

Treatment status

Completion rate of protocol treatment was 76.5% in the S-1 group and 73.4% in the UFT/LV group (Table 2). Discontinuation of protocol treatment was most common during course 1 and then decreased with courses. Among the 377 patients with discontinuation of the protocol treatments, 138 (77.5% of 178 discontinuation cases) in the S-1 group and 133 (66.8% of 199 discontinuation cases) in the UFT/LV group did within the first two courses (Table 2). Treatment discontinuation because of AEs was observed in 132 patients in the S-1 group and in 134 in the UFT/LV group. Among these patients, treatment was discontinued in 54 patients by the AEs listed in the discontinuation criteria of the protocol, in 34 by physician's decision for other than protocol criteria, and in 44 by patient's refusal related to AEs of the S-1 group, and in 67, 34, 41 of the UFT/LV group, respectively.

As for drug compliance, more than 90% of patients in both groups were reported to take '≥90%' of prescribed dose for each course (Figure 2). The mean of relative dose intensity, including discontinuation cases, was 76.5% in the S-1 group and 76.0% in the UFT/LV group; the median was 95% in both groups.

Safety profile

A total of 605 patients (80.8%) in the S-1 group and 551 (73.7%) in the UFT/LV group experienced AEs (any grades). In all, 121

patients (16.0%) in the S-1 group and 108 (14.4%) in the UFT/LV group experienced ≥grade 3 AEs. The incidences of AEs pre-specified as 'priority survey items' are shown in Table 3. The common AEs in any grades were anorexia, diarrhoea, fatigue, anaemia, and hyperbilirubinemia. Stomatitis, anorexia, rash/desquamation, hyperpigmentation, leukopenia, anaemia, and thrombocytopenia were more frequent in the S-1 group. Increased ALT and AST levels were more frequent in the UFT/LV group.

In the UFT/LV group, 5 patients (0.7%) experienced grade 4 increased ALT levels, and 3 (0.4%) had grade 4 increased AST levels (some overlap). One patient in the S-1 group had grade 4 increased AST level. All these events occurred during course 1.

Table 3 Incidence of AEs for entire treatment period (worst grade)

Events	S-1 n = 756				UFT/LV n = 748			
	Any grades		≥ Grade 3		Any grades		≥ Grade 3	
	n	(%)	n	(%)	n	(%)	n	(%)
Clinical findings								
Stomatitis	146	(19.3)	9	(1.2)	103	(13.8)	3	(0.4)
Anorexia	242	(32.0)	37	(4.9)	187	(25.0)	26	(3.5)
Nausea	166	(22.0)	12	(1.6)	142	(19.0)	9	(1.2)
Vomiting	48	(6.3)	6	(0.8)	58	(7.8)	6	(0.8)
Diarrhoea	177	(23.4)	33	(4.4)	178	(23.8)	41	(5.5)
Rash/Desquamation	114	(15.1)	2	(0.3)	75	(10.0)	4	(0.5)
Hyperpigmentation	201	(26.6)	—	—	95	(12.7)	—	—
Fatigue	208	(27.5)	18	(2.4)	186	(24.9)	11	(1.5)
Laboratory findings								
Leukocytes	136	(18.0)	5	(0.7)	93	(12.4)	3	(0.4)
Haemoglobin	246	(32.5)	7	(0.9)	199	(26.6)	1	(0.1)
Platelets	96	(12.7)	1	(0.1)	55	(7.4)	3	(0.4)
Total bilirubin	195	(25.8)	9	(1.2)	173	(23.1)	11	(1.5)
AST	114	(15.1)	6	(0.8)	152	(20.3)	16	(2.1)
ALT	100	(13.2)	8	(1.1)	160	(21.4)	25	(3.3)
Creatinine	36	(4.8)	0	(0)	34	(4.5)	4	(0.5)

Abbreviations: AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LV = leucovorin.

Table 2 Discontinuation and completion of protocol treatment

	S-1		UFT/LV	
	n = 756	(%)	n = 748	(%)
No. of patients completed the protocol treatment	578	(76.5)	549	(73.4)
No. of patients with discontinuation	178	(23.5)	199	(26.6)
During course 1	86	(11.4)	78	(10.4)
During course 2	52	(6.9)	55	(7.4)
During course 3	37	(4.9)	34	(4.5)
During course 4	3	(0.4)	27	(3.6)
During course 5	—	—	5	(0.7)

Abbreviation: LV = leucovorin.

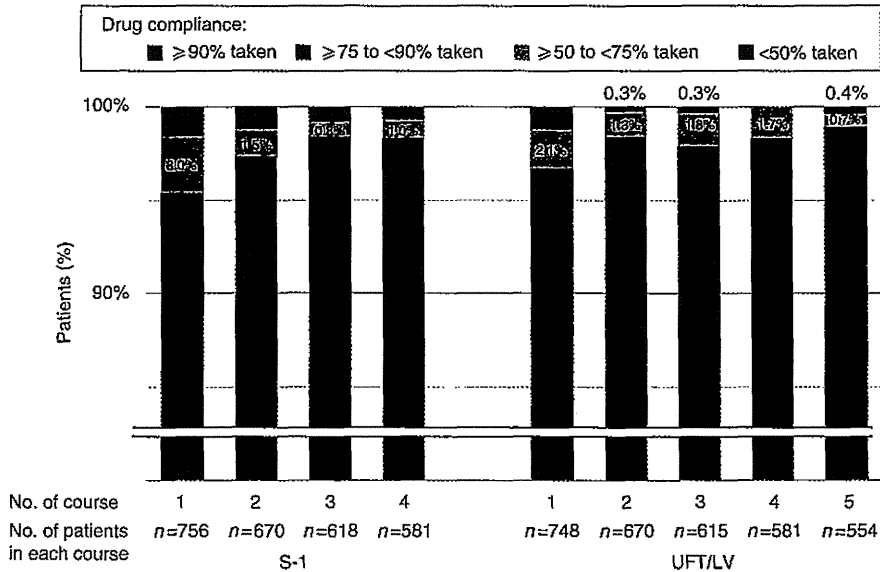


Figure 2 Drug compliance in each course. Each shaded region represents the percentage of patients receiving the indicated proportion of the scheduled dose per protocol in a given course. Abbreviation: LV = leucovorin.

Grade 4 haematological toxicities were as follows: anaemia in one patient, leukocytopenia in two, neutropenia in one in the S-1 group (some overlap), and anaemia in one patient in the UFT/LV group. Grade 3 neutropenia was developed in 10 patients (1.3%) in the S-1 group and 2 (0.3%) in the UFT/LV group.

The other common AEs in any grades were taste alteration (4.0% in the S-1 group and 3.2% in the UFT/LV group) and eye-related symptoms, including tearing, keratitis, and conjunctivitis (3.8% in the S-1 group and 0.4% in the UFT/LV group).

There were two deaths in the UFT/LV group, which was not ruled out to be related to the protocol treatment. One patient had diarrhoea leading to dehydration, metabolic acidosis, and acute respiratory distress syndrome during the first course. In the other patient, aspiration pneumonia associated with postoperative bowel obstruction, which developed during course 5, lead to respiratory failure.

DISCUSSION

This paper reported the results of an interim analysis of safety data obtained from the phase III study of 1504 patients with stage III colon cancer, who received postoperative adjuvant chemotherapy with UFT/LV or S-1.

The overall incidence of AEs (any grades) was 80.0% in the S-1 group and 73.7% in the UFT/LV group, and that of \geq grade 3 AEs were 16.0% and 14.4%, respectively. In short, about 80% of AEs were mild or moderate AEs such as grade 1 to 2. The completion rate of protocol treatment was favourable (76.5% in the S-1 group and 73.4% in the UFT/LV group), and treatment was discontinued in some patients during the early courses in both groups. Careful watch in early courses, adequate supportive care, and temporary suspension is important to complete the adjuvant chemotherapy with UFT/LV or S-1.

The present study is the first large trial of adjuvant chemotherapy with S-1 in patients with CRC. As compared, AEs of the S-1 group in this study with those of the ACTS-GC trial in which 1-year S-1 was used for adjuvant chemotherapy in GC (Sakuramoto *et al*, 2007), AE profiles in both trials were similar; the common AEs were anaemia, anorexia, diarrhoea, fatigue, and hyperpigmentation. However, the overall incidence of AEs was higher in the ACTS-GC trial. It may be because of the longer

treatment duration of S-1 in the ACTS-GC trial. The proportion of patients who were in treatment at 6 months was similar: 77.9% in the ACTS-GC trial and 76.5% in this study.

On the other hand, potential racial differences of the tolerability for fluoropyrimidines had been reported (Haller *et al*, 2008). When the pharmacokinetics and pharmacodynamics of S-1 were compared between Caucasian and East Asian patients with solid malignancy including CRC, grade 3–4 gastrointestinal toxicities were more common in Caucasians than Asians, although exposure to 5-FU concentration was similar in both groups (Chuah *et al*, 2011).

In the NSABP C-06 trial (Lembersky *et al*, 2006), which was conducted in the United States, AEs in 774 patients who received UFT/LV was observed in 93.5% (\geq grade 3, in 38.2%). Gastrointestinal toxicity (i.e., diarrhoea, nausea, and vomiting) was considerably less developed in this study, whereas the incidence of haematological toxicity was similar in both studies (Table 4). The difference of AE profiles between Japan and the United States of the bridging study of UFT/LV for unresectable CRC showed similar tendency (Shirao *et al*, 2004).

