinotecan | 0                        | 29                          |
| Fluoropyrimidine + taxane     | 24                       | 0                           |
| Fluoropyrimidine + platinum + taxane | 23 | 0 |
| Fluoropyrimidine + platinum + irinotecan | 0 | 1 |
| Fluoropyrimidine + others     | 13                       | 1                           |
| Others                        | 3 (1%)                   | 0                           |

ECOG PS, Eastern Cooperative Oncology Group performance status; 5-FU, 5-fluorouracil
Table 2. Characteristics of patients with complicated chemotherapy-induced diarrhea who underwent capsule endoscopy

| No. | Cancer | PS | Treatment | Cycle | Diarrhea grade | Complicating signs | Schedule time* | Redness | Erosion |
|-----|--------|----|-----------|-------|----------------|-------------------|---------------|---------|---------|
| 1   | Gastric | 1  | S-1       | 1     | 1              | Cramping          | 19            | +       | +       |
|     |        |    | Docetaxel |       |                |                   |               |         |         |
|     |        |    | Cisplatin |       |                |                   |               |         |         |
| 2   | Gastric | 1  | 5-FU      | 4     | 3              | Cramping          | 8             | +       | +       |
| 3   | Gastric | 2  | S-1       | 1     | 3              | Cramping, fever   | 11            | +       | +       |
|     |        |    | Oxaliplatin |      |                |                   |               |         |         |
| 4   | Gastric | 1  | S-1       | 1     | 2              | Cramping          | 2             | -       | -       |
|     |        |    | Oxaliplatin |      |                |                   |               |         |         |
| 5   | Gastric | 1  | S-1       | 1     | 1              | Oral mucositis    | 2             | +       | +       |
|     |        |    | Cisplatin |       |                |                   |               |         |         |
| 6   | Gastric | 1  | S-1       | 5     | 3              | -                 | 7             | +       | -       |
|     |        |    | Cisplatin |       |                |                   |               |         |         |
| 7   | Gastric | 1  | Capecitabine | 1   | 3              | Cramping, sepsis  | 9             | +       | -       |
| 8   | Gastric | 1  | Capecitabine | 1   | 2              | Cramping, sepsis  | 14            | +       | +       |
|     |        |    | Cisplatin |       |                |                   |               |         |         |
|     |        |    | Trastuzumab |      |                |                   |               |         |         |
| 9   | Gastric | 1  | S-1       | 8     | 1              | Camping           | 5             | -       | -       |
| 10  | Colon  | 2  | 5-FU      | 1     | 1              | Cramping, ileus   | 3             | +       | +       |
|     |        |    | Oxaliplatin |      |                |                   |               |         |         |
| 11  | Colon  | 1  | S-1       | 1     | 2              | Cramping, vomiting| 13            | +       | -       |
|     |        |    | Irinotecan |       |                |                   |               |         |         |
|     |        |    | Bevacizumab |     |                |                   |               |         |         |
| 12  | Colon  | 1  | Capecitabine | 1   | 3              | Cramping          | 21            | +       | +       |
|     |        |    | Oxaliplatin |      |                |                   |               |         |         |

PS, performance status; 5-FU, 5-fluorouracil.

