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—Short Communication—

Success Rate of Collagen Gel Droplet-embedded Culture Drug Sensitivity Test in Colorectal Cancer: Are Antibiotics a Prerequisite for Specimen Irrigation?

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Abstract

The collagen gel droplet-embedded culture drug sensitivity test (CD-DST) is one of the best chemosensitivity tests owing to its high success rate. However, CD-DST is often a culture method, and contamination is a serious problem, especially in the case of colorectal cancer, which is contaminated by enteric bacteria. It has been reported that the success rate of CD-DST is 64.0% in the case of colorectal cancer. Therefore, the sampling and washing of specimens before culture are extremely important. By washing specimens carefully with normal saline containing antibiotics, we achieved a success rate of 85.3% in the case of colorectal cancer. To improve the success rate, we started specimen irrigation with a large amount of normal saline in January 2007. As a result, a success rate exceeding 90% was acquired. For the success of CD-DST for colorectal cancer, it is important to irrigate specimens many times with a large amount of normal saline.
(J Nippon Med Sch 2012; 79: 163–165)

Key words: collagen gel droplet-embedded culture drug sensitivity test, colon cancer, chemosensitivity test

Introduction

The progress of colorectal cancer chemotherapy has been remarkable. Excellent treatment guidelines are available, and the standard treatment regimen is FOLFOX (leucovorin, fluorouracil, and oxaliplatin) or FOLFIRI (leucovorin, fluorouracil, and irinotecan) with or without molecularly targeted agents. Although response rates range from 40% to 50%[1,2], many patients have adverse effects or do not benefit from chemotherapy. Consequently, determining whether an anticancer drug will be effective for individual patients would be of enormous benefit, as would personalized therapy.

Anticancer drug chemosensitivity tests support personalized therapy by predicting the effect of chemotherapy, and one of the best such tests is the collagen gel droplet-embedded culture drug sensitivity test (CD-DST)[3]. However, the CD-DST is a culture method, and contamination is a serious problem, especially in the case of colorectal cancer,

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which is contaminated by enteric bacteria. Therefore, the sampling and washing of specimens before culture are extremely important.

We have worked toward improving the success rate of the CD-DST in colorectal cancer. To that end, preventing contamination is most important. We believe that irrigation of specimens with a large amount of normal saline is required. The purpose of this study was to evaluate the effect of specimen irrigation with a large volume of normal saline on the success rate of the CD-DST in colorectal cancer.

Patients and Methods

Patients

Our research subjects were 87 patients with colorectal cancer who underwent surgery from January 2004 through August 2010 in our department. We divided the subjects into 2 groups: group A (36 patients) underwent surgery from January 2004 through December 2006, and group B (51 patients) underwent surgery from January 2007 through August 2010.

Specimen Preparation

At the end of surgery, we obtained specimens by stripping off the surface of a cancer tissue. We can collect the largest number of cancer cells from the surface. The specimens from group A were irrigated 5 times with 20 mL of saline containing 200 U/mL penicillin (Gibco, Grand Island, NY, USA), 200 μg/mL streptomycin (Gibco) and 50 μg/mL amphotericin B. On the other hand, specimens from group B were irrigated 10 times with 40 mL of saline without antibiotics. After irrigation, the specimens from both groups were stored in Eagle's minimal essential medium (Gibco) at 4℃ until the start of the CD-DST.

CD-DST

We performed the CD-DST with the method of Kobayashi et al[3]. This sensitivity test was performed in the BML Laboratories (Saitama, Japan). We considered the CD-DST to be successful when the culture in a dish with an anticancer drug and that in a dish without an anticancer drug (control) were both successful.

Bacteriological Analysis

To judge the effect of specimen irrigation with a large volume of normal saline, we counted the number of bacterial cells in the irrigation solution of specimens from 5 patients. We counted the number of bacterial cells in the first irrigation solution (sample 1), the fourth irrigation solution (sample 2), and the last irrigation solution (sample 3).

Table 1a Patient background

	Group A (n = 38)	Group B (n = 45)
Sex (M : F)	31 : 7	23 : 22
Age (years)	67.4	67.2
Pathologic type (well-differentiated : moderately differentiated : poorly differentiated)	19 : 15 : 4	27 : 13 : 5
T classification (1 : 2 : 3 : 4)	4 : 7 : 22 : 5	2 : 4 : 36 : 3

Table 1b CD-DST success rates

Group	A	B
Total cases	38	45
Successful cases	29	36
Success rate	76.3%	80.0%
Contaminated cases	6	4
Contamination rate	15.8%	8.9%

Results

There were no cases from which we could not gather a sufficient number of cells. There were 2 cases each in group A and group B which showed a poor proliferation capability of cancer cells, and these 4 cases were excluded from the study. Thus, 34 cases belonged to group A, and 49 cases belonged to group B.

There were no significant differences in clinicopathologic factors between the groups (**Table 1a**). The success rate did not differ significantly between group A (85.3%) and group B (91.8%; **Table 1b**).

In all cases, the number of bacterial cells decreased with irrigation (**Table 2**). We found 10^3 to 10^5 bacterial cells per milliliter of the first irrigation solution but only 10^3 bacterial cells or less per milliliter of the last irrigation solution.

Table 2 Bacteriological analysis

Case	Age (years)	Sex	Number of cells		
			Sample 1	Sample 2	Sample 3
1	73	F	10^5	10^4	10^3
2	67	M	10^3	0	0
3	76	M	10^5	10^4	10^3
4	79	M	10^5	10^4	10^3
5	66	M	10^4	10^4	10^3

Discussion

In cases of lung or breast cancer, the success rate of the CD-DST is 80% or higher[4]. However, in cases of colorectal cancer the success rate of the CD-DST is 64.0%[5], which indicates the limitation of the CD-DST in playing a key role in personalized therapy for colorectal cancer.

The most important problem of CD-DST is contamination, especially in colorectal cancer. Because bacterial contamination cannot occur in the absence of bacteria, the success rate can be increased by minimizing the number of bacterial cells before starting the CD-DST. Therefore, careful irrigation of specimens is extremely important. To our knowledge, there have been no reports of how many bacterial cells adhere to colonic specimens or how much irrigation solution is needed to prevent contamination.

We have succeeded in performing the CD-DST by washing specimens carefully with normal saline containing high concentrations of antibiotics. To improve the success rate, we started irrigating specimens with large amounts of normal saline without antibiotics in January 2007. The present study shows the importance of specimen irrigation with a large amount of normal saline, and our success rate is higher than previously reported rates[5]. By irrigating 10 times, the number of bacterial cells decreased to 1/1,000, and the irrigation solution contained 10^3 or fewer bacterial cells per milliliter. Although 4 irrigations (total volume, 160 mL) decreased the number of bacterial cells to 1/10, many bacterial cells still adhered to the specimen. If the number of bacterial cells adhering to a specimen is 1,000 or less, antibiotics contained in the culture solution will prevent contamination in almost all cases. As a result, a success rate exceeding 90% was obtained. With this high success rate, we can establish personalized therapy on the basis of the CD-DST. To establish the CD-DST as an accurate method, we must increase its success rate and review the sampling and irrigation methods. Can an increase in the amount of irrigation solution decrease the number of bacterial cells adhering to colonic specimens and increase the success rate of CD-DST? These questions must be addressed by future studies.

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Outcome in disappearing colorectal cancer liver metastases during oxaliplatin-based chemotherapy

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Abstract. Some colorectal cancer liver metastases (CLMs) disappear on serial imaging during chemotherapy and the optimal treatment strategy for such lesions remains undetermined. The purpose of this study was to investigate the outcome in disappearing CLMs, as few studies have focused on this topic, with conflicting results. Among 125 patients with CLMs treated with modified FOLFOX6 with or without bevacizumab, those in whom all CLMs disappeared on computed tomography were identified. Recurrence of such disappearing lesions *in situ* was examined on a tumor-by-tumor basis. Five (4%) patients with a total of 44 CLMs met the evaluation criteria. The median number of CLMs prior to chemotherapy was 8 (range, 2-16). The median maximal diameter of the CLMs was 1.8 cm (range, 1.0-2.4). The median time-to-disappearance of all eligible lesions was 6.5 months (range, 4.5-7.5). Histological examination of scar lesions on the liver surface revealed no viable cancer cells. Two lesions were surgically resected. During clinical follow-up of the remaining 42 lesions, *in situ* recurrence was observed in 8. The cumulative 1-, 2- and 3-year rates of relapse *in situ* were 9.1, 9.1 and 31.1%, respectively. Given the low risk of recurrence *in situ*, the results suggest that the sites of disappearing CLMs may be left unresected but should be carefully monitored during follow-up, with resection an option if the lesion should recur. However, to validate such a treatment strategy, further investigation with a larger series of patients is warranted.