The UFT/LV treatment sometimes causes liver dysfunction (i.e., increased AST, ALT levels, and hyperbilirubinemia). In this study, five patients (0.7%) in the UFT/LV group had grade 4 liver dysfunction; all cases developed during course 1. The survey performed by the pharmaceutical company reported the similar observations of liver dysfunction caused by UFT, with the highest incidence within 2 months after start of treatment. Therefore, patients treated with UFT/LV are better to be watched carefully about liver dysfunction, and liver function is recommended to be regularly evaluated in early period in treatment.

Because of the different mechanisms of action between S-1 and UFT/LV, AE profiles were expected to differ between two groups. The common AEs were stomatitis, anorexia, rash/desquamation, hyperpigmentation, leukopenia, anaemia, and thrombocytopenia in the S-1 group, and increased ALT and AST levels in the UFT/LV group. Derivatives of 5-FU have been reported to cause keratoconjunctival epithelial disorders due to impaired DNA synthesis, which lead to secondary tear-duct occlusion accompanied by lacrimation (Hassan *et al*, 1998). This study disclosed that the incidence of eye-related symptoms differs between S-1 and UFT/LV. This study is designed to investigate mRNA expression levels and DNA copy numbers of 5-FU-related enzymes, and to clarify relationship between AEs profiles and the results

Table 4 Reported incidence of AEs with other regimens

Events	Lembersky <i>et al</i> (2006)				Twelves <i>et al</i> (2005)		André <i>et al</i> (2004)	
	UFT/LV (n = 774)		i.v. 5-FU/LV ^a (n = 759)		Capecitabine (n = 995)		FOLFOX4 (n = 1108)	
	Any grades (%)	\geq Grade 3 (%)	Any grades (%)	\geq Grade 3 (%)	Any grades (%)	\geq Grade 3 (%)	Any grades (%)	\geq Grade 3 (%)
Clinical findings								
Stomatitis	26	1.3	24	0.5	22	2	42	3
Nausea	54	7	65	7	36	3	74	5
Vomiting	28	4	31	7			47	6
Diarrhoea	75	29	79	29	46	11	56	11
Skin disorders	22 ^b	1.3 ^b	20 ^b	1.1 ^b	—	—	32 ^b	2 ^b
HFS	—	0.7	—	0.2	60	17	—	—
Paraesthesia	—	—	—	—	—	—	92	12
Laboratory findings								
Leukocytes	17	0	22	0.7	<10	—	—	—
Granulocytes	20	1.3	27	1.3	32	2	79	41
Haemoglobin	—	—	—	—	<10	—	76	0.8
Platelets	—	—	—	—	<10	—	77	1.7
Total bilirubin	7	0.3	4	—	50	20	—	—

Abbreviations: AEs = adverse events; FOLFOX = 5-FU/LV plus oxaliplatin; HFS = hand–foot syndrome; i.v. = intravenous; LV = leucovorin. ^aTreatment schedule reported from the Roswell Park Memorial Institute. ^bIncluding HFS.

of molecular study. When final results will be open, causes of different profiles of AEs will be disclosed.

The profiles and severity of AEs in this study were not worse than the reported AEs with other regimens of adjuvant chemotherapy (Table 4), and were acceptable. Hand-foot syndrome (HFS) was more common in capecitabine (Twelves *et al*, 2005), whereas \geq grade 3 HFS in this study was 1.3% in the S-1 group and 0.9% in the UFT/LV group. Haematological toxicities were more common in the regimens containing oxaliplatin (André *et al*, 2004). As mentioned above, gastrointestinal toxicities were fewer in this study, possibly because of racial differences.

In conclusion, the present analysis showed that the AE profiles differed between UFT/LV and S-1, whereas the incidence of \geq grade 3 AEs was low in both groups. The high completion rate of the protocol treatment with good drug compliance may indicate both regimens are acceptable treatment as adjuvant chemotherapy for CRC.

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STUDY PROTOCOL

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Study protocol of the SACURA trial: a randomized phase III trial of efficacy and safety of UFT as adjuvant chemotherapy for stage II colon cancer

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Abstract

Background: Adjuvant chemotherapy for stage III colon cancer is internationally accepted as standard treatment with established efficacy, but the usefulness of adjuvant chemotherapy for stage II colon cancer remains controversial. The major Western guidelines recommend adjuvant chemotherapy for "high-risk stage II" cancer, but this is not clearly defined and the efficacy has not been confirmed.

Methods/design: SACURA trial is a multicenter randomized phase III study which aims to evaluate the superiority of 1-year adjuvant treatment with UFT to observation without any adjuvant treatment after surgery for stage II colon cancer in a large population, and to identify "high-risk factors of recurrence/death" in stage II colon cancer and predictors of efficacy and adverse events of the chemotherapy. Patients aged between 20 and 80 years with curatively resected stage II colon cancer are randomly assigned to a observation group or UFT adjuvant therapy group (UFT at 500–600 mg/day as tegafur in 2 divided doses after meals for 5 days, followed by 2-day rest. This 1-week treatment cycle is repeated for 1 year). The patients are followed up for 5 years until recurrence or death. Treatment delivery and adverse events are entered into a web-based case report form system every 3 months. The target sample size is 2,000 patients. The primary endpoint is disease-free survival, and the secondary endpoints are overall survival, recurrence-free survival, and incidence and severity of adverse events. In an additional translational study, the mRNA expression of 5-FU-related enzymes, microsatellite instability and chromosomal instability, and histopathological factors including tumor budding are assessed to evaluate correlation with recurrences, survivals and adverse events.

Discussion: A total of 2,024 patients were enrolled from October 2006 to July 2010. The results of this study will provide important information that help to improve the therapeutic strategy for stage II colon cancer.

Trial registration: ClinicalTrials.gov NCT00392899.

Keywords: Colon cancer, Stage II, Adjuvant chemotherapy, UFT, Risk factor, Predictive factor, Prognostic factor, Surgery-alone, Randomized controlled trial, Japan

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Background

In Japan, colorectal cancer is the second most common cancer following stomach cancer, and the third most fatal cancer following lung cancer and stomach cancer [1]. Postoperative adjuvant chemotherapy has been demonstrated to improve the outcome in stage III colon cancer and is internationally accepted as standard treatment. On the other hand, no consensus has been reached on the usefulness of adjuvant chemotherapy for stage II colon cancer.

A meta-analysis using the studies C-01 to C-04 of the National Surgical Adjuvant Breast & Bowel Project (NSABP) [2] showed that adjuvant chemotherapy significantly decreased the risk of recurrence/death in both Dukes' B and C. However, other pooled analysis or large population database review revealed no statistically significant additive survival benefit of adjuvant therapy including 5-FU + leucovorin exclusively in stage II colon cancer [3,4].

In Japan, Sakamoto et al. [5] reported the results of the meta-analysis that adjuvant therapy with oral 5-FU drugs (without concomitant use of leucovorin) contributed to significant improvement in recurrence-free survival (RFS) and overall survival (OS) in stage II colon cancer. UFT (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is one of the most widely used oral 5-FU agent as adjuvant chemotherapy for colorectal cancer in Japan. UFT is a combination drug of tegafur and uracil at a molar ratio of 1:4 and is characterized by long maintenance of a high 5-FU concentration level converted from tegafur in blood/tumors due to inhibition of degeneration of 5-FU by uracil. In the randomized controlled trial (RCT) comparing 2-year adjuvant therapy using UFT (400 mg/body) with observation without adjuvant therapy in 289 patients after surgery for stage II/III colon and rectal cancer [6], the 5-year RFS was significantly better in the UFT group. However, the analysis exclusively for colon cancer (160 patients) revealed no significant difference (77.4% in the UFT group, 74.0% in the observation group, $p=0.71$). In the RCT comparing 1-year adjuvant therapy using UFT (400 mg/m²/day) with observation without adjuvant therapy in 610 patients after surgery for stage III colon and rectal cancer [7], 1-year treatment with UFT was well tolerated and significantly improved the RFS and OS in rectal cancer, while the analysis for 332 patients with colon cancer showed no significant difference in both the 5-year RFS (71.3% in the UFT group, 69.6% in the observation group, $p=0.56$) and OS.

Although both of the abovementioned two RCTs [6,7] failed to demonstrate an additive effect, 1- or 2-year postoperative adjuvant therapy with UFT alone has often been used for stage II colon cancer in clinical practice in Japan, because of its good feasibility [8]

and low-cost. The Japanese Study Group for Post-operative Follow-up of Colorectal Cancer reported that the 5-year survival rate of 1,262 patients with stage II colon cancer who underwent surgery between 1977 and 2000 was 82.1% [9]. Given such a good outcome, it is necessary to clarify in a larger population whether postoperative adjuvant treatment with UFT alone has an additive effect on stage II colon cancer compared with observation only.

