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Analysis of Preoperative Prognostic Factors for Long-term Survival After Hepatic Resection of Liver Metastasis of Colorectal Carcinoma

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Hepatic resection is the most effective therapy for liver metastasis of colorectal carcinoma. To clarify indications for this therapy, the clinicopathologic and follow-up data of 103 consecutive patients who underwent hepatic resection for metastases of colorectal carcinoma were analyzed. Factors influencing overall survival rate were investigated by multivariate analysis. Thereafter, patients who underwent resection were stratified according to the number of independent risk factors present, and their outcomes were compared with those of 14 nonresection patients with fewer than six liver tumors and without extrahepatic metastasis. The overall survival rate of the 103 resection patients was 43.1%. The clinicopathologic factors shown to affect on long-term survival after hepatic resection were the interval between colorectal and hepatic surgery (<12 months), preoperative carcinoembryonic antigen level (≥10 ng/ml), and number of hepatic metastases (four or more). The 5-year overall survival rates were 75.0% with no risk factors (n = 16), 53.6% with one risk factor (n = 46), 23.0% with two risk factors (n = 36), and 0% with three risk factors (n = 5). Survival rates did not differ between resection patients with three risk factors and nonresection patients. Therefore, hepatic resection may be appropriate for patients with fewer than three risk factors. (J GASTROINTEST SURG 2005;9:374–380)

KEY WORDS: Colorectal carcinoma, liver metastasis, hepatic resection, risk factor, prognosis

The incidence of colorectal carcinoma has increased worldwide, and synchronous or metachronous liver metastasis occurs in about 30% of cases. Hepatic resection is considered the most effective therapy for metastasis of colorectal carcinoma to the liver, and the overall survival rate after hepatic resection is reported as 26%–51%.[1–10] Several clinicopathologic factors predictive of patient survival after hepatic resection have been identified: status of the primary colorectal carcinoma (tumor stage and grade),[1,2,4,6,8,9] interval between colorectal and hepatic surgery,[1,2,4,5,9] number of hepatic metastases,[1,3–9] distribution of hepatic tumors,[3,7] size of the liver tumor,[3,4,5] preoperative serum carcinoembryonic antigen (CEA) level,[10] and nodal metastasis in the hepatic hilum.[1,3,8] Most investigators agree that the interval between colorectal and hepatic surgery, number of hepatic tumors, and status of the primary colorectal cancer are the most important predictors of long-term survival.

Several investigators have proposed staging of colorectal liver metastasis; stages would predict postoperative survival of patients.[3,4,9,11] Fortner et al.[11] listed the risk factors as invasion of a major intrahepatic vessel or bile duct, distribution of the hepatic tumors, invasion of perihepatic organs, and distant metastasis including nodal metastasis. Gayowski et al.[3] listed factors such as the number of metastatic tumors (solitary versus multiple), size of metastasis (larger or smaller than 2 cm in diameter), location of the liver tumor (one or both lobes), major vessel invasion, and extrahepatic metastasis. Ueno et al.[9] proposed a preoperative staging system based on the primary tumor features (degree of tumor budding and nodal status), time to the diagnosis of liver metastases, and number of liver tumors. Unfortunately, all three of these staging systems include many factors and are too complex for preoperative use. The search continues

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for a simple preoperative staging system for liver metastasis of colorectal carcinoma.

The prognosis of patients with colorectal liver metastasis who undergo nonsurgical treatment or who do not undergo treatment remains very poor, despite advances in chemotherapy.[12–15] The median survival time of patients who receive nonsurgical treatment is reportedly less than 20 months.[12–15] In a randomized controlled study of the outcomes of patients who underwent various treatments for multiple (<15) resectable colorectal liver metastases, Wagman et al.[14] observed no significant difference between resection and nonresection patients. Their results and results of other investigations into risk factors have led to the notion that careful selection of patients for hepatic resection of metastases from colorectal cancer is necessary to improve long-term survival, but the indications for hepatic resection for liver metastasis of colorectal cancer have not been well established. Absolute contraindications for resection of liver metastases from colorectal carcinoma have not been clearly defined, but most investigators agree that patients should not be offered hepatic resection if they have uncontrolled primary disease or such widespread hepatic involvement that residual liver function after resection would be inadequate.[16] Aggressive surgical management of multiple colorectal liver metastases has reportedly improved survival of selected patients.[17,18]

In the present study, we attempted to clarify the preoperative risk factors affecting long-term survival after hepatic resection for colorectal liver metastasis and to propose a staging system for predicting long-term postoperative results. In addition, to clarify the indications for resection in cases of liver metastasis of colorectal carcinoma, we compared the long-term survival of resection patients stratified by risk factors with that of nonresection patients.