Introduction

Recent advances in chemotherapy have resulted in an increasing number of patients with colorectal cancer liver metastases (CLMs) being treated with systemic chemotherapy prior to hepatic metastasectomy, either as neoadjuvant treatment for initially resectable lesions or in an attempt to make unresectable lesions resectable. When used as first-line chemotherapy for CLMs, new and effective regimens, including 5-fluorouracil (5-FU)/leucovorin (LV), irinotecan and oxaliplatin in combination with targeted agents, have yielded a complete response in 1 to 9% of patients with CLMs (1-3). The optimal treatment strategy in such cases, however, remains to be determined as, to the best of our knowledge, little research has been carried out on this topic and the results thus far have been conflicting.

Patients and methods

Patients. The study protocol conformed to the standards of good practice and ethics of our institution. Informed consent was obtained from the individuals included in the study. A retrospective review of all consecutive patients who had been diagnosed with CLM and who were treated with first-line oxaliplatin-based chemotherapy (modified FOLFOX6; mFOLFOX6) with or without bevacizumab between January 2006 and December 2010 was carried out. The mFOLFOX6 regimen comprised intravenous infusion of oxaliplatin (80 mg/m^2) over 2 h, followed by rapid intravenous bolus infusion of 5-FU (400 mg/m^2) for 5 min and continuous intravenous infusion of 5-FU (2,400 mg/m^2) over 46 h. This regimen was repeated every 2 weeks. When used in combination with the mFOLFOX6 regimen, bevacizumab (5 mg/kg) was infused intravenously over 60-90 min prior to the administration of oxaliplatin. In Japan, the use of oxaliplatin and bevacizumab for metastatic colonic cancer was approved by the governmental health insurance system in March 2005 and April 2007, respectively. During this period, mFOLFOX6 with or without bevacizumab was the standard first-line chemotherapy for metastatic colorectal cancer at our institute.

Data were collected on patients in whom all CLMs initially detected by computed tomography (CT) disappeared during first-line chemotherapy, focusing on time-to-disappearance and time-to-recurrence on a tumor-by-tumor basis.

The clinicopathological patient data recorded included age, gender, site of primary lesion, disease stage at diagnosis of primary lesion, site and number of liver metastases and carcinoembryonic antigen (CEA) level prior to chemotherapy. Adverse events during chemotherapy were evaluated according to the Common Toxicity Criteria of Adverse Events (CTCAE) ver. 4.0 (4). The relative dose intensity of oxaliplatin was also evaluated.

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Key words: colorectal cancer, liver metastases, oxaliplatin

Table I. Clinical features and details of treatment for each patient.

Case	Age (years)	Gender	Stage at initial diagnosis	Site of primary lesion	CEA at initial diagnosis (ng/ml)	No. CLMs before mF6	Maximal diameter of tumor (cm)	No. mF6 cycles	Bev	Additional mF6+ Bev after disappearance	Recurrence *in situ*
1	69	M	IV	Rectum	6.6	16	2.0	15	-	+	+
2	35	F	IV	Colon	14.3	8	1.8	12	+	-	-
3	60	F	II	Colon	4.5	2	1.0	11	+	-	+
4	68	M	I	Rectum	2.0	5	2.4	13	+	-	+
5	68	F	IV	Colon	5.1	13	1.4	9	+	+	-

mF6, modified FOLFOX6; Bev, bevacizumab. M, male; F, female; CEA, carcinoembryonic antigen; CLMs, colorectal cancer liver metastases.

The extent of metastasis was determined during the pretreatment workup, which usually involved enhanced triple-phase helical CT of the chest, abdomen and pelvis in 5-mm thick slices. CT was periodically performed at 3-4 month intervals. Disappearance was defined as no further lesion or abnormality, including a low attenuated mass, calcification and ring enhancement, at the site of a previously identified CLM. Other imaging modalities, including intravenously enhanced magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT, were also used whenever CT proved inadequate or in order to confirm disappearance on CT.

Statistical analysis. Continuous variables were expressed as the median and range. Time-to-disappearance and time-to-recurrence were estimated on a tumor-by-tumor basis. Time-to-disappearance was defined as the time from the initiation of chemotherapy to radiographic diagnosis of disappearance. Time-to-recurrence was defined as the time from disappearance to the time of initial radiographic evidence of relapse *in situ*. To calculate the *in situ* time-to-recurrence of disappearing CLMs, the CLMs were censored at the time of the last image in which no evidence of recurrence was visible. Biopsied lesions without evidence of viable tumor cells were also censored at the time of surgery. The cumulative rates of disappearance and recurrence were estimated using the Kaplan-Meier method.

Results

Patient characteristics and clinical course. A total of 125 patients diagnosed with CLMs were treated with mFOLFOX6 with or without bevacizumab. In 5 of the patients (4%), all CLMs disappeared during chemotherapy. Three of the patients were female. The primary site was the colon in 3 patients and the rectum in 2. At diagnosis of the primary lesion, pathological stage was I in 1 patient, II in 1 and IV in 3. Histological examination revealed well- or moderately differentiated adenocarcinoma in 4 patients and poorly differentiated adenocarcinoma in 1. The median CEA level (cut-off, 6.7 ng/ml) prior to chemotherapy was 5.1 ng/ml (range, 2.0-14.3). The median number of liver metastases was 8 (range, 2-16). The median maximal diameter of liver metastases per patient was 1.8 cm (range, 1.0-2.4). The median number of cycles of oxaliplatin-based chemotherapy to disappearance of all CLMs per patient was 12 (range, 9-15), with a median relative dose intensity of oxaliplatin at 79% (range, 78-88). All patients required a prolonged chemotherapy interval and/or dose reduction due to neutropenia. No peripheral neurotoxicities >grade 3 were observed.

The details of treatment for each patient are summarized in Table I. In Patient 1, CT revealed a large rectal cancer occupying the pelvic space and 16 bilobular metastatic lesions. After 5 and 11 cycles of mFOLFOX6, 12 and 3 CLMs disappeared, respectively. After 15 cycles, the one remaining lesion also disappeared and the primary lesion showed a marked reduction in size. Low anterior resection and biopsy of a scar lesion on the liver surface were performed. Histological examination revealed viable well-differentiated adenocarcinoma cells in the primary lesion but no viable tumor cells in the biopsy specimen. The patient received an additional 6 cycles of mFOLFOX6 postoperatively. At 8 and 9 months after surgery, *in situ* relapse was detected in 1 and 3 lesions, respectively, on CT and MRI. The patient was administered mFOLFOX6 plus bevacizumab for these 4 lesions, resulting in disappearance of all lesions after 7 cycles. Four months later, one of the 4 lesions reappeared and was subsequently resected. At the second laparotomy, a scar lesion was also resected, revealing no viable tumor cells by histological examination. The patient remains free of disease at 54 months after the initiation of first-line chemotherapy.

In patient 2, CT revealed 8 bilobular synchronous liver metastases from moderately differentiated adenocarcinoma of the transverse colon associated with familial adenomatous polyposis. Chemotherapy comprised mFOLFOX6 plus bevacizumab. After 3 and 12 cycles of mFOLFOX6 plus bevacizumab, 6 and 2 lesions disappeared, respectively. Two months later, the patient underwent total colectomy and biopsy of a scar lesion on the liver surface. Histological examination revealed moderately differentiated adenocarcinoma in the primary tumor but no viable cells in the biopsy specimen. No chemotherapy was administered postoperatively. The patient remains free of disease at 40 months after the initiation of chemotherapy.

Patient 3 received mFOLFOX6 plus bevacizumab therapy for 2 recurrent liver metastases detected at 13 months after Hartmann's procedure for perforated stage II sigmoid colon well-differentiated adenocarcinoma. No hepatectomy was performed due to patient refusal. After 12 cycles of chemotherapy, the 2 metastases disappeared, but reappeared 2 months

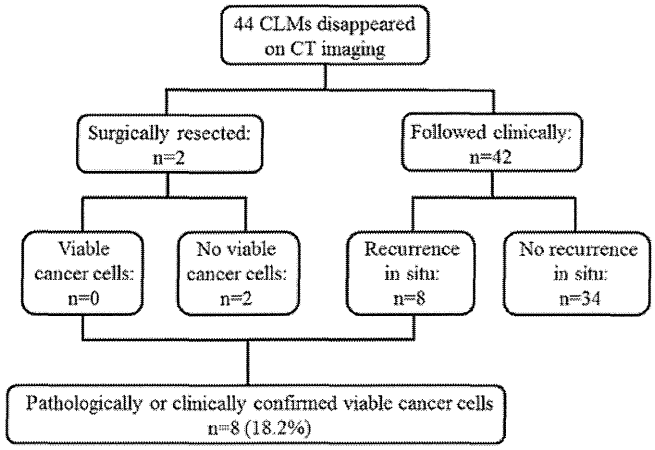

Figure 1. Flow chart of outcome in disappearing CLMs. CLMs, colorectal cancer liver metastases; CT, computed tomography.