*Number of days after the end of chemotherapy courses and capsule endoscopy

Table 3. Univariate and multivariate analyses of factors associated with complicated chemotherapy-induced diarrhea
| Factor                               | N   | Univariate analysis | Multivariate analysis |
|--------------------------------------|-----|---------------------|-----------------------|
|                                      |     | OR                  | 95% CI                | p         | OR                  | 95% CI                | p         |
| Cancer sites                         |     |                     |                       |           |                     |                       |           |
| Colorectum                           | 280 | 1.00                |                        |           | 1.38                | 0.55-3.47             | 0.48      |
| Stomach                              | 256 | 2.53                | 1.17-5.47             | 0.01      | 1.38                | 0.55-3.47             | 0.48      |
| Sex                                  |     |                     |                       |           |                     |                       |           |
| Male                                 | 357 | 1.00                |                        |           | 1.38                | 0.55-3.47             | 0.48      |
| Female                               | 179 | 1.39                | 0.67-2.88             | 0.37      | 1.38                | 0.55-3.47             | 0.48      |
| Age, years                           |     |                     |                       |           |                     |                       |           |
| <70                                  | 342 | 1.00                |                        |           | 1.38                | 0.55-3.47             | 0.48      |
| ≥70                                  | 194 | 1.26                | 0.58-2.72             | 0.54      | 1.38                | 0.55-3.47             | 0.48      |
| PS                                   |     |                     |                       |           |                     |                       |           |
| 0–1                                  | 450 | 1.00                |                        |           | 1.38                | 0.55-3.47             | 0.48      |
| ≥2                                   | 86  | 1.03                | 0.38-2.76             | 0.94      | 1.38                | 0.55-3.47             | 0.48      |
| Resection of primary sites           |     |                     |                       |           |                     |                       |           |
| Yes                                  | 104 | 1.00                |                        |           | 1.38                | 0.55-3.47             | 0.48      |
| No                                   | 432 | 2.42                | 0.72-8.11             | 0.15      | 1.38                | 0.55-3.47             | 0.48      |
| Peritoneal metastasis                |     |                     |                       |           |                     |                       |           |
| No                                   | 375 | 1.00                |                        |           | 1.38                | 0.55-3.47             | 0.48      |
| Yes                                  | 161 | 1.42                | 0.68-2.99             | 0.34      | 1.38                | 0.55-3.47             | 0.48      |
| Number of metastatic sites           |     |                     |                       |           |                     |                       |           |
| 0–1                                  | 337 | 1.00                |                        |           | 1.38                | 0.55-3.47             | 0.48      |
| ≥2                                   | 199 | 1.75                | 0.85-3.59             | 0.12      | 1.38                | 0.55-3.47             | 0.48      |
| Fluoropyrimidine type                |     |                     |                       |           |                     |                       |           |
| 5-FU                                 | 260 | 1.00                |                        |           | 2.95                | 1.06-8.19             | 0.03      |
| S-1 or capecitabine                  | 276 | 3.59                | 1.52-8.47             | 0.003     | 2.95                | 1.06-8.19             | 0.03      |
| Chemotherapy regimens                |     |                     |                       |           |                     |                       |           |
| Fluoropyrimidine alone               | 69  | 1.00                |                        |           | 2.95                | 1.06-8.19             | 0.03      |
| Combination chemotherapy             | 467 | 0.78                | 0.29-2.11             | 0.63      | 2.95                | 1.06-8.19             | 0.03      |

OR, odds ratio; CI, confidence interval; PS, performance status; 5-FU, 5-fluorouracil

Figures
536 received chemotherapy containing fluoropyrimidine
  (Gastric cancer (GC):256, colorectal cancer (CRC):280)

503 did not developed complicated diarrhea (GC:233, CRC:270)

32 developed complicated diarrhea (GC:22, CRC:10)
  Diarrhea grade 1  7 (22%)
                 2  12 (38%)
                 3  12 (38%)
                 4  1  (3%)

24 developed complicating signs (GC:18, CRC:6)
  Cramping        15 (63%)
  Vomiting        8 (33%)
  Sepsis          2  (8%)
  Ileus           1  (4%)
  others          11 (46%)

20 did not received capsule endoscopy(GC:13, CRC:7)

12 received capsule endoscopy (GC:9, CRC:3)

Figure 1

Flow diagram of data collection and analysis. GC gastric cancer, CRC colorectal cancer.
Figure 2

Cumulative incidence of complicated chemotherapy-induced diarrhea (CID). Most patients showed CID within a month after administration of chemotherapy.
Figure 3

Representative capsule endoscopy images of small intestinal mucosal injuries. Redness is a reddened fold (left), erosion is a white spot surrounded by a halo (middle), and ulcer is a depression with a white coating (right).