On the other hand, the reports using a large-scale database disclosed that stage II colon cancer included subpopulations with different prognosis [9,10]. The major Western guidelines recommended to select the "high-risk group of recurrence" in stage II colon cancer and to give postoperative adjuvant chemotherapy. The NCCN guidelines of 2012 [11] lists T4 lesions, number of lymph-nodes examined <12, perforation, lymphovascular involvement, poorly differentiated histopathology, and perineural invasion as high-risk factors, while the ASCO guidelines of 2004 [12] lists inadequately sampled nodes, T4 lesions, perforation, and poorly differentiated histology as factors for considering for adjuvant chemotherapy in stage II colon cancer. In addition to these, high CEA is listed as high-risk factor in the ESMO guidelines [13]. Recently, the biomarker studies have proposed new risk factors for recurrence/prognosis.

It seems appropriate to use adjuvant chemotherapy for a subgroup with poor prognosis in stage II colon cancer. However, the definition of "high-risk stage II" is not clear yet, and the efficacy of adjuvant chemotherapy for those patients has not been demonstrated. We therefore conducted the SACURA trial (Surgical Adjuvant Chemotherapy with UFT for Curatively Resected Stage II Colon Cancer), a multicenter phase III RCT to verify the efficacy of adjuvant chemotherapy for curatively resected stage II colon cancer in a large population through evaluating the superiority of 1-year adjuvant treatment with UFT to observation without any adjuvant treatment, and to identify "high-risk factors of recurrence" in stage II colon cancer and predictors of efficacy and adverse events (AEs) of the chemotherapy.

Methods/design

The design of study

This study is a multicenter randomized phase III trial, in which patients with curatively resected stage II colon cancer are randomly assigned to either the observation group or UFT adjuvant therapy group (Figure 1). The primary endpoint is disease-free survival (DFS), and the secondary endpoints are OS, RFS, and incidence and severity of AEs. Superiority of adjuvant therapy with UFT compared to observation without any adjuvant therapy

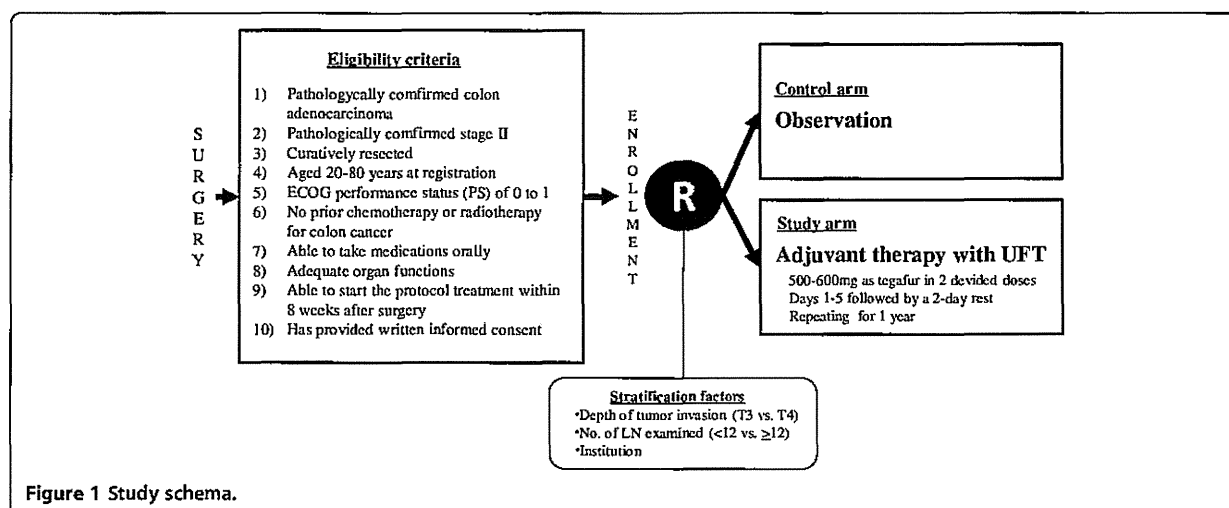


Figure 1 Study schema.

is evaluated. As an additional translational study, the surgical specimens are collected for histopathological and biomolecular assessments.

Enrollment and allocation

Eligible patients are enrolled at the Translational Research Informatics Center using a web-based system. Patients are randomly assigned, in a 1:1 ratio, to either an observation group or UFT adjuvant therapy group, using minimization by introducing a random element with a 0.8 assignment probability [14], balanced on the following stratification factors: depth of tumor invasion (T3 vs. T4), number of lymph-nodes examined (<12 vs. ≥12) and institution (Figure 1). Treatment assignment is not masked from the investigators and patients.

The main eligibility criteria are as follows:

Inclusion criteria

- 1) Histologically confirmed stage II colon cancer
- 2) Histologically confirmed adenocarcinoma
- 3) Has undergone curative surgery
- 4) Age: 20–80 years
- 5) ECOG performance status: 0–1
- 6) No prior chemotherapy or radiotherapy for colon cancer
- 7) Able to take medications orally
- 8) Adequate organ functions as listed below (at ≤14 days prior to enrollment)
 - i) Leukocytes: 3,500/mm³ to 12,000/mm³
 - ii) Neutrophil: ≥ 1,500/mm³
 - iii) Hemoglobin ≥ 9.0 g/dL
 - iv) Platelet count ≥ 100,000/mm³
 - v) Total bilirubin ≤ 2.0 mg/dL
 - vi) Aspartate aminotransferase (AST), alanine aminotransferase (ALT): ≤ 100 IU/L
 - vii) Creatinine: ≤1.5 mg/dL

- 9) Able to start the protocol treatment within 8 weeks after surgery
- 10) Has provided written informed consent

Exclusion criteria

- 1) Other active malignancies (i.e. diagnosed within 5 years) (Tis colorectal cancers are allowed to enroll)
- 2) Hereditary colorectal cancer
- 3) Severe comorbidities:
 - i) Severe postoperative complication
 - ii) Uncontrollable diabetes mellitus
 - iii) Uncontrollable hypertension
 - iv) Myocardial infarction within 6 months
 - v) Unstable angina pectoris
 - vi) Cirrhosis or liver failure
 - vii) Interstitial pneumonia, pulmonary fibrosis, or severe emphysema
 - viii) Psychiatric disorder
- 4) Concern about pregnancy
- 5) The investigator considers the patient not suitable for the study

Protocol treatment

Assigned treatment is started within 8 weeks after surgery.

Observation group

Patients are followed-up without adjuvant treatment, according to the schedule defined in the study protocol for 5 years until recurrence, other malignancy or death is confirmed (Figure 2).

UFT adjuvant therapy group

UFT is given at a dose of 500–600 mg/day as tegafur in 2 divided doses after meals for 5 days, followed by a

2-day rest [8]. This one-week cycle is repeated for one year. During protocol treatment, clinical findings and laboratory values are evaluated every month.

Protocol treatment is started and continued when the patients fulfill the following criteria: leukocytes $\geq 3,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, AST and ALT $\leq 100 \text{ IU/L}$, total bilirubin $\leq 2.0 \text{ mg/dL}$, no greater than grade 2 anorexia, nausea, vomiting, or diarrhea. If the criteria for starting/continuing treatment are not met, treatment is postponed or temporarily suspended until AEs improve to meet the criteria. And then, treatment is resumed at one dose level lower (-200 mg). The dose can be reduced if the physician judges that dose reduction is necessary. Once the dose has been reduced, it is not to be subsequently re-increased.

Protocol treatment is discontinued in the cases as follows: treatment fails to be resumed within 29 days after being postponed or temporarily suspended (the planned drug rest is not included), the physician judges that the protocol treatment is difficult to continue due to AEs, recurrence or other malignancies develop, the patient requests discontinuation of protocol treatment, and the patients withdraw informed consent.

After the completion of protocol treatment, patients are followed-up following the same schedule as for the observation group (Figure 2) until recurrence, other malignancy or death is confirmed.

Evaluation of treatment delivery and adverse events

Treatment delivery (UFT adjuvant therapy group only)

Physicians report the treatment delivery via a web-based case report system, including the followings: daily dose, drug compliance*, temporary suspension (+/-), number of days of suspension, reason for suspension, dose reduction (+/-), etc.

* The drug compliance for each 3 months period is defined as the ratio of the dose actually taken to the prescribed dose, and is classified to the following 4 categories: 1) $\geq 90\%$ taken, 2) $\geq 75\%$ to $<90\%$ taken, 3) $\geq 50\%$ to $<75\%$ taken, and 4) $<50\%$ taken.