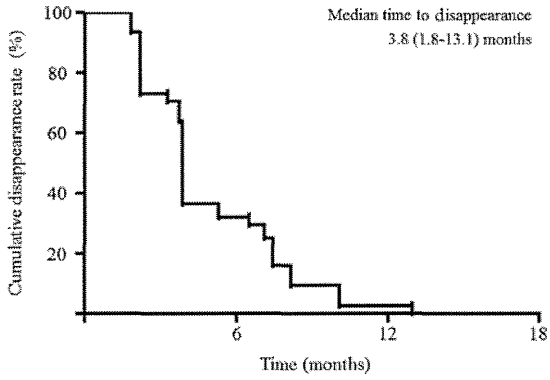

Figure 2. Cumulative disappearance rate of eligible CLMs by Kaplan-Meier method. CLMs, colorectal cancer liver metastases.

later. Subsequent additional chemotherapy included irinotecan plus 5-FU/LV (FOLFIRI) plus bevacizumab and thereafter irinotecan plus cetuximab. However, the patient succumbed to progressive disease at 24 months after the initiation of first-line chemotherapy.

Patient 4 received mFOLFOX6 plus bevacizumab for 5 recurrent bilobular liver metastases at 6 months after abdomino-perineal resection for stage I poorly differentiated adenocarcinoma of the lower rectum. After 12 and 13 cycles of chemotherapy, 2 and 3 lesions disappeared on CT and/or PET/CT, respectively. Lymph node metastasis along the right internal iliac artery was suspected after 13 cycles. Therefore, the patient was started on FOLFIRI plus bevacizumab. Two metastatic lesions reappeared during chemotherapy. The patient succumbed to progressive disease at 17 months after the initiation of first-line chemotherapy.

Patient 5 received mFOLFOX6 plus bevacizumab for 13 synchonous liver metastases and paraaortic lymph node metastasis at 1 month after resection of moderately differentiated adenocarcinoma of the ascending colon. After 4 and 6 cycles of chemotherapy, 9 and 3 lesions disappeared, respectively. After 9 cycles, the one remaining lesion disappeared and a marked reduction was also observed in the size of the lymph node metastasis. An additional 6 cycles of the same regimen were then administered. Lymph node metastasis was detected

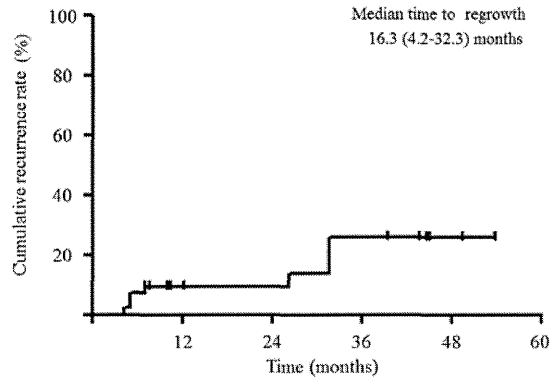

Figure 3. Cumulative recurrence rate of *in situ* disappearing CLMs by Kaplan-Meier method. CLMs, colorectal cancer liver metastases.

in the hepatoduodenal ligament 3 months later. Percutaneous transhepatic drainage for obstructive jaundice due to hepatic lymph node metastasis was successful, but the patient refused additional chemotherapy. The patient succumbed to disease at 26 months after initiation of first-line chemotherapy.

Time-to-disappearance and time-to-recurrence in situ. Of the 44 lesions evaluated, 2 were resected, revealing no viable tumor cells by histological examination. Of the 42 lesions followed clinically with a median follow-up period of 35.4 months (range, 10.5-58.3), 8 recurred *in situ* and the remaining 34 did not recur according to radiological evidence. The crude *in situ* recurrence rate was 18% (8/44), and the true complete response rate, meaning either no viable tumor cells on histological examination or durable local remission of an unresected site, was 80.5% (36/44; Fig. 1). The median time-to-disappearance was 3.8 months (1.8-13.1; Fig. 2). The cumulative 1-, 2- and 3-year rates of recurrence *in situ* were 9.1, 9.1 and 31.1%, respectively (Fig. 3).

Discussion

The optimal treatment strategy for CLMs that have disappeared due to new and effective chemotherapy regimens remains to be determined, and a number of problems must be addressed in deciding what the strategy should be. The number of CLMs which disappear or show a reduction in size is not important if they are initially included in the extent of resection. However, when CLMs involve the entire liver, it becomes necessary to consider how the lesions should be dealt with when they disappear without apparent trace. In such cases, a complete cure may be jeopardized if lesions recur due to incomplete eradication of cancerous cells. In fact, no data are available on outcome in patients in whom all sites of CLMs disappearing *in situ* were left unresected.

In the present study, the true complete response rate was 18% of disappearing CLMs. The crude recurrence rate *in situ* may be influenced by the length of the follow-up period, making it difficult to compare between studies. Therefore, we calculated the cumulative rate of *in situ* recurrence and demonstrated that the 1-, 2- and 3-year rates were 9.1, 9.1 and 31.1%, respectively.

To the best of our knowledge, including the present study, only 7 studies (5-10) have evaluated the outcome in

Table II. Studies that evaluated disappearing CLMs on a tumor-by-tumor basis.

Author (ref.)	Residual cancer in resected specimen (%)	Regrowth of clinically followed lesion (%)	Residual cancer in disappeared CLMs (%)
Benoist (5)	12/15 (80.0)	23/31 (74.2)	55/66 (83.3)
Fiorentini (6)	Not shown	Not shown	86/106 (81.1)
Tanaka (10)	11/45 (24.4)	11/27 (40.7)	22/72 (30.6)
Auer (8)	24/68 (35.3)	19/50 (38.0)	43/118 (36.4)
van Vledder (9)	41/67 (61.2)	21/45 (46.7)	62/112 (55.4)
Present study	0/2 (0.0)	8/42 (19.0)	8/44 (18.2)

CLMs, colorectal cancer liver metastases.

disappearing CLMs following chemotherapy. In 3 of these studies, patients were treated with either systemic or hepatic arterial chemotherapy, or both. One study (6) evaluated patients treated with hepatic arterial chemotherapy only. The molecularly-targeted agent bevacizumab or cetuximab were used in combination with systemic chemotherapy in 3 studies, including the present study, with a variety of incidence, ranging from 7.7 to 80% (6,9). In the present study oxaliplatin-based chemotherapy (mFOLFOX6) was used in all 5 patients and in combination with bevacizumab in 4 patients, since the use of mFOLFOX6 plus bevacizumab was one of the standard therapies for metastatic colorectal cancer during the study period in Japan. Bevacizumab is also known to improve oxaliplatin-related hepatic injuries, including sinusoidal dilatation, sinusoidal obstruction and fibrosis (11), and is thus considered to be suitable for candidates for hepatectomy after oxaliplatin-based chemotherapy.

The details of the 5 studies that evaluated disappearing CLMs on a tumor-by-tumor basis, including our study, are summarized in Table II. Benoist *et al* (5) examined data on 38 hepatectomized patients with a total of 66 CLMs that disappeared after neoadjuvant systemic chemotherapy with various regimens and reported that persistent macroscopic or microscopic residual disease or early recurrence *in situ* were observed in 55 lesions (83%). When the analysis was restricted to lesions left in place at surgery, 23 (74%) of 31 CLMs were found to have recurred *in situ*. Fiorentini *et al* examined 48 patients with a total of 106 CLMs that disappeared following 5-FU-based intra-arterial chemotherapy and reported persistent macroscopic or microscopic evidence of residual disease or early recurrence *in situ* in 86 lesions (81%) (6). Auer *et al* (8) examined data on 39 hepatectomized patients with 118 disappearing CLMs following neoadjuvant chemotherapy comprising various regimens. In their study, 75 of 118 disappearing lesions (64%), the sites of which were left unresected in subsequent surgery, were considered true complete responses, including 44 pathological complete responses and 31 durable clinical complete responses. A total of 19 disappearing CLMs (38%) recurred *in situ*. Tanaka *et al* (10) reported microscopic evidence of persistent metastases or recurrence *in situ* in 22 (31%) of 72 CLMs no longer radiographically visible after neoadjuvant chemotherapy, with 11 (41%) of 27 subsequently unresected lesions recurring *in situ*. In another study, van Vledder *et al* (9) analyzed data on 17 hepatectomized patients with disappearing CLMs who were treated with modern anticancer drugs such as oxaliplatin or irinotecan, among whom 91.1% received concomitant bevacizumab and 41.1% cetuximab. Of the 45 disappearing CLMs that were unresected, 21 (46.7%) recurred *in situ* during a median follow-up period of 20 months. The crude rate of recurrence *in situ* in our study (18%) appears to be lower than that reported in earlier studies, which ranges from 38 to 74%. In terms of the cumulative rate of recurrence *in situ*, the Kaplan-Meier curve in our study appeared identical to or slightly more favorable than that reported in two previous studies (8,9)

CT appears to be the most commonly used imaging modality in the evaluation of the effect of chemotherapy according to RECIST criteria (12). It has been reported that the sensitivity of helical CT is 66-84% (13-16). In patients with persistent macroscopic disease at surgery, morphological changes in the structure of the liver due to chemotherapy, including steatosis, sinusoidal dilatation and fibrosis, may be responsible for underestimation of liver metastases (17). This raises the question of whether other imaging modalities, such as MRI with liver-specific contrast agents or PET/CT, should be used in patients in whom CLMs are no longer visible on helical CT. Previous studies evaluating the outcome of disappearing CLMs used enhanced CT routinely in combination with ultrasonography (8,9), contrast-enhanced MRI (10,12) or PET/CT (12). In our study, despite a lack of sufficient data on the usefulness of these alternative diagnostic modalities, either enhanced MRI or PET/CT was additionally performed to confirm judgment of the disappearance of lesions on CT imaging.