MATERIAL AND METHODS

During the period of January 1985 through December 2003, 125 patients with liver metastases from colorectal cancer underwent hepatic resection at the Department of Surgery I, Oita University Faculty of Medicine. Twenty-two patients were excluded from the study: three (2.4%) who died of postoperative complications within 30 days, two who had obvious residual tumor at the time of surgery, seven who underwent hepatic resection and thermal ablation therapy for residual hepatic tumors, seven who had extrahepatic metastasis before or at the time of hepatic resection, one who was lost to follow-up, and two for whom clinicopathologic data were unclear. All 103 patients were regularly followed at our outpatient clinic and monitored for recurrence by assessment of serum tumor markers every 2 months and by ultrasonography or contrast-enhanced computed tomography scanning every 4 to 6 months.

We investigated 10 clinicopathologic variables pertaining to patient characteristics, clinical data, and histopathologic findings such as gender, age, interval between colorectal and hepatic resection, number of hepatic metastases, tumor diameter, preoperative CEA level, site of primary tumor, Dukes classification, tumor differentiation of primary tumor, and extent of surgical resection (Table 1). The extent of surgical resection was defined according to Couinaud's classification system; minor hepatic resection as resection of less than two segments and major hepatic resection as resection of two or more segments. Patient outcomes were determined on the basis of clinical data obtained from files as of January 31, 2004. Thus, the mean and median follow-up periods of the 103 patients after hepatic resection were 37.8 and 24.0 months, respectively (range, 1–226 months). The prognostic significance of clinicopathologic factors in relation to cancer-related overall survival rates was investigated by univariate and multivariate analyses. Data were censored in the analysis of overall survival if a patient was living or had died of unrelated disease and in the analysis of disease-free survival if a patient was living or had died of unrelated disease without recurrent colorectal carcinoma. Survival rates were calculated by the Kaplan-Meier method and compared statistically by univariate log-rank analysis. Variables with a value of $P < 0.1$ in univariate analysis were used in subsequent multivariate analysis based on Cox's proportional hazards model.

During the same period, 27 patients with colorectal liver metastasis and no extrahepatic metastasis received nonsurgical treatment at our hospital. Fourteen of these patients who had fewer than seven liver metastases were compared on the basis of clinicopathologic factors and outcome after admission with the 103 resection patients stratified by the number of risk factors. In the comparisons of clinicopathologic factors and treatment methods, continuous variables were analyzed by Kruskal-Wallis test, and nominal variables were analyzed by Fisher's exact probability test. A value of $P < 0.05$ was considered significant in all analyses. Statistical analysis was performed with JMP software (JMP, SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

The 103 patients who underwent hepatic resection with a curative intent included 56 men and 47

Table 1. Results of univariate analysis of clinicopathologic factors affecting overall survival rate after hepatic resection

Clinicopathologic variable	No. of patients	5-Year survival rate (%)	Univariate analysis: *P* value	MULTIVARIATE ANALYSIS	
				Relative risk (CI)	*P* value
Gender					
Male	56	41.1	0.89	—	—
Female	47	46.6			
Age (yrs)					
≤60	32	40.7	0.47	—	—
>60	71	45.0			
Interval (mos)*					
<12	66	33.1	0.03	2.12	0.04
≥12	37	61.2		(1.04–4.74)	
No. of metastasis					
<4	97	45.8	<0.01	3.22	0.04
≥4	6	0		(1.06–8.11)	
Tumor diameter (cm)					
<5	76	47.7	0.14	—	—
≥5	27	32.6			
Preoperative CEA (ng/ml)					
<10	42	65.2	0.01	2.17	0.04
≥10	61	30.0		(1.05–4.95)	
Primary site					
Colon	71	40.4	0.85	—	—
Rectum	32	48.5			
Dukes stage					
A or B	44	48.0	0.32	—	—
C	59	39.6			
Tumor differentiation					
Well	48	39.4	0.21	—	—
Nonwell	54	45.9			
Surgical procedure†					
Minor	60	40.4	0.66	—	—
Major	43	47.9			

CEA = carcinoembryonic antigen; CI = confidence interval.
*Interval between colorectal and hepatic surgery.
†Minor hepatic resection as resection of less than two segments and major hepatic resection as resection of two or more segments.

women with a mean age of 64.0 years. The mean interval between colorectal and hepatic surgery was 13.4 months (range, 0–103 months). The mean number and size of hepatic tumors were 1.6 (range, 2–6) and 42.4 mm (range, 10–130 mm), respectively. Sixty-seven patients had one metastatic liver tumor, 19 had two, 11 had three, 3 had four, 2 had five, and 1 had six. The mean preoperative serum level of CEA was 91.9 ng/ml (range, 0–1637 ng/ml; median, 17.6 ng/ml). The primary tumor was located in the colon in 71 (68.9%) patients and in the rectum in 32 (31.1%) patients. According to the Dukes classification system, 44 (42.7%) of the primary tumors were stage A or B and 59 (57.3%) were stage C. Histologically, there were 48 well-differentiated primary tumors (including one papillary adenocarcinoma) and 54 non–well-differentiated primary tumors (50 moderately differentiated and 3 poorly differentiated tumors and 1 adenosquamous carcinoma). Forty-three patients underwent major hepatic resection and 60 underwent minor hepatic resection (limited resection, 38; segmentectomy, 18; segmentectomy plus limited resection, 4).