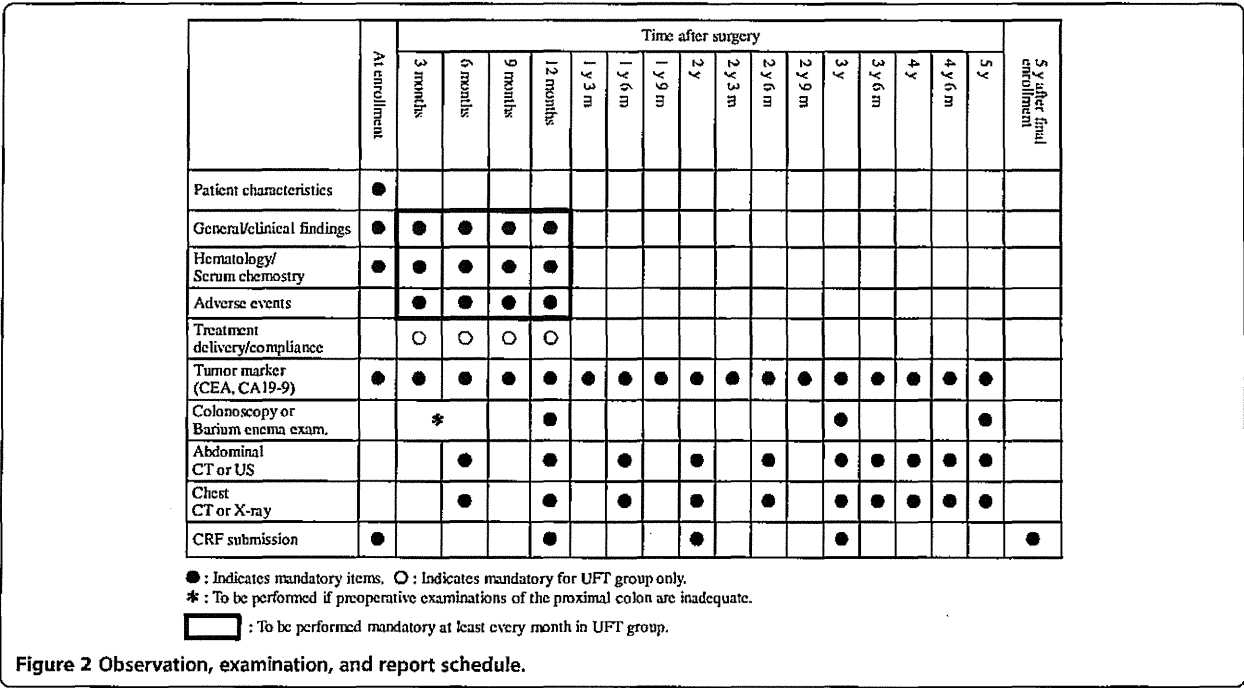
Safety profile (both groups)

The types and severities of AEs from the start of protocol treatment to 30 days after the last administration are evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The most severe grade of each AE is reported every 3 months. The following AEs are required to be reported as "priority survey items": leukocytes, hemoglobin, platelets, total bilirubin, AST, ALT, stomatitis, anorexia, nausea, vomiting, diarrhea, rash/desquamation, hyperpigmentation, and fatigue.

Statistical background

Definition of endpoint

The primary endpoint of this study is DFS, and the secondary endpoints are OS, RFS, and incidence and



severity of AEs. DFS is defined as the time to recurrence, other malignancies or death, whichever comes first. Patients alive and free of recurrence or other malignancies are censored at time of last follow-up. RFS is defined as the time to recurrence or death. Patients alive and free of recurrence are censored at time of last follow-up. The intervals are calculated from the date of enrollment.

Definition of target sample size

In two clinical studies conducted in Japanese patients with colon cancer in the 1990's, the 5-year DFS rate in patients without adjuvant chemotherapy was 74.3% (Dukes' B) [15] and 74.0% (Dukes' B and C) [6]. Given a recent improved surgical outcome, it was assumed that the 5-year DFS rate would be 80% in the control group (observation group). With an expected 5-year DFS rate of 85% (hazard ratio: 0.729) in the study treatment group (UFT adjuvant therapy group), a two-sided significance level of 5%, and a power of 90%, the necessary sample size was calculated to be 970 patients per group according to the method described by Schoenfeld et al. [16]. A target sample size of 1,000 patients per group (a total of 2,000 patients in two groups) was determined in consideration of a 3% excluded rate.

Analysis plan

The primary analyses are done on an intent-to-treat basis. The survival curves (DFS, OS, and RFS) are estimated by the Kaplan-Meier method, and the stratified log-rank test, stratified by the depth of tumor invasion and the number of lymph-nodes examined, are used to test the null hypothesis that the respective curves are equal between the two groups. The hazard ratio is

estimated using a stratified proportional hazard model. A two-sided significance level of 5% is used. Subgroup analyses are performed according to sex, age, depth of tumor invasion, and number of lymph-nodes examined for comparison between the two groups.

The treatment delivery in the UFT adjuvant therapy group is summarized. The incidence of AEs between two groups is compared with the Fisher's exact test.

An interim analysis of the efficacy is planned at 3 years after enrollment of the last patient. For the primary endpoint (DFS), the significant levels in interim and final analyses are determined according to α spending function (the O'Brien-Fleming type) to keep the overall type I error at 5%.

Additional translational study

The assessments shown in Figure 3 are made in paraffin-embedded thin sections of surgical specimens from primary tumors to evaluate the correlation with recurrences, survivals and AEs. The details of methods and analytical procedures will be reported separately.

Ethical matters

This study is conducted in accordance with the "Declaration of Helsinki" and "Ethical Guidelines for Clinical Research," and has been approved by the Institutional Review Boards of each participating institute. Written informed consent is obtained from all patients before enrollment.

Discussion

This study is conducted to prospectively evaluate adjuvant chemotherapy for stage II colon cancer in terms of the efficacy, safety and feasibility in a large population.

- 1) Analysis of mRNA expression of enzymes related to nucleic acid metabolism, folic acid metabolism, and tumor progression
 - TS (thymidylate synthase)
 - DPD (dihydropyrimidine dehydrogenase)
 - TP (thymidine phosphorylase)
 - OPRT (otate phosphoribosyl transferase)
 - FPGS (folylpolyglutamate synthetase)
 - VEGF (vascular endothelial growth factor)
 - COX-2 (cyclooxygenase-2)
- 2) Analysis of microsatellite instability (MSI) and chromosomal instability (i.e., 18qLOH)
- 3) Evaluation of histopathological factors in HE-stained specimens
 - tumor budding
 - extent of the poorly differentiated component
 - Crohn's-like lymphoid reaction
 - fibrotic cancer stroma etc.

Figure 3 Items included in additional translational study.

According to the Japanese "Guidelines for the Treatment of Colorectal Cancer" [17] published by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), adjuvant chemotherapy is recommended for stage III colorectal cancer. However, in line with the major Western guidelines [11-13], the JSCCR guidelines states that adjuvant chemotherapy for stage II colon cancer is considered for patients with a "high-risk factor of recurrence" after adequate informed consent, although the efficacy of adjuvant chemotherapy for stage II colon cancer is not clearly demonstrated and "high-risk stage II" is not clearly defined. No definite conclusion has been reached on this clinically important issue, probably for the following reasons: 1) large number of patients would be required to evaluate the efficacy of adjuvant chemotherapy for stage II colon cancer because of good surgical outcome; and 2) no high-quality RCT for stage II colon cancer alone has been conducted.

The SACURA trial is a RCT in patients with curatively resected stage II colon cancer, evaluating whether 1-year adjuvant treatment with UFT improves the DFS and OS compared with observation without adjuvant treatment (superiority study). Between October 2006 and July 2010, a total of 2,024 patients were enrolled from the 270 institutes. In Japan, complete mesocolic excision with central vascular ligation (D3 dissection) [17-19] is the standard surgery for colon cancer. The institutions which met the conditions that the member of the JSCCR, more than 80 colorectal cancer surgery each year and D3 dissection as routine surgery were selected for the study to insure the quality of the study.

In the present study, the observation group is used to investigate the clinicopathological high-risk factors for recurrence, and the UFT adjuvant therapy group is used to evaluate the effect of adjuvant therapy on the patients with those "high-risk factors". These assessments will provide useful information to determine the indication of adjuvant therapy for patients with stage II colon cancer.

New reliable risk factors of recurrence other than routine items in histopathological examination are expected. The present study evaluates the following histopathological markers as promising prognostic factors for stage II colorectal cancer: tumor budding [20], extent of the poorly differentiated component [21], Crohn's-like lymphoid reaction [22], and fibrotic cancer stroma [23]. This is the first study to evaluate those new possible prognostic histopathological markers prospectively using a large sample size.

In recent years, risk classification for recurrence/prognosis and prediction of efficacy to chemotherapy based on the biomolecular profiles are intensively studied. The meta-analysis reported that MSI-high stage II colorectal

cancer was characterized by a lower recurrence rate and better prognosis, compared with MSI-low and microsatellite-stable stage II colorectal cancer [24]. On the other hand, the pooled analysis disclosed that adjuvant chemotherapy with 5-FU drugs for MSI-high colorectal cancer resulted in poorer OS than those of patients without the chemotherapy [25], indicating that MSI may be interesting as a predictor of efficacy to 5-FU based chemotherapy. Deletion or loss of heterozygosity (LOH) of the long arm of chromosome 18 (18q) is considered as an indicator of chromosomal instability [26,27], which can be related to carcinogenesis and tumor progression. In the PETACC-3 molecular study [28], both the univariate and multivariate analyses in 420 patients without adjuvant chemotherapy after surgery for stage II colon cancer revealed that 18qLOH was a significant factor for poor prognosis and that MSI-high was a significant factor for good prognosis. In the present study, MSI and 18qLOH are evaluated in more patients collected prospectively than those in the PETACC-3 study.

The efficacy and AEs of 5-FU drugs may be related to 5-FU-related enzymes in blood or tumor [29,30]. In Japan, several oral 5-FU drugs with differing mechanisms of action have been frequently used, but few prospective studies with a large sample size about this issue have been conducted. In the present study, the tumor mRNA expression levels of enzymes related to nucleic acid metabolism, folic acid metabolism, and tumor progression are measured to evaluate the correlation with the prognosis and AEs to identify predictors of efficacy and safety. In the future, it is expected that oral 5-FU drugs can be used in personalized ways based on differences in the appearance of these enzymes.