The present study had a number of limitations, including its retrospective nature and small patient sample. However, the results suggest that outcome in disappearing CLMs during oxaliplatin-based chemotherapy is more favorable than previously reported. Although the precise reason for this improvement remains unclear, one possible explanation is that 4 of the 5 patients were administered mFOLFOX6 plus bevacizumab and that 3 of the 5 patients received additional chemotherapy. It should be noted that there are no supporting data from earlier studies for this supposition. The present data do suggest, however, that studies are warranted on a larger series of patients with disappearing CLMs treated with new anticancer drugs and molecularly-targeted agents.

In terms of the treatment strategy or approach to disappearing CLMs, owing to the high rate of *in situ* recurrence,

Benoist *et al* (5) noted that i) a complete response on imaging did not mean cure in most patients; ii) medical oncologists should refer patients with resectable CLMs to surgeons before any lesions have completely disappeared; and iii) the sites of lesions disappearing with chemotherapy should be resected. Elias *et al* (7) and Auer *et al* (8) reported a satisfactory rate of *in situ* recurrence with hepatic arterial chemotherapy, indicating a satisfactory level of efficacy. However, given the range of new and effective chemotherapy regimens now available worldwide, this approach should be reconsidered given the concomitant technical problems associated with placement and maintenance of the catheter system. van Vleddler *et al* (9) proposed that aggressive surgery should be considered in patients showing a marked response to chemotherapy, even when all CLM sites could not be identified.

Despite the favorable results observed in the present study, we believe that it is prudent to resect all initially detected sites of CLMs whenever possible. Taking the results of earlier studies into consideration, the following strategies may be appropriate: i) if all the lesions are initially resectable and chemotherapy is administered in an adjuvant setting, then the duration of chemotherapy should be limited; and ii) where preoperative chemotherapy is administered to make initially unresectable lesions resectable, careful follow-up imaging is important to ensure that they are not reduced in size to the point where identifying them intraoperatively would be difficult or impossible for the surgeon. However, the low rate of *in situ* recurrence of approximately 30% at 3 years in our study suggests that the sites of disappearing CLMs may be left untouched, only resecting should they recur.

In conclusion, given the low risk of recurrence *in situ*, the results of the present study suggest that the sites of disappearing CLMs may be left unresected but should be carefully monitored during follow-up, with resection an option if the lesion should recur. These results provide important data on the treatment of disappearing CLMs in the era of new and effective chemotherapy. However, to validate such a treatment strategy, further investigation with larger series of patients is warranted.

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Köhne's Index を用いた切除不能大腸癌肝転移に対する二次治療 FOLFIRI 療法の効果予測

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Predictive Value of Köhne's Index on the Efficacy of FOLFIRI Regimen in the Treatment of Unresectable Liver Metastasis of Colorectal Cancer: Keiichiro Ishibashi, Norimichi Okada, Yusuke Tajima, Kunihiko Amano, Satoshi Hatano, Kouki Kawabara, Jun Sobajima, Toru Ishiguro, Tomonori Ohsawa, Kensuke Kumamoto, Yoichi Kumagai, Hiroyuki Baba, Yoshitaka Tsuji, Norihiro Haga and Hideyuki Ishida (*Dept. of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University*)

Summary

The aim of this retrospective study was to analyze the predictive value of Köhne's index on the efficacy of FOLFIRI regimen in the treatment of unresectable liver metastasis of colorectal cancer. The subjects were 44 patients with unresectable liver metastasis from colorectal cancer treated with FOLFIRI regimen as second-line, for all of whom oxaliplatin-based regimen had previously failed. Bevacizumab was concomitantly used in 23 patients. Classification of the Köhne's index revealed high risk in 22 patients, intermediate risk in 7 patients, and low risk in 15 patients. The response rate was 13.6% in the patients with high risk (H group) and 27.3% in the patients with intermediate or low risk (non-H group) ($p=0.45$). The disease control rate was 50% in the H group and 68.2% in the non-H group ($p=0.36$). In the H group, the median progression-free survival time was 4.1 months and in the non-H group it was 7.1 months ($p=0.33$). Compared with the H group, the non-H group showed significantly better overall survival (10.8 months vs 23.9 months, $p=0.03$). None of the patients has received hepatectomy (conversion therapy). These results suggest that the predictive value of Köhne's index is limited in terms of the effect of shrinkage of liver metastases, including conversion therapy. **Key words**: Colorectal cancer, Köhne's index, Liver metastasis, Chemotherapy

要旨　目的: 切除不能大腸癌肝転移に対し二次治療の効果予測に関する Köhne's index (KI) の有用性について，retrospective に検討した。対象・方法: 切除不能・再発大腸癌肝転移に対し，oxaliplatin ベースの一次治療に failure 後，二次治療に FOLFIRI 療法（bevacizumab 併用 23 例）を施行した 44 例を対象に，二次治療の治療効果と KI との関係について検討した。結果: KI により，high risk 22 例，intermediate risk 7 例，low risk 15 例に分類された。H 群（high risk）と non-H 群（intermediate risk + low risk）の間で，奏効率（14% vs 27%，$p=0.45$），病態制御率（50% vs 68%，$p=0.36$），無増悪生存期間（中央値: 4.1 か月 vs 7.1 か月，$p=0.33$）に差を認めなかったが，全生存期間は non-H 群のほうが有意に良好であった（中央値: 10.8 か月 vs 23.9 か月，$p=0.03$）。肝切除（conversion therapy）が行われた症例はなかった。結語: 大腸癌肝転移に対する二次治療 FOLFIRI 療法の効果予測としての KI の有用性は限定的であり，conversion therapy を踏まえた腫瘍縮小効果の予測に用いることはできないことが示唆された。

はじめに

Köhne ら[1] が切除不能・再発大腸癌に対する 5-fluorouracil (5-FU) を基軸レジメンとした臨床試験のメタアナリシスから，その効果を予測する指標（Köhne's index: KI）を提唱した。近年では，oxaliplatin，irinotecan を含む一次治療における効果予測に関する報告が散見される[2-5] が，二次治療における効果予測に関し KI の有性を検討した報告はほとんどない。

今回，切除不能・再発大腸癌肝転移に対する二次治 FOLFIRI 療法の効果予測に関する KI の有用性を明らにするために retrospective に検討した。

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I. 対象・方法

1. 対 象

当科で2005年12月～2011年3月の間に，肝転移巣を含む切除不能・再発大腸癌に対し二次治療としてFOLFIRI療法を施行した44例を対象とした。全例oxaliplatinベースの一次治療に不応となった症例で，23例（52%）にbevacizumabを併用した。年齢は64.5（31～85）歳，男性27例，女性17例。performance status（PS）はPS 0 20例，PS 1 17例，PS 2が7例であった。初発大腸癌（Stage IV）36例，再発大腸癌8例で，原発巣は結腸27例，直腸17例であった（表1）。

2. 方 法

各々の症例の二次治療導入時のEastern Cooperative Oncology Group（ECOG）のPS，転移臓器数，白血球数，血清アルカリフォスファターゼ値からKIを求め，high risk群，intermediate risk群，low risk群の3群に分けた。high risk（H群）とintermediate risk＋low risk（non-H群）の間で，患者背景，腫瘍縮小効果，無増悪生存期間，全生存期間，肝切除への移行率について比較検討した。腫瘍縮小効果の判定にはRECIST ver1.1[6]を用いた。

3. 統 計

連側変数は中央値（範囲）で記載した。2群間の比較にはχ^2検定またはFischerの直接確率法を，連続変数の比較にはMann-Whitney検定を用いた。生存率はKaplan-Meier法に従って算出し，生存期間の比較にはlog-rank testを用いた。$p<0.05$を有意差ありとした。

表1 患者背景

年齢（歳）*		64.5(31～85)
性別（男性：女性）		27：17
PS	0	20
	1	17
	2	7
初発・再発	初発（Stage IV）	36
	再発	8
原発巣占居部位	結腸	27
	直腸	17
Bevacizumab併用		23（52%）

*: median（range）

表2 H群，non-H群における患者背景

	H群（n=22）	non-H群（n=22）	p value
年齢（歳）*	61.5（32～82）	68（33～81）	>0.99
性別（男性：女性）	10：12	17：5	0.06
二次治療におけるbevacizumab併用	12（55%）	11（50%）	0.17
肝以外の転移臓器	22（100%）	6（27%）	<0.01
一次治療			
mFOLFOX6	13	16	
XELOX	0	1	
mFOLFOX6＋bevacizumab	7	5	
mFOLFOX7＋bevacizumab	2	0	
FOLFIRI投与回数	9（1～44）	9.5（1～70）	0.36
Irinotecanのrelative dose intensity	70.7（34.3～100）	61.6（28.3～100）	0.37
抗EGFR抗体薬使用（三次治療）	6（27%）	6（27%）	>0.99