Survival Analyses

Of the 103 patients who underwent hepatic resection with a curative intent, 45 patients had died by January 31, 2004. The causes of death were colorectal cancer (n = 39), liver failure unrelated to viral infection (n = 2), liver cirrhosis related to hepatitis viral infection (n = 1), acute myocardial infarction (n = 1), pneumonia (n = 1), and necrotizing myositis (n = 1). The 5-year overall and disease-free survival

rates of the 103 patients were 43.1% and 30.0%, respectively. Univariate analysis identified a short interval between colorectal and hepatic resection (<12 months), increased number of hepatic metastases (four or more tumors), and elevated preoperative CEA level (≥10 ng/ml) as adverse prognostic factors ($P < 0.1$) for overall survival after hepatic resection. Multivariate analysis also indicated that a short interval between colorectal and hepatic resection (relative risk [RR], 2.12; confidence interval [CI], 1.04–4.74], increased number of hepatic metastases (RR, 3.22; CI, 1.06–8.11), and elevated preoperative CEA level (RR, 2.17; CI, 1.05–4.95) were significant factors affecting overall survival after hepatic resection.

Preoperative Staging for Colorectal Liver Metastasis and Comparison Between Resected and Nonresected Patients

All patients were assigned a score (0–3) according to the number of risk factors present (Table 2). In the resection group, 16 patients had a score of 0, 46 had a score of 1, 36 had a score of 2, and 5 had a score of 3. In the nonresection group, 1 patient had a score of 0, 6 had a score of 1, 12 had a score of 2, and 12 had a score of 3. Survival curves were drawn for resection patients, who were stratified by the number of risk factors present. The 5-year cumulative survival rates after hepatic resection were 75.0% in score 0 patients, 53.6% in score 1 patients, 23.0% in score 3 patients, and 0% in score 3 patients (Fig. 1). The survival rate after hepatic resection was significantly lower in patients with a score of 3 than in patients with other scores ($P < 0.01$ for each, log-rank test).

To clarify the contribution of hepatic resection to survival outcomes, we compared the survival curves of resection and nonresection patients. The nonresection patients had not undergone hepatic resection because of multiple bilobar metastases (n = 8), poor residual liver function (n = 2, due to idiopathic portal hypertension and with liver cirrhosis related to hepatitis C virus infection), refusal of hepatic resection (n = 2), tumor thrombosis in the portal trunk (n = 1), and extensive invasion to the inferior vena cava (n = 1). The preoperative serum CEA level was not determined in one patient in the nonresection group. Clinicopathologic factors are shown according to risk scores and in comparison with those in the nonresection group in Table 3. The number of hepatic metastases was significantly higher ($P = 0.02$) in the score 3 resection group than in the nonresection group. There were no significant differences in other clinicopathologic factors between the score 3 resection group and the nonresection group, and there was no significant difference in survival between the score 3 resection group and the nonresection group (Fig. 1).

Table 2. Proposed criteria for preoperative staging of colorectal liver metastasis without extrahepatic metastasis

Positive risk factor	Score
Interval between hepatic and colorectal surgery	
≥12 mo	0
<12 mo	1
No. of liver metastases	
<4	0
≥4	1
Preoperative CEA level (ng/ml)	
<10	0
≥10	1

CEA = carcinoembryonic antigen.

DISCUSSION

Hepatic resection is accepted as the most effective therapy for patients with colorectal liver metastasis. Patient outcomes after hepatic resection have improved during the past two decades. According to recent studies, the 5-year survival rates after hepatic resection have been about 40%.[5,7,8,10] This improvement in survival is due not only to improvements in surgical techniques and postoperative management but also to selection of patients for resection based on risk factors affecting survival. Many investigators report risk factors for adverse outcome after hepatic resection and propose that these factors be used for patient selection. The interval between colorectal and hepatic surgery,[1,2,4,5,9] number of hepatic tumors,[1,3–9] preoperative CEA level,[10] and status of the primary colorectal cancer[1,2,4,6,8,9] are considered the most important predictors of outcome. As in previous studies, the important predictors of adverse patient outcome in this study were a short interval between colorectal and hepatic resection (<12 months), high number of liver metastases (four or more), and elevated preoperative CEA level (≥10 ng/ml). Many authors include therapeutic factors such as surgical margin[1,2,4–7,10] or histologic features of hepatic tumors[7,19] in their assessment of survival risks. Because the aim of this study was to clarify the preoperative risk factors affecting long-term survival after hepatic resection and to propose a preoperative staging system, we excluded therapeutic factors and histopathologic characteristics of hepatic tumors from the analysis.

Several authors have proposed preoperative staging systems for liver metastasis of colorectal cancer to predict patient survival after hepatic resection.