In conclusion, the SACURA trial is a large, multicenter phase III RCT intended to demonstrate the efficacy and safety of postoperative adjuvant therapy in patients with stage II colon cancer by showing the superiority of 1-year adjuvant treatment with UFT to observation without any adjuvant treatment. The results will identify 1) "high-risk stage II" colon cancer, 2) predictors of efficacy and AEs of adjuvant chemotherapy with 5-FU drugs and 3) subgroup benefited from adjuvant chemotherapy, and will contribute to establish an improved therapeutic strategy for stage II colon cancer.

Abbreviations

AEs: Adverse events; MSI: Microsatellite instability; OS: Overall survival; RCTs: Randomized controlled trials; RFS: Recurrence-free survival; DFS: Disease-free survival; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; JSCCR: Japanese Society for Cancer of the Colon and Rectum; LOH: Loss of heterozygosity.

Competing interest

SACURA trial (BRI_CC0501, BRI_CC0502) was conducted by "Foundation for Biomedical Research and Innovation, Translational Research Informatics Center" with funding from Taiho Pharmaceutical Co. Ltd., Japan.

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SM has no competing interest.
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Authors' contributions

MI, as a task manager, participated in entire coordinating of the study, data collection, data analysis, data interpretation, and writing of the manuscript. HM, NT, YS, KT, KK, MW, YK, and KS, as a steering committee, participated in all phases of this study, including design and writing of the protocol, data collection, data analysis, data interpretation, and preparation of the manuscript. H. Ueno, TI, and H. Uetake, as a steering committee for additional translational study, carried out the molecular and pathological evaluation, and participated in all phases of this study, including design and writing of the protocol, data collection, data analysis, data interpretation and preparation of the manuscript. SM and ST, as a chief of statistical analysis, participated in statistical setting of study design and data analysis. All authors reviewed and approved the final manuscript.

Authors' information

No relevant information.

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Trastuzumab for a Patient With Heavily Pretreated Gastric Cancer Plus Massive Ascites and Ovarian Metastasis

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CASE REPORT

A 42-year-old female with a chief complaint of anorexia and abdominal fullness was diagnosed with gastric cancer and referred to our hospital in September 2008. Her oral intake was decreased to one-third of her normal intake. She was the mother of three children and had no significant past medical history. On physical examination, her abdomen was distended with fluid. Her ECOG performance status was 2. Gastroduodenoscopy revealed diffuse infiltration of gastric cancer with the appearance of linitis plastica. Pathological examination showed poorly differentiated adenocarcinoma (Figure 1A) with a signet-ring-cell carcinoma component. Computed tomography (CT) scan revealed massive ascites, thickened gastric wall, and bilateral ovarian metastases.

Beginning in October 2008, chemotherapy with weekly 5-fluorouracil, and methotrexate was administered as first-line chemotherapy. After three chemotherapy cycles, her abdominal distension and oral intake improved. Although the same regimen was continued for one additional month on an outpatient basis, the patient was again admitted in December 2008 with anorexia and abdominal distension due to increased ascites, which necessitated routine twice weekly paracentesis. She refused peritoneovenous shunt placement.

Second-line chemotherapy using paclitaxel was administered four times, with no tumor or ascites response. However, following chemotherapy with docetaxel and intraperitoneal cisplatin injection,

there was a decrease in her ascites, and the patient could be discharged.

In April 2009, she was readmitted with fatigue, anorexia, and increased ascites. Paracentesis showed hemorrhagic ascites, which required twice weekly drainage, and she also required weekly transfusions. After two cycles of chemotherapy with triweekly pemetrexed, there was transient response, with a decrease in ascites that changed from hemorrhagic to serous.

In June, the patient's general status worsened, with frequent vomiting caused by gastrointestinal stenosis, massive ascites, and enlarged ovarian metastases (Figures 2A–B). Additionally, she also developed dyspnea with dry cough, and lymphangitic pulmonary metastases of the right lower lung were suspected (Figure 3A). Since she and her family strongly desired additional chemotherapy, the HER2 status of her gastric cancer biopsy specimen was evaluated by immunohistochemistry (IHC; HercepTest™, DAKO, Copenhagen, Denmark) and was found to be strongly positive (3+) (Figure 1B) in accordance with high gene amplification of *HER2* (red signal, Figure 1C).

Because of her deteriorated performance status, trastuzumab monotherapy was initiated (4 mg/kg first dose, then 2 mg/kg weekly). A percutaneous transesophageal gastrostomy was also performed. After three cycles, her dyspnea improved (Figure 3A). After six administrations of trastuzumab, the volume of ascites was

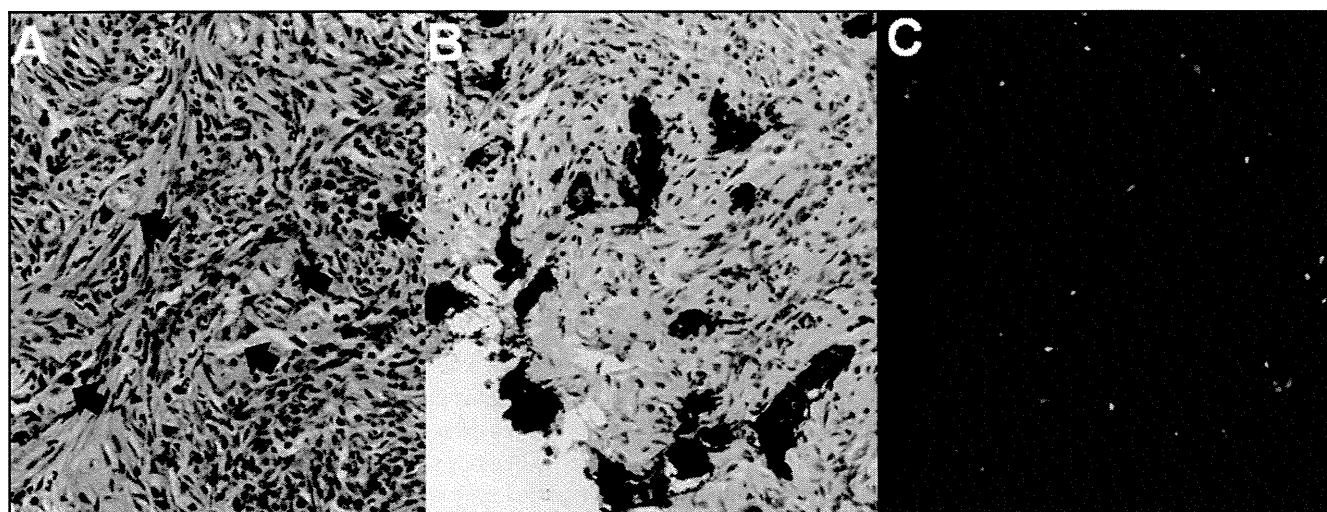


Figure 1. Pathological specimen of the primary gastric cancer. (A) Endoscopic biopsy specimen showed poorly-differentiated adenocarcinoma cells (arrows). (B) HER2 status was evaluated by IHC (HercepTest), and was found to be strongly positive (3+). (C) High gene amplification of HER2 was also seen by FISH (red signal).