*: median（range）

II. 結 果

1. 患者背景

high risk群22例，intermediate risk群7例，low risk群15例であった。H群よりnon-H群のほうが男性の比率が高い傾向であったが（$p=0.06$），年齢，bevacizumabの併用については両群間で差を認めなかった。肝以外の転移臓器については，H群では全例に認められたのに対し，non-H群では6例（27%）のみに認めた（$p<0.01$）。FOLFIRIの投与回数，irinotecanのrelative dose intensity，三次治療としての抗EGFR抗体療法の導入率のいずれにおいても，両群間に差を認めなかった（表2）。

2. 腫瘍縮小効果

奏効率はH群14%，non-H群27%（$p=0.45$），病態制御率はH群50%，non-H群68%（$p=0.36$）と，いずれの両群間に有意差を認めなかった（図1）。

3. 無増悪生存期間

無増悪期間中央値はH群4.1か月，non-H群7.1か月（$p=0.33$）で，両群間に有意差を認めなかった（図2a）。

4. 全生存期間

全生存期間中央値はH群10.8か月，non-H群23.9か月で，non-H群のほうが有意に良好であった（$p=0.03$）（図2b）。

5. 肝切除への移行率

肝切除への移行（conversion）が行われた症例は，両群のいずれにも認めなかった。

III. 考 察

KIは，5-FUを基軸レジメンとした場合に全生存期間を予測する指標として提唱されたものである。その後，irinotecanベースの一次治療における全生存期間[2-4]，oxaliplatin，irinotecan，capecitabine併用レジメンにおける腫瘍縮小効果と無増悪生存期間[5]，IFL（irinotecan＋5-FU）±bevacizumab療法における無増悪生存期間[3]との関連があることが報告されている。

今回の結果から，二次治療FOLFIRI療法の効果予測の指標としてKIを用いることの有用性は限定的であり，特に肝転移縮小効果の予測には有用性が乏しいことが明らかになった。

今回，FOLFIRI治療後の全生存期間とKIには関連性が認められたことは注目に値する。わが国では一次治療としてoxaliplatinベースのレジメンが選択されることが多く，したがって二次治療にFOLFIRI療法が選択されることが多い。分子標的薬として何を併用するかという問題は別として，基軸となるFOLFIRI療法を導入する

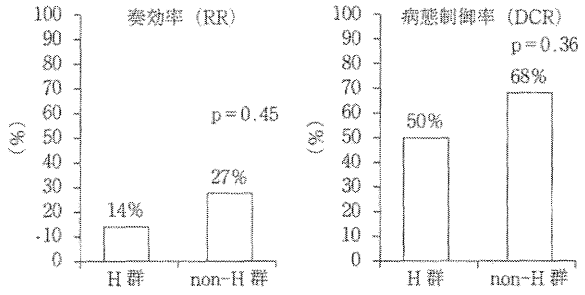

図 1 直接腫瘍縮小効果

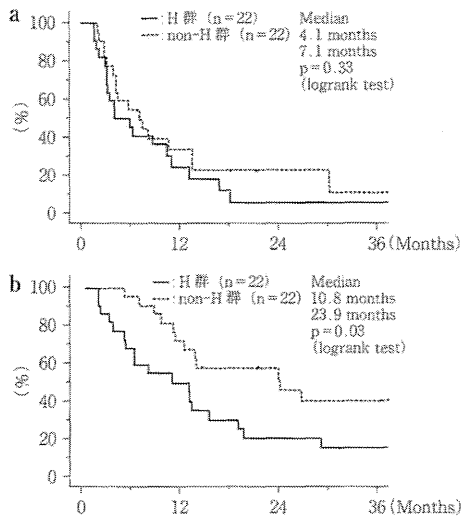

図 2 生存期間
a：無増悪生存期間。b：全生存期間。

際，二次治療開始後の生存期間をある程度予測することは特に重要である。KIでhigh risk群に分類されるような症例ではFOLFIRI療法を選択せず，化学療法を行うのであれば有害事象の少ないレジメン，あるいはbest supportive careを選択することも考慮すべきと思われる。

肝転移が予後規定因子と考えられる症例では，一次治療がfailureした場合には腫瘍縮小効果が速やかに得られるレジメンが望まれることはいうまでもないが，その観点からは確固たるエビデンスは創出されていない。したがって現在においては，二次治療として選択したレジメンの腫瘍縮小効果が予測できれば理想的である。今回の検討では，KIは腫瘍縮小効果をほとんど反映しないことが明らかになった。

大腸癌肝転移の肝切除移行（conversion therapy）は，一次治療で2.5～22%と報告されている[7-10]。実地臨床における二次治療後の肝切除移行率に関する詳細な報告はほとんどない。腫瘍縮小効果はconversion therapyと密接に関連する問題であり，実際，今回の結果からKIは二次治療FOLFIRI療法中のconversionを予測する指標にもなり得ないことが推察され，今回の検討症例のなかでconversion therapyに移行できた症例はなかった。

今回の検討は症例数も少なく単一施設からの後方視的検討であるが，切除・不能再発大腸癌肝転移に対する二次治療FOLFIRI療法において，肝切除（conversion）も含めた治療戦略にKIを積極的に利用する意義は乏しいと考えられた。しかしながら，二次治療FOLFIRI療法後の全生存期間の予測には有用であることが判明した点は興味深い。今後，今回の結果を多数の症例で前向きに確認する必要がある。

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Köhne's Indexによる切除不能・再発大腸癌肝転移に対する一次治療mFOLFOX療法の効果予測

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Prediction of the Efficacy of First-Line Oxaliplatin-Based Chemotherapy for Unresectable Liver Metastases of Colorectal Cancer by Köhne's Index: Norimichi Okada, Keiichiro Ishibashi, Tomonori Ohsawa, Jun Sobajima, Kouki Kuwabara, Kunihiko Amano, Satoshi Hatano, Okihide Suzuki, Kensuke Kumamoto, Yoichi Kumagai, Hiroyuki Baba, Norihiro Haga, Yoshitaka Tsuji and Hideyuki Ishida (*Dept. of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University*)

Summary

Purpose: This retrospective study was undertaken to examine the usefulness of Köhne's index (KI) for predicting the efficacy of first-line oxaliplatin-based chemotherapy for unresectable liver metastases of colorectal cancer. Patients and methods: The subjects were 84 patients with unresectable liver metastases of colorectal cancer in whom first-line oxaliplatin-based chemotherapy was administered. The outcome of treatment was analyzed in relation to the KI. Results: The patients were classified into 3 groups: high risk group (n=12), intermediate risk group (n=20), and low risk group (n=52). There were no significant differences between the groups with regard to response rate, disease control rate, disease-free survival, overall survival, and the rate of conversion to hepatic metastatectomy. Conclusion: Our results suggest that KI might not be useful for predicting the efficacy of first-line oxaliplatin-based chemotherapy for unresectable liver metastases of colorectal cancer. **Key words:** Colorectal cancer, Liver metastases, Chemotherapy, Köhne's index

要旨 目的: 切除不能・再発大腸癌肝転移に対するoxaliplatinベースの一次治療の効果予測に関するKöhne's index (KI) の有用性について, retrospectiveに検討した。対象・方法: oxaliplatinベースの一次治療を行った切除不能・再発大腸癌肝転移84例を対象とし, 治療効果とKIとの関係について検討した。結果: KIにより, high risk群12例, intermediate risk群20例, low risk群52例に分類された。奏効率, 病態制御率, 無再発生存期間, 全生存期間, 肝切除移行率のいずれにおいても, 3群間に有意差を認めなかった。結語: KIは, 切除不能・再発大腸癌肝転移に対するoxaliplatinベースの一次治療の効果予測には有用でないと考えられた。

はじめに

FOLFOX, XELOXなどのoxaliplatinベースの化学療法は, 切除不能大腸癌に対する標準的レジメンとして位置付けられている。近年, このような有効な化学療法は生存期間を著しく延長するだけでなく, 切除不能な転移巣を切除可能にすること (conversion therapy) が報告されている。このconversion therapyは肝転移に対して行われることが多い。しかしながら, oxaliplatinは類洞閉塞[1]や線維化[2]といった肝障害を惹起することが知られている。このような背景から, 切除不能・再発大腸癌肝転移に対しoxaliplatinベースの治療を行う際に, 治療効果が予測できれば理想的である。

2002年にKöhneら[3]が提唱した大腸癌化学療法の効果予測に対する簡便な指標がある (Köhne's index: KI)。このKIは5-fluorouracil (5-FU) ベースの臨床試験のメタアナリシスから導かれたもので, その後の他の臨床試験 (文献) の解析でも生存期間の予測に有用性が認めら

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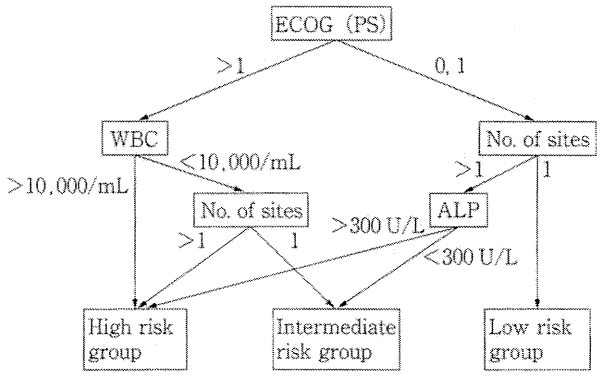
Table 1 Patient characteristics

Sex	
Male	60
Female	24
Age	
Median, Range	68 (32–82)
Liver metastases	
Synchronous	56
Metachronous	28
Location of the primary cancer	
Colon	63
Rectum	21
Regimen	
mFOLFOX6	73
XELOX	11
Bevacizumab	25
Target organ	
Liver only	27
Liver + other	57



Cases	12	20	52
mFOLFOX6	11	18	44
XELOX	1	8	8

(文献[3]より改変)

Fig. 1 Classification of cases according to Köhne's index

れるとする報告[4-6]が散見されるが，oxaliplatin ベースの治療に関する報告[4,6]は少ない。

今回，切除不能・再発大腸癌肝転移に焦点を絞り，oxaliplatin ベースの一次治療の治療効果予測(conversion therapy の可能性も含めて)に関する KI の有用性について，retrospective に検討したので報告する。

I. 対象・方法

1. 対 象

当科にて肝転移を含む切除不能・再発大腸癌に対し，一次治療として mFOLFOX6 または XELOX 療法を施行した 84 例を対象とした。年齢は 68 (32～82) 歳，男性 60 例，女性 24 例。同時性 56 例，異時性 28 例。原発巣は結腸 (RS 含む) 63 例，直腸 21 例。レジメンは mFOLFOX6 73 例 (うち bevacizumab 併用 17 例)，XELOX が 11 例 (同 8 例) であった (Table 1)。なお，二次治療へは 50 例が移行し，移行率は 70.4% であった。

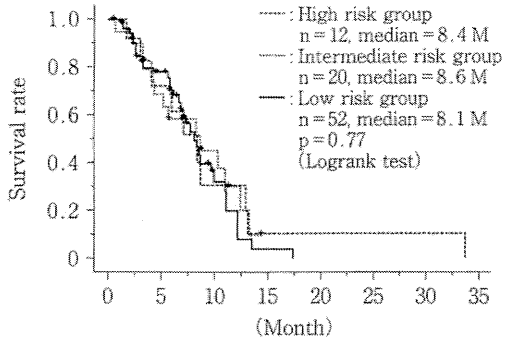


Fig. 2 Survival curve of time to progression (Kaplan–Meier's method)

2. 方 法

各々の症例の mFOLFOX6 あるいは XELOX 導入時の Eastern Cooperative Oncology Group (ECOG) の performance status (PS)，転移臓器数，白血球数，血清アルカリフォスファターゼ値から KI を求め，high risk 群，intermediate risk 群，low risk 群の 3 群に分けた。KI と肝転移縮小効果，生存期間，肝切除移行率との関係について検討した。

3. 統 計

連続変数は中央値 (範囲) で記載した。比率の比較は χ^2 検定で行った。生存率は Kaplan–Meier 法で算出し，生存期間の比較は logrank 検定で行った。$p<0.05$ を有意差ありと判定した。

II. 結 果

1. KI による分類

high risk 群 12 例，intermediate risk 群 20 例，low risk 群 52 例であった (Fig. 1)。

2. 肝転移縮小効果

奏効率は high risk 群 41.6%，intermediate risk 群 44.4%，low risk 群 36.0% で，3 群間に有意差を認めなかった ($p=0.80$)。病勢制御率も high risk 群 83.3%，intermediate risk 群 72.2%，low risk 群 80.0% で，3 群間で有意差を認めなかった ($p=0.72$)。

3. 生存期間

無増悪生存期間中央値は high risk 群 8.4 か月，intermediate risk 群 8.6 か月，low risk 群 8.1 か月であり，3 群間に有意差を認めなかった ($p=0.77$) (Fig. 2)。全生存期間中央値は high risk 群 13.5 か月，intermediate

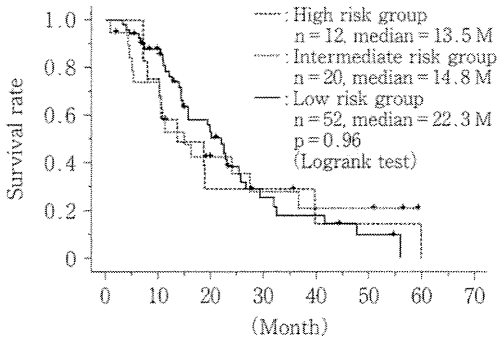


Fig. 3　Survival curve of overall survival (Kaplan-Meier's method)

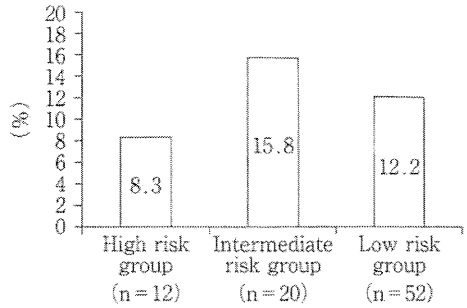


Fig. 4　Ratio of hepatic resection

risk 群 14.8 か月，low risk 群 22.3 か月であり，3 群間に有意差を認めなかった（p = 0.96）（Fig. 3）。

4．肝切除移行率

肝切除移行率は high risk 群 1 例（8.3%），intermediate risk 群 3 例（15.8%），low risk 群 6 例（12.2%）で，3 群間に差を認めなかった（p = 0.82）（Fig. 4）。

III．考　察

KI は，5-FU を基軸に Leucovorin，mitomycin C，methotrexate，interferon などを併用した臨床試験のメタアナリシスから導かれたもので，リスクを前述の 3 群に評価する。オリジナルの報告では，全生存期間と有意に相関することが示されている[3]。その後，KI と大腸癌化学療法の効果の関係について，いくつかの報告がされている。N9741 試験[4] では，FOLFOX，IFL，IROX が行われた患者全体の全生存期間，および無増悪期間と KI の間に有意な相関を認めた。FOLFOX のみのサブ解析では，high risk 群より low risk 群のほうが全生存期間において良好な傾向がみられたものの，統計学的有意差は認めなかった。また Díaz ら[6] も，5-FU と irinotecan あるいは oxaliplatin を含むレジメンにおいて全生存期間の予測に関し KI の有用性を報告している。以上より oxaliplatin ベースの治療では，KI と生存期間の関係については未だ controversial であるといえる。また，KI と腫瘍縮小効果との関係はほとんど検討されていない。

今回の結果から，切除不能・再発大腸癌肝転移に対し一次治療として mFOLFOX6/XELOX 療法を導入した場合，肝転移の縮小効果，肝切除移行率，予後を KI から予測することは困難であることが判明した。その理由は不明であるが，KI の報告ではメタアナリシスに用いた臨床試験が 5-FU を基軸としていたことがあげられる。すなわち，FOLFOX/XELOX よりも PS が低い患者にも投与可能で，しかも治療効果自体が強力でなかったことがあげられる。また，mFOLFOX6/XELOX では PS が比較的保たれている患者に投与される傾向がある上，抗腫瘍効果が腫瘍量の多寡にかかわらず高いために，アルカリフォスファターゼ値のように腫瘍量を間接的に反映する因子が治療効果を反映しなかった可能性がある。実際，近年注目されている conversion は high risk 群においても認めたことはむしろ注目に値する。

今回の検討は症例数が少なく単一施設からの後方視的検討ではあるが，切除不能・再発大腸癌肝転移に対する conversion therapy も含めた治療戦略に KI を積極的に利用する意義は乏しいと考えられた。

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大腸癌同時性・異時性転移切除後の補助化学療法としてのmFOLFOX6療法

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〔*Jpn J Cancer Chemother* 39(12): 2192-2194, *November*, 2012〕

Adjuvant Chemotherapy Comprising Modified FOLFOX6 after Curative Resection of Synchronous or Metachronous Metastasis from Colorectal Cancer: Satoshi Hatano, Keiichiro Ishibashi, Kunihiko Amano, Toru Ishiguro, Kouki Kuwabara, Jun Sobajima, Tomonori Ohsawa, Norimichi Okada, Yoichi Kumagai, Kensuke Kumamoto, Hiroyuki Baba, Yoshitaka Tsuji, Norihiro Haga and Hideyuki Ishida (*Dept. of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University*)