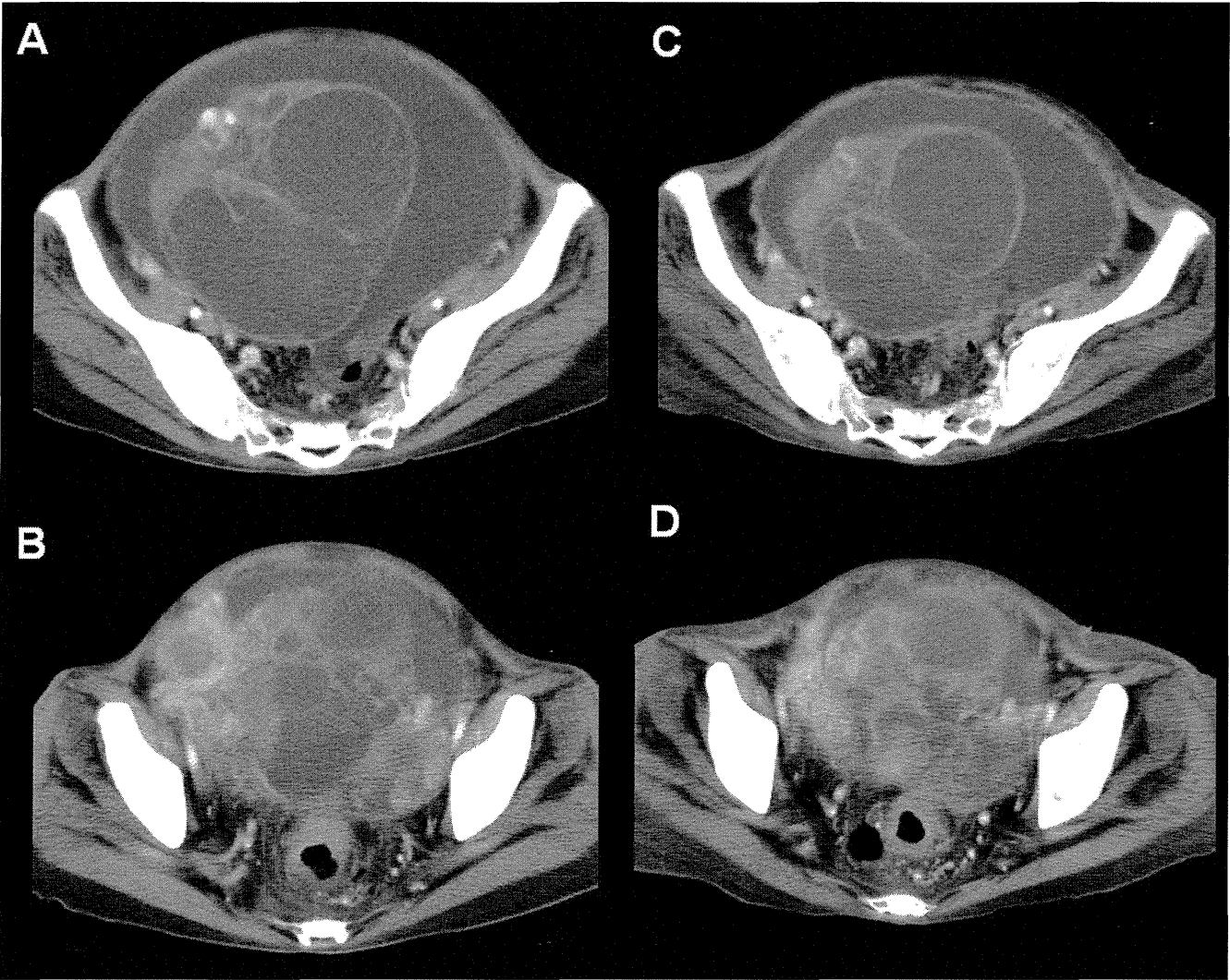


Figure 2. CT scan before and on trastuzumab monotherapy. (A–B) CT scans before treatment showed large ovarian metastasis with ascites. (C–D) CT scans after 6 administrations of trastuzumab showed that her ovarian tumors were slightly reduced.

decreased, and the frequency of paracentesis was reduced from twice to once weekly. A CT scan showed that her ovarian tumors were slightly reduced (Figures 2C–D). No apparent trastuzumab toxicity was observed, and her performance status was maintained for two and a half months. Trastuzumab monotherapy was continued for 3 months until the patient became icteric in September 2009, 11 months after the first admission and 9 months since routine paracentesis was begun. Best supportive care was offered thereafter.

DISCUSSION

Trastuzumab, a recombinant, human–mouse chimeric monoclonal IgG1k antibody that specifically targets HER2 protein, has improved survival in HER2-positive breast cancer patients. In the first pivotal trial of breast cancer, trastuzumab plus paclitaxel or an anthracycline improved overall survival by a hazard ratio of 0.80 (95% confidence interval [CI], 0.64–1.0, $P = .046$) compared with chemotherapy alone.¹ In another trial, trastuzumab plus docetaxel also improved breast cancer survival compared with chemotherapy alone.² After these results, trastuzumab-containing chemotherapy became the standard of care for breast cancer patients with HER2 overexpression.³

Because HER2-positive gastric cancers have been reported, the efficacy of trastuzumab for HER2-positive gastric cancer has also been anticipated. The ToGA study⁴ comparing 5-fluorouracil plus cisplatin with or without trastuzumab showed improved survival in the trastuzumab arm with a hazard ratio for death of 0.74 (95% CI, 0.60–0.91, $P = .046$). In contrast to breast cancer, HER2 amplification revealed by fluorescence in situ hybridization (FISH) was seen in gastric cancers with IHC results of 0 or 1+ by modified HercepTest. Therefore, when survival analysis in the TOGA study was limited to HER2 cancers that were 2–3+ by IHC and FISH-positive, the reduction in risk of death became more apparent (HR 0.65; 95% CI, 0.51–0.83). No apparent increase in toxicity was seen in the trastuzumab arm⁴; therefore combination chemotherapy using trastuzumab may become the standard of care for HER2-positive gastric cancer and has been approved in the United States for this indication.

In the TOGA study screening data,⁵ the HER2-positive rate was higher in gastroesophageal junction cancer (33.2%) than in gastric cancer (20.9%). In addition, the diffuse type had a lower positive rate (6%) than the intestinal type (34%) of gastric cancer. However,

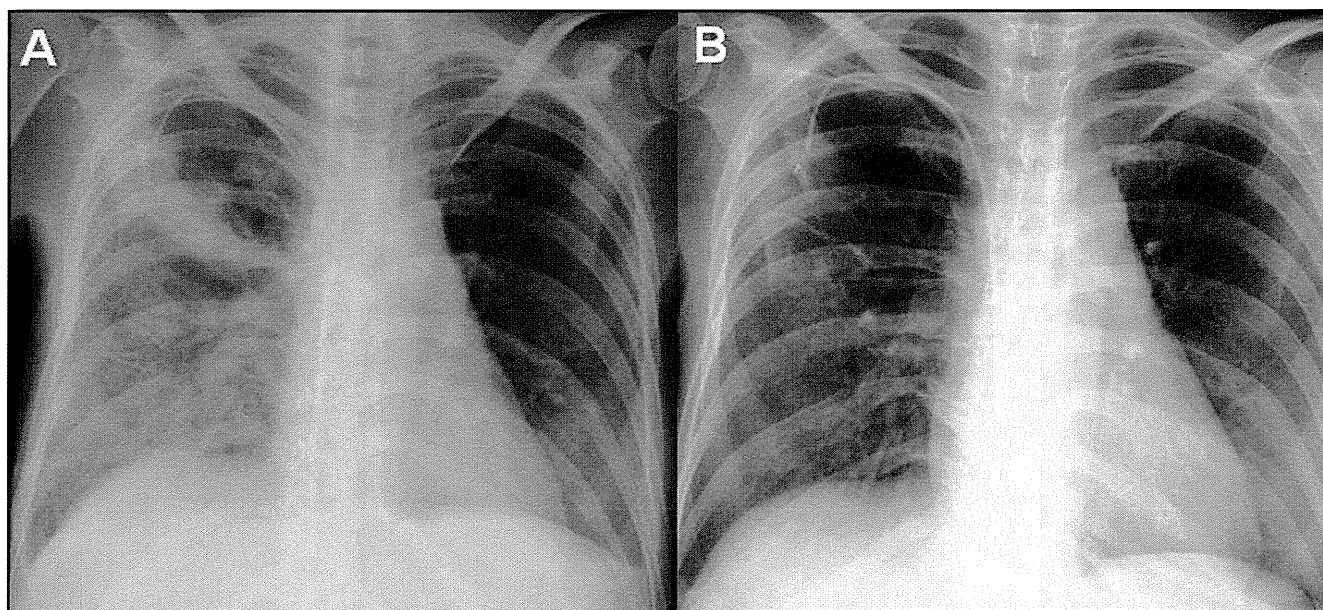


Figure 3. Chest x-ray before and on trastuzumab monotherapy. (A) Lymphangitic pulmonary metastases of right lower lung were suspected. (B) Abnormal finding improved with trastuzumab.

as confirmed by experience with our patient, although patients with diffuse-type gastric cancer are frequently HER2 negative, HER2 status of all gastric cancer types should be evaluated.

Because the ToGA study included chemonaïve patients with gastric cancer, the benefit or efficacy of chemotherapy using trastuzumab for patients pretreated with chemotherapy is not currently known. In addition, the antitumor effect of trastuzumab monotherapy is not known. However, trastuzumab monotherapy has been shown to be active with a response rate of 15% in pretreated breast cancer (18% for 3+ IHC),⁶ although this is a slightly lower response rate than for monotherapy in chemonaïve breast cancer (35% in 3+ IHC),⁷ and trastuzumab monotherapy has been adopted for patients who are not considered suitable for cytotoxic chemotherapy.³

In summary, this case was instructive for the following reasons: (1) trastuzumab monotherapy was feasible in this heavily pretreated patient with gastric cancer plus massive ascites, (2) trastuzumab and sufficient supportive care were effective in improving the cancer-related symptoms in this patient, (3) although chemotherapy using trastuzumab may become standard first-line chemotherapy for patients with HER2-positive gastric cancer, trastuzumab may even be effective in the salvage setting.