Summary

Purpose: This retrospective study evaluated the outcome of adjuvant chemotherapy comprising modified FOLFOX6 (mFOLFOX6) after potentially curative metastasectomy from colorectal cancer. Patients and methods: The subjects were 40 patients with colorectal cancer who underwent potentially curative metastatectomy without any prior chemotherapy between December 2003 and November 2011. Patient background, type of adjuvant chemotherapy, and prognosis were examined. Results: Adjuvant chemotherapy was given in 30 patients (mFOLFOX6, n=26; oral fluoropyrimidines, n=4). The median relapse-free survival tended to be longer in patients treated with mFOLFOX6 compared to those treated with fluoropyrimidines (28.5 months vs 14.8 months; p=0.11). The median overall survival did not differ significantly between the 2 groups (37.9 months vs 31.3 months, p=0.56). When the analysis was restricted to patients treated with mFOLFOX6, no significant differences were found in relapse-free survival (p=0.46), overall survival (p=0.29), and frequency of adverse events during chemotherapy (Grade 3, p=0.32) between patients with synchronous metastasis (n=11) and those with metachronous metastasis (n=15). Conclusion: These results suggest that mFOLFOX6 might contribute to prolonging the time to relapse and that the timing of developing metastasis (synchronously or metachronously) may not have any effect on the outcome of adjuvant mFOLFOX6. **Key words**: Colorectal cancer, Metastasis, Adjuvant chemotherapy

要旨　目的: 大腸癌転移巣切除後の補助化学療法としてのmFOLFOX6療法の成績について検討した。対象・方法: 2003年12月～2011年11月の間に，術前化学療法を施行せずに転移巣を切除した大腸癌40例を対象とし，患者背景，術後補助化学療法，予後について検討した。結果: 補助化学療法は30例に施行された（mFOLFOX6: 26例，5-FU系経口薬: 4例）。mFOLFOX6施行例のほうが5-FU経口，または化学療法非施例より無再発生存期間が長い傾向（28.5か月 vs 14.8か月，p=0.11）であったが，全生存期間に差がなかった（37.9か月 vs 31.3か月，p=0.56）。mFOLFOX6施行例を同時性転移切除11例と異時性転移切除15例に分けて検討すると，両者の間に無再発生存期間（p=0.46），全生存期間（p=0.29），Grade 3の有害事象発生率（p=0.32）に有意差を認めなかった。結語: ① 大腸癌転移巣切除後のmFOLFOX6療法は無再発生存期間の延長に寄与する，② 転移巣の出現時期は転移切除後のmFOLFOX6の成績に影響を及ぼさないことが示唆された。

はじめに

大腸癌転移再発において，根治切除例に対する術後補助化学療法の有効性を示すエビデンスは認められていない。しかし，stage III結腸癌に対する補助化学療法の有効性が確立されている現在，さらに再発リスクが高いstage IV（同時性）・再発切除（異時性）大腸癌症例に対し，補助化学療法を行うことは容認されるべきものと考えられる。

今回，当科における大腸癌転移巣切除後のmFOLFOX6療法の治療成績を明らかにするためretrospective studyを行った。

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I. 対象・方法

2003年12月～2011年11月の間に，術前化学療法を施行せずに原発巣と同時性転移巣を切除したstage IV大腸癌と，異時性転移巣を切除した大腸癌患者を対象とした。治療法の内訳，mFOLFOX6施行の有無による全生存期間（OS），無再発生存期間（RFS）を検討した。また，mFOLFOX6施行例の患者背景，OS，RFS，再発部位，mFOLFOX6による有害事象について，同時性転移例と異時性転移例の間で比較検討した。なお，転移巣切除後の補助化学療法としてのmFOLFOX6は最低6コース，最高12コースを目標に行った。

有害事象はNational Cancer InstituteによるCTCAE v4.0[1]に基づいて記載した。

統計: 連続変数は中央値（範囲）で記載し，連続変数の2群間の比較はMann-Whitney検定で行った。2群間の頻度（比率）の比較には，Yates補正χ^2検定またはFisherの直接検定を用いた。生存率をKaplan-Meier法で算出し，生存期間の比較はlogrank検定で行った。いずれも$p<0.05$をもって有意差ありと判定した。

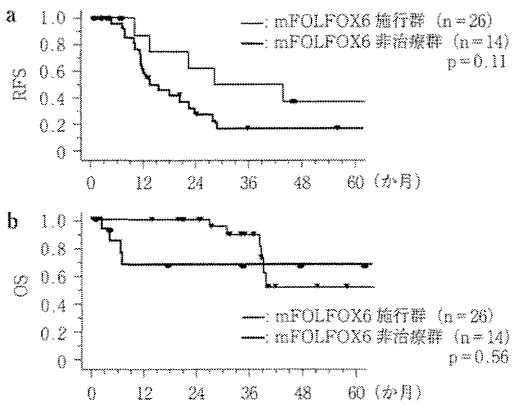

図1　mFOLFOX6の施行，非施行によるRFS，OS

II. 結　果

1. 対象全体の背景因子

同時性・異時性転移切除例は，各々18例，22例であった。補助化学療法は30例に導入され，mFOLFOX6が26例，5-FU系経口薬が4例であった。経口抗癌薬の内訳はS-1とUFT 1例ずつ，UFT＋Leucovorin（LV）が2例であった。術後補助化学療法を導入しなかった理由は，高齢6例，患者本人の希望2例，術後ADLの低下が2例であった。

2. mFOLFOX6導入例・非導入例の比較

mFOLFOX6導入例，mFOLFOX6非導入例（経口5-FU投与例＋補助化学療法非導入例）のRFSの中央値は，各々28.5か月，14.8か月でmFOLFOX6施行例のほうが良好な傾向を認めた（$p=0.11$）（図1a）。OSの中央値は，各々37.9か月，31.3か月で両者に有意差を認めなかった（$p=0.56$）（図1b）。

3. mFOLFOX6導入例の検討

mFOLFOX6施行26例のうち，同時性転移切除（同時性）は11例，異時性転移切除（異時性）は15例であった。表1にmFOLFOX6施行例の臨床病理学的特徴を示した。主な切除臓器は同時性・異時性ともに肝が最多であったが，異時性では肺転移切除の頻度が高い傾向がみられた（$p=0.11$）。年齢（$p=0.66$），性別（$p=0.70$），mFOLFOX6投与回数（$p=0.47$）やoxaliplatin（L-OHP）のdose intensity（$p=0.67$），切除後の再発臓器の種類

表1　Clinicopathological profile of 26 colorectal cancer patients with synchronous and asynchronous distant metastasis

	同時性転移（n＝11）	異時性転移（n＝15）	p値
年齢（歳）	64（42～85）	61（42～88）	0.66
性別（男性/女性）	6/5	7/8	0.7
投与回数	6（5～10）	6（5～12）	0.47
L-OHPのrelative dose intensity（%）	76.9（52.9～100）	85.7（57.0～100）	0.67
転移切除臓器			
肝	6	7	
肺	1	6	
腹膜	3	1	0.11
大動脈周囲リンパ節	1	0	
卵巣	1	1	
（重複あり）			
切除後再発臓器			
肝	1	4	
肺	5	7	
腹膜	2	1	0.74
大動脈周囲リンパ節	0	1	
その他	0	1	
（重複あり）			

表 2　Frequencies of adverse events during adjuvant chemotherapy

	同時性転移群（n＝11）		異時性転移群（n＝15）		p 値	
	Grade 1～3	Grade 3	Grade 1～3	Grade 3	Grade 1～3	Grade 3
All toxicities	11（100%）	5（45%）	15（100%）	4（27%）	>0.99	0.32
Leukopenia	4（36%）	0（0%）	8（53%）	2（13%）	0.39	0.21
Neutropenia	7（64%）	6（55%）	14（93%）	4（27%）	0.06	0.15
Anemia	8（73%）	0（0%）	7（47%）	0（0%）	0.18	>0.99
Anorexia	8（73%）	0（0%）	13（87%）	0（0%）	0.37	>0.99
Vomiting	5（45%）	0（0%）	8（53%）	0（0%）	0.69	>0.99
Diarrhea	4（36%）	0（0%）	11（73%）	0（0%）	0.06	>0.99
Stomatitis	4（36%）	0（0%）	6（40%）	0（0%）	0.85	>0.99
Alopecia	2（18%）	0（0%）	5（33%）	0（0%）	0.39	>0.99
Allergic reaction	1（9%）	0（0%）	1（7%）	0（0%）	0.23	>0.99
Peripheral neuropathy	10（91%）	0（0%）	12（80%）	0（0%）	0.45	>0.99
Protein urea	0（0%）	0（0%）	0（0%）	0（0%）	>0.99	>0.99
Hypertension	0（0%）	0（0%）	0（0%）	0（0%）	>0.99	>0.99

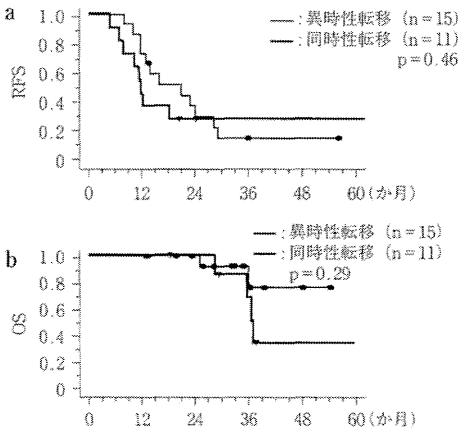

図 2　同時性，異時性別の RFS，OS

（p＝0.74）についても，同時性・異時性の間で有意差を認めなかった。RFS（p＝0.46），OS（p＝0.29）いずれも同時性・異時性の間で有意差は認めなかった（図 2）。

mFOLFOX6 施行中の有害事象を表 2 に示す。Grade 4 の有害事象は認めなかった。Grade 1 以上の何らかの有害事象は全例に認めた。同時性・異時性にかかわらず，白血球減少および好中球減少の頻度が高かった。Grade 3 の有害事象の頻度には同時性・異時性の間で有意差を認めなかった（45% vs 27%，p＝0.32）。

III．考　察

大腸癌遠隔転移切除後の補助化学療法についてのエビデンスは確立されていない。しかしながら近年では，L-OHP ベースの化学療法が進行・再発大腸癌のみならず，stage II，III の結腸癌に対する術後補助化学療法としても有効性が確認されるようになった。MOSAIC 試験[2] では，FOLFOX4 療法は 5-FU＋LV 療法と比較して，5 年無再発生存率，6 年全生存率ともに有意に良好であることが報告された。したがって現状では，stage III 大腸癌よりも術後の再発リスクが高い転移巣切除後の補助化学療法として，エビデンスには乏しいものの実臨床における選択肢の一つとして，FOLFOX などの L-OHP ベースの化学療法が行われていることが多いと思われる。

今回の検討の結果，ランダム化された結果ではないものの，mFOLFOX6 の補助化学療法を受けた症例のほうが受けていない症例より RFS が良好な傾向が得られた点は興味深い。また，大腸癌治療においては一般に，転移巣切除のほうが原発巣切除より，同時性転移切除（原発巣切除とともに行う場合）のほうが異時性転移切除より手術侵襲が大きいと考えられる。今回，stage III 大腸癌治癒切除後と直接比較していないが，有害事象については転移巣切除後の mFOLFOX6 は認容できると考えられた。しかしながら，頻度が高い好中球減少，白血球減少には特に注意が必要であることが判明した。いずれにしても，今後とも症例を集積し，大腸癌転移巣切除後の L-OHP ベースの補助化学療法の効果と安全性について結論をだすべきと考えられる。

文　献

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K-Ras 野生型切除不能再発大腸癌における一次治療 Bevacizumab 併用 Oxaliplatin ベース化学療法の治療成績

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〔*Jpn J Cancer Chemother* 39(12): 2185-2188, *November*, 2012〕

Clinical Outcomes in Refractory Colorectal Cancer Patients with Wild-Type K-Ras Treated with Bevacizumab and Oxaliplatin-Based Chemotherapy as a First-Line Treatment: Hideko Imaizumi, Keiichiro Ishibashi, Norimichi Okada, Yusuke Tajima, Kunihiko Amano, Satoshi Hatano, Kouki Kuwabara, Jun Sobajima, Toru Ishiguro, Tomonori Ohsawa, Kensuke Kumamoto, Yoichi Kumagai, Norihiro Haga and Hideyuki Ishida (*Dept. of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University*)

Summary

The clinical outcomes, including adverse events, in 34 unresectable advanced colorectal cancer patients with wild-type K-ras, who were treated with bevacizumab and oxaliplatin-based chemotherapy as a first-line treatment, were analyzed for confirmation of the effectiveness and safety of this treatment. The response rate of the patients was 44% (complete remission, 2 patients; and partial remission, 13 patients). The median progression-free survival and overall survival in these patients was 11.1 and 25.1 months, respectively. Adverse events of greater than grade 3 were observed in 18 patients. Of these patients, 10 exhibited grade 3/4 neutropenia, and 6 had peripheral neuropathy. Our results were similar to those of randomized phase III trials from abroad, including those using anti-epidermal growth factor receptor antibody, with respect to effectiveness and safety. Furthermore, patients with liver metastasis had poor prognosis compared to those with metastasis to organs other than the liver. Further analysis will be required to better understand these results. **Key words:** Unresectable advanced colorectal cancer, Wild-type K-ras, Chemotherapy

要旨　一次治療で bevacizumab（Bmab）併用 oxaliplatin（L-OHP）ベースの化学療法を行った K-ras 野生型の切除不能再発大腸癌 34 例を対象に治療成績を調べ，その有効性と安全性について検討した。奏効率は，CR 2 例，PR 13 例で 44%であった。無増悪期間の中央値は 11.1 か月，全生存期間は 25.1 か月であった。有害事象は，grade 3 以上が 18 例（53%）に認められ，好中球減少 10 例と末梢神経障害 6 例であった。今回の結果は，これまで報告されてきた抗 EGFR 抗体を含む第 III 相試験での治療成績とほぼ同等の成績であり，一次治療での Bmab 併用の L-OHP ベースの化学療法の有効性と安全性を確認することができた。また，肝転移を標的病変とする症例と肝以外を標的病変とする症例では，肝転移を標的とする症例の予後が不良であることが示唆された。この点については今後の症例を集積し，さらなる検討が必要であると考えられた。

緒　言

切除不能再発大腸癌に対する化学療法は，新規分子標的薬の登場により治療レジメンが多様化している。特に一次治療では，oxaliplatin（L-OHP）や irinotecan（CPT-11）を基軸とした化学療法に抗 VEGF 抗体である bevacizumab（Bmab），あるいは K-ras 野生型に対しては抗 EGFR 抗体薬である cetuximab や panitumumab の分子標的薬を併用することが可能である。そこで，K-ras 野生型の切除不能再発大腸癌症例に一次治療でどのレジメンを用いるかは，施設間によって異なっているのが現状である。今回，一次治療で Bmab 併用の L-OHP ベースの化学療法を行った K-ras 野生型の切除不能再発大腸癌症例を対象に retrospective に治療成績を調べ，その有効性と安全性について検討した。また，今回の成績について抗 EGFR 抗体薬を併用した海外の大規模臨床試験の治療成績と比較した。

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表 1 患者背景

野生型（n＝34）			
年齢 68（34～84）歳			
性別（男性：女性）18：16			
レジメン			
一次治療	二次治療		三次治療	
mFOLFOX6＋Bmab（18 例）	FOLFIRI	1 例	Cmab	1 例
	FOLFIRI＋Bmab	13 例	CPT-11/Cmab	5 例
			FOLFIRI＋Pmab	1 例
			Pmab	1 例
mFOLFOX7＋Bmab（4 例）	FOLFIRI＋Pmab	1 例		
	FOLFIRI＋Bmab	2 例		
XELOX＋Bmab（12 例）	FOLFIRI	1 例		
	FOLFIRI＋Bmab	3 例		
対象臓器個数 2（1～4）				
対象病変 肝 19				
肺 19				
リンパ節 12				
腹膜 3				
原発巣 7				
骨 2				
L-OHP DI 73.0（60.0～100）				

表 2 直接奏効割合

効果	野生型（n＝34）
CR	2
PR	13
SD	18
PD	1
奏効率 CR＋PR	15（44.1%）
病態制御率 CR＋PR＋SD	33（97.1%）

I. 対象・方法

2007 年 1 月～2011 年 12 月の間に，標的病変を有する切除不能再発大腸癌に対して Bmab 併用 L-OHP ベースの化学療法が施行され，retrospective な検討により腫瘍の K-ras status が確認できた 53 例のうち，K-ras 野生型であった 34 例を対象とした。患者背景を表 1 に示す。年齢の中央値は 68 歳，男女比は 18：16 であり，一次治療として mFOLFOX6＋Bmab が 18 例，mFOLFOX7＋Bmab が 4 例，XELOX＋Bmab が 12 例に施行された。また二次治療は 21 例に行われ，三次治療は 8 例に行われた。対象臓器個数の中央値は 2 個であり，L-OHP の dose intensity は 73.0%であった。また，34 例中で肝転移を標的病変とした症例は 19 例（56%）であり，標的としない病変は 15 例（44%）であった。

対象症例での腫瘍縮小効果，無増悪生存期間（progression-free survival: PFS），全生存期間（overall survival: OS），有害事象について検討し，また肝転移を標的病変とする症例と肝以外の標的病変を有する症例間でも同様の項目を検討した。治療の効果判定は，RECIST ver1.1 分類に従った。有害事象の評価は，Common Terminology Criteria for Adverse Events（CTCAE）ver4.03 に準じた。

連側変数の記載は中央値（範囲）で記載した。生存率は，Kaplan-Meier 法を用いて算出し，生存期間は log-rank 検定にて比較し，$p<0.05$ を有意差ありとした。

II. 結 果

腫瘍縮小効果: CR 2 例，PR 13 例，SD 18 例，PD が 1 例であり，奏効率 44.1%，病態制御率は 97.1%であった（表 2）。

生存期間: PFS の中央値は 11.1 か月，OS の中央値は 25.1 か月であった（図 1）。

有害事象: 全症例に何らかの有害事象が認められた（表 3）。grade 3 以上の有害事象は 53%に認められ，好中球減少症が 10 例（29%）と最も多く，次いで末梢神経障害が 6 例（18%）にみられた。Bmab に特有の有害事象では，高血圧 1 例で grade 3 が認められ，消化管穿孔を伴った症例が 1 例あった。

肝とそれ以外の臓器を標的病変とする症例間の治療成績: 肝転移を標的病変とする症例（L 群）19 例と，肝以外の臓器を標的病変とする症例（NL 群）15 例について