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4. 腹膜播種病変に対する 腹腔内化学療法－臨床における効果－

*Intraperitoneal chemotherapy for peritoneal metastasis
from gastric carcinoma: Clinical benefits*

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Summary

胃癌では、転移再発形式として頻度の高い腹膜転移の制御が重要である。抗癌剤の局所濃度を上昇させ、最大限の効果を得るには、腹腔内投与が合理的と思われる。過去にはシスプラチンの投与が試みられたが、十分な効果は示されなかった。近年、腹腔内投与時の薬理動態からパクリタキセル (PTX) が有望と考えられており、実際に、この薬剤の腹腔内投与と経静脈投与を S-1 と組み合わせた併用療法 (東大レジメン) が第 II 相試験において胃癌腹膜転移例に対してきわめて良好な治療効果を示した。PTX の腹腔内投与には保険適応がないが、現在、切除可能胃癌を対象とした PTX 腹腔内投与 vs 経静脈投与と、非切除例を対象とした東大レジメン vs S-1/シスプラチン療法の 2 件のランダム化試験が、高度医療評価制度を利用して行われている。その成果として PTX 腹腔内投与が保険収載され、実地臨床で腹膜転移の制御を目的に使用可能となることに期待したい。

Key Words

胃癌、癌性腹膜炎、腹膜転移、腹腔内化学療法、腹腔内投与

胃癌腹膜転移は根治切除後に最も多くみられる再発形式であるのみならず、診断時にすでに同時性にみられる場合も少なくない。癌の浸潤が漿膜面に到達し、ここからはがれた癌細胞が腹腔内に播種するというのがその主な発生機序とされる。このような遊離癌細胞は、腹腔内洗浄液の細胞診で検出可能であり、胃癌取扱い規約では洗浄細胞診陽性は CY1 と記載され、ほかに非治癒因子を認めなくても Stage IV となる。現実には、肉眼的に腹膜転移を認める場合 (P1) と同等に予後不良であることが、多数の施設から報告されている。胃癌治療ガイドラインによれば、

Stage IV の胃癌は根治手術の適応とはならない。

腹膜転移は胃癌のほか、卵巣癌でもしばしばみられる転移形式である。興味深いことに、卵巣癌では洗浄細胞診が陽性でも肉眼的な腹膜転移を認めなければ Stage I であり、肉眼的な転移を認めても、径 1 cm 未満の病巣以外を (すなわち、主だった転移巣を) 切除できれば optimally debulked cancer とされ、化学療法で一定の治療成績を見込めるとする見解がある。すなわち、化学療法がよく効く癌であるため、胃癌では意義が少ないと考えられてきた減量手術 (debulking surgery)

◆メモランダム◆

保険適応と高度医療評価制度

現在、胃癌に使用されている薬剤の腹腔内投与は保険適応ではない。腹腔内投与を研究費で、ほかの医療行為を保険でまかなうと混合診療となる。しかし、全治療を研究費でまかなうとコストがかかりすぎるので、臨床試験は実施できない。高度医療評価制度においては、厚生労働省に申請し承認を受けた新規治療法を特定の医療機関で行う場合、新規治療法のコストは自費や研究費で補い、ほかの医療行為は保険診療として研究を進めることができる。

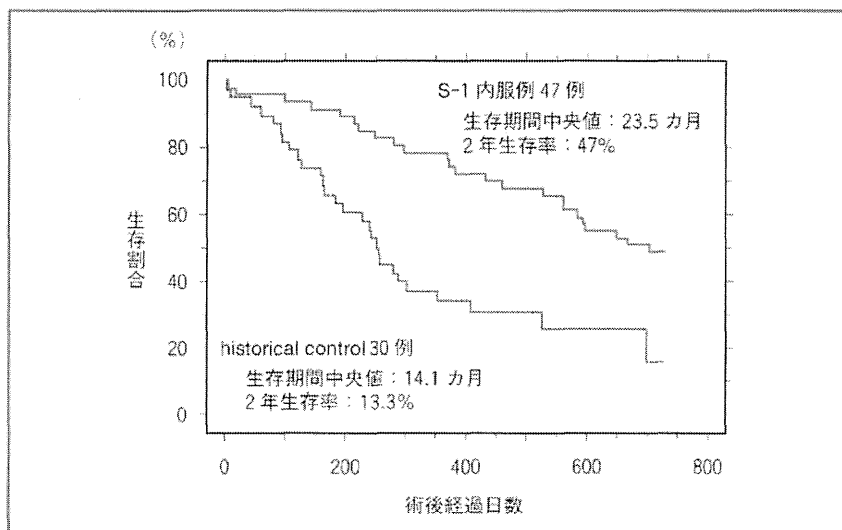


図1 CY1症例に対する胃切除後S-1療法の治療成績 historical control との比較
(文献1より一部改変引用)

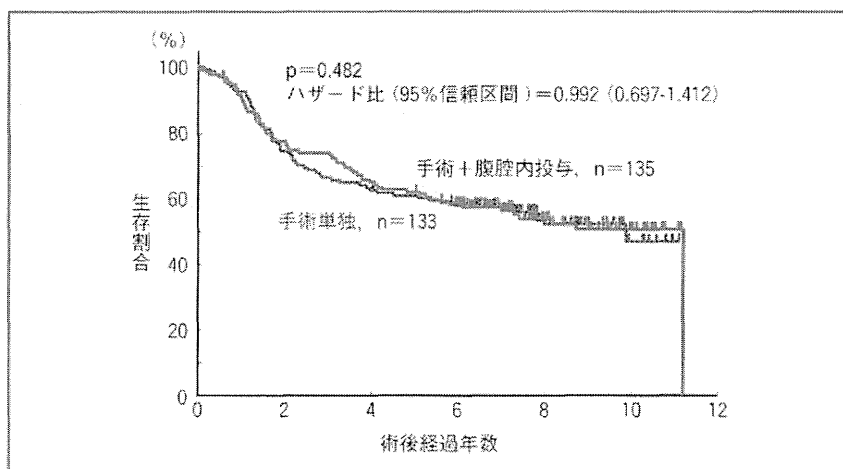


図2 洗浄細胞診陰性・漿膜浸潤陽性胃癌に対するCDDP IPを含む術後補助化学療法を検証するランダム化試験JCOG9206-2
(文献2より一部改変引用)

に意義が認められ、顕微鏡レベルの遺残については必ずしも悲観する必要はないようである。胃癌においても化学療法が奏効するようになれば、減量手術の意義が再浮上する可能性がある。

現実に筆者らはCY1以外に非治療因子を認めない胃癌(ただし、少量の腹膜転移であれば、胃切除と同時にすべて切除できれば適格とした)に定型手術を施行したうえでS-1を投与する

第II相試験を行い¹¹⁾、過去の報告を大幅に上回る47%という2年生存率を得ている(図1)。また、現在進行・再発胃癌の標準治療となっているS-1とシスプラチン(CDDP)の併用療法も、腹膜転移例に相性がよいようである。

CY0で治癒切除がなされた漿膜浸潤陽性胃癌に対する手術当日のCDDPの腹腔内投与(intraperitoneal administration: IP)を含む補助化学療法が、JCOGの第III相試験で検証されたが、大方の予想に反し手術単独群と全く同等の成績しか得られなかった(図2)¹²⁾。術後に行われる1コースの5FU/CDDPと、その後のUFTによる補助化学療法のコンプライアンスが不良であったのも一因とされているが、少なくとも手術当日のCDDPのIPはほぼもれなく行われていたはずであり、少なくともこれについては全く効果がなかったものと考えられる。IPされたCDDPは血中への移行がきわめて良好で、腹腔内に短時間しかとどまらないため、単回投与での局所への効果には限界があったものと思われる。なお、臨床試験が行われた当時も現在もCDDPの腹腔内投与は保険適応ではない。したがって、本臨床試験をJCOGで実施できたのは時代背景の相違という以外に説明の術はない。本臨床試験の結果をかんがみても、現在わが国でCDDPのIPを実地臨床として行うべきではない。近年、韓国の単施設での第III相試験において、CDDPの単回投与を含む補助化学療法が、これを含まない補助化学療法に

比し有意に良好な生存期間を得たとの報告があり、長期観察でも有意差は維持されていることが2012年のGastrointestinal Cancers Symposiumで報告された。しかし、CDDP IP投与群では、手術当日にマイトマイシンCも投与され、術後にカベシタピン/CDDP療法が行われ(CDDP IP非投与群はカベシタピン単剤)、さらにそのコース数も多いなど、IP以外にも両群間に多数の相違点があるため、本試験の結果をもってCDDP単回投与の失地を回復することはできないと考えられる。

わが国でIPが再度注目を集めたのは、腹腔内投与時の薬理動態ゆえに腹腔内投与に適していると考えられる(図3)タキサンが使用されるようになってからである。しかし、タキサンのIPが保険適応でないことから、手順を踏んで用量設定試験などを行うのは事実上不可能であった。ただ、米国では卵巣癌を対象にパクリタキセル(PTX)のIPの臨床試験が多数行われており、ここでは週に1度単剤での投与を行う場合の至適投与量が 60 mg/m^2 に設定されていた。筆者らは、高度医療評価制度を用いてPTXのIPを検証する臨床試験を計画した。単回投与では物足りないため、腹腔リザーバーを挿入し、術後10週間にわたりPTXのIPのみの治療を行うこととした。このため、エビデンスのある術後S-1療法を遅らせても倫理的に問題が少ないと思われる、特段に腹膜転移再発のリスクの高い症例(スキルス胃癌の根治切除例、CY1症例、同時性のP

因子を同時に完全切除した症例、微量のP因子が遺残した症例)を対象とした。そして、手術当日を含む計7回のPTXのIPを試験アームとし、同一スケジュールでPTXの点滴静脈注射

(DIV)をreferenceとするランダム化第II相試験、INPACT試験を開始するに至った⁴⁾(図4)。プロトコル治療後は根治度に応じ、S-1単剤ないしはS-1/CDDP併用療法を継続すること

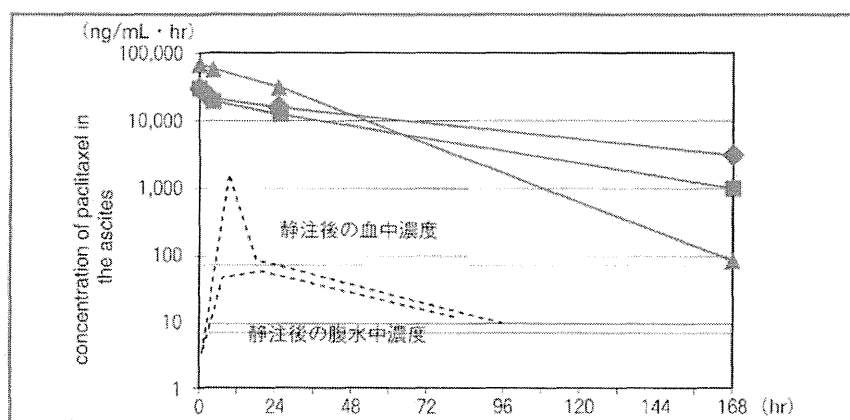


図3 腹腔内投与されたPTXの薬理動態

腹水を有する3症例にPTX 60 mg/m^2 を腹腔内投与した場合の腹水中濃度の推移を実線で示す。点線は、腹水を有する症例にPTX 80 mg/m^2 を経静脈投与した場合の血中濃度と腹水中濃度をsuperimposeしたものである。

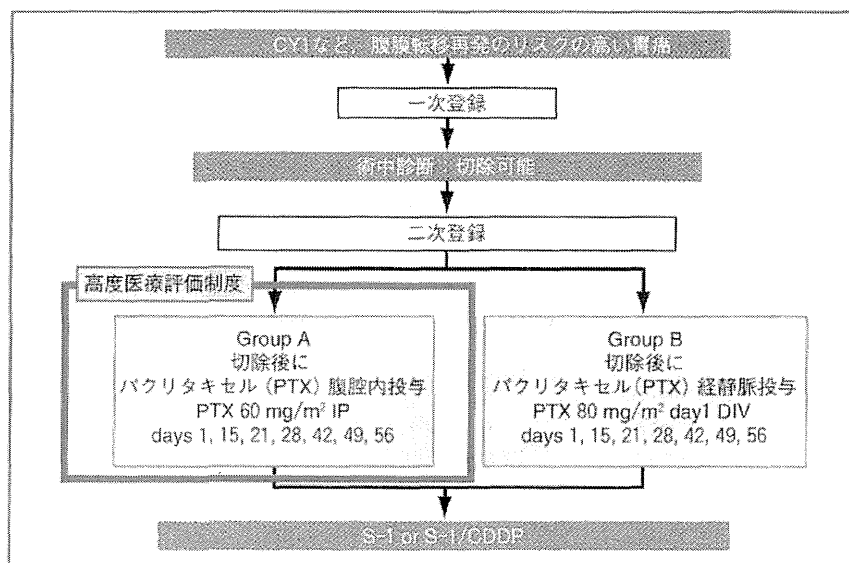


図4 INPACT試験(多施設共同ランダム化第II相試験)

としている。DIV 投与群に割り付けられ PTX 終了後に S-1 単剤に移行する場合にも、術後 S-1 単独療法に代わる新たな補助化学療法の候補として第Ⅲ相試験 (SAMIT 試験) で検証中である PTX/S-1 の逐次併用療法と同様の治療法となり、有用な治療法である可能性は秘めている。また、S-1/CDDP 療法は胃切除後すぐに行うには毒性が強く、忍容性に乏しいとされている¹⁹⁾が、1 コース目に CDDP をスキップすれば、2 コース目からは導入可能であることが示唆されている。INPACT 試験の DIV 群で S-1/CDDP 療法を行う場合には、術後早期には PTX を使用し、時間が経過してから S-1/CDDP 療法を導入することになり、胃切除後に S-1/CDDP 療法を行う手段のひとつとして期待される。INPACT 試験は、2012 年 1 月現在、目標症例数の 25% に相当する症例集積を得ている。

一方、切除不能な同時性腹膜転移例

や再発症例を対象に、Ishigami らは独自に校費負担で S-1 内服、PTX DIV、PTX IP を併用する新たなレジメン (東大レジメン) の第Ⅰ相試験を行い、推奨用量を設定した²⁰⁾。すでに確立されている S-1/PTX 療法 (S-1 は 80 mg/m² で 2 週間内服・1 週間休薬、PTX は 50 mg/m² で day 1, 8 に点滴静注) に PTX IP を追加するかたちのレジメン (図 5) であるため、IP の用量は 20 mg/m² と少ない設定となったが、IP によって圧倒的に高い腹腔内濃度が得られる薬理動態を考慮すれば、本用量でも十分に効果が見込まれた。引き続き行われた第Ⅱ相試験では、高度な腹膜転移例 (旧取り扱い規約における P3 症例が主体) を対象としたにもかかわらず、1 年生存率は 78%、洗浄細胞診が 86% で陰性化するなど、驚異的な治療成績が得られ、腹膜転移例に対するきわめて有望なレジメンと位置付けられた (図 5)²¹⁾。筆者らも P3 症例 5 例にこれを行い、うち 2 例で P

因子の消失を確認し、conversion surgery に至っている。現在、東大レジメン対 S-1/CDDP の第Ⅲ相試験 PHOENICS 試験が同じく高度医療評価制度を用いて行われており、同時性腹膜転移を有する切除不能例を対象に症例集積中である。

さらに、Ishigami らは S-1 既治療例 (S-1 による補助化学療法後再発例を含む) を対象に PTX と CDDP の併用腹腔内化学療法を開発し²²⁾、第Ⅰ相試験で PTX DIV、PTX IP、CDDP IP の biweekly の推奨用量がおのおの 80 mg/m²、20 mg/m²、25 mg/m² に設定された。これも現段階では高度医療評価制度か校費負担によってのみ検証が可能な治療法であるが、先に述べたランダム化試験からエビデンスが得られることにより、PTX IP が保険収載されこうした治療法の検証が容易となり、IP 法の開発が加速することに期待したい。

以上、PTX の腹腔内投与は有望な

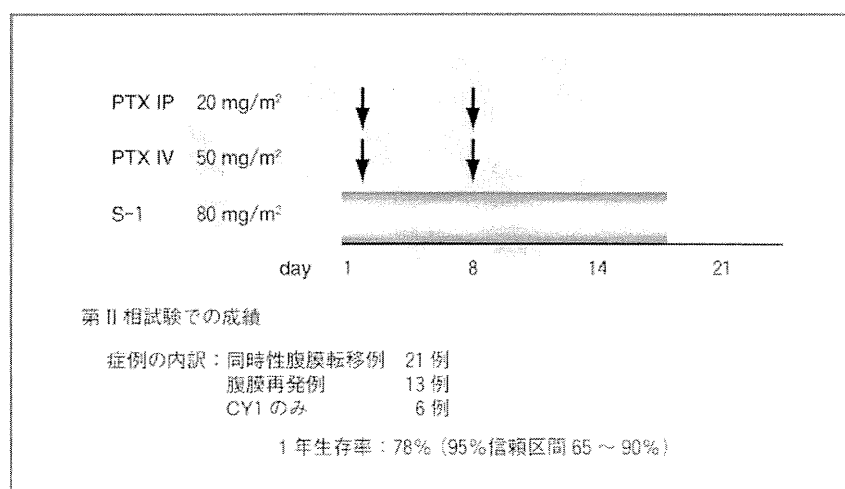


図 5 東大レジメンの内容と治療成績

治療法であり、単剤、および併用の両面から、臨床試験による検証が行われている。

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Long-term follow up of patients who were positive for peritoneal lavage cytology: final report from the CCOG0301 study

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Ken Kondo · Michitaka Fujiwara

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Abstract

Background In gastric cancer patients who have positive results for peritoneal lavage cytology the disease is defined as CY1, and classified as stage IV, and this population has generally suffered a dismal outcome. For this population, we had conducted a phase II trial, with the 2-year survival rate as the primary endpoint, to test the strategy of D2 dissection followed by chemotherapy with single-agent S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium). Forty-eight patients were enrolled, of whom 47 were found to have been eligible for analysis. The 2-year survival rate of 46 % exceeded our expectations.

Methods Further follow up was conducted to confirm whether radical surgery could be recommended for the CY1 population.

Results The 5-year overall and relapse-free survival rates were 26 and 21 %, respectively.

Conclusions Gastrectomy with curative intent could be considered for patients with CY1 disease provided they are scheduled to receive effective postoperative chemotherapy.

Keywords Gastric cancer · S-1 · Cytologic examination · Peritoneal carcinomatosis

Introduction

Stage IV gastric cancer is generally considered incurable and this population is usually ineligible for radical surgery. Treatment options for this population, recommended by the Japanese Guidelines, are chemotherapy, radiotherapy, palliative surgery and palliative care medicine [1]. However, several case series suggest that the possibility of cure cannot be ignored in some carefully selected populations of stage IV patients, given the improvements in multimodal treatment [2–4]. Patients with free cancer cells in the peritoneal cavity could constitute such a population. Detection of free cancer cells by peritoneal lavage cytology predicts the risk of peritoneal carcinomatosis with high specificity [5]. When cancer cells are detected, the positive cytology status is designated as CY1 by the *Japanese classification of gastric carcinoma, 2nd English edition* [6]. Patients with CY1 status are classified as stage IV even in the absence of macroscopic evidence of peritoneal seeding. Whether this population should be treated radically or palliatively has been an issue for debate [7].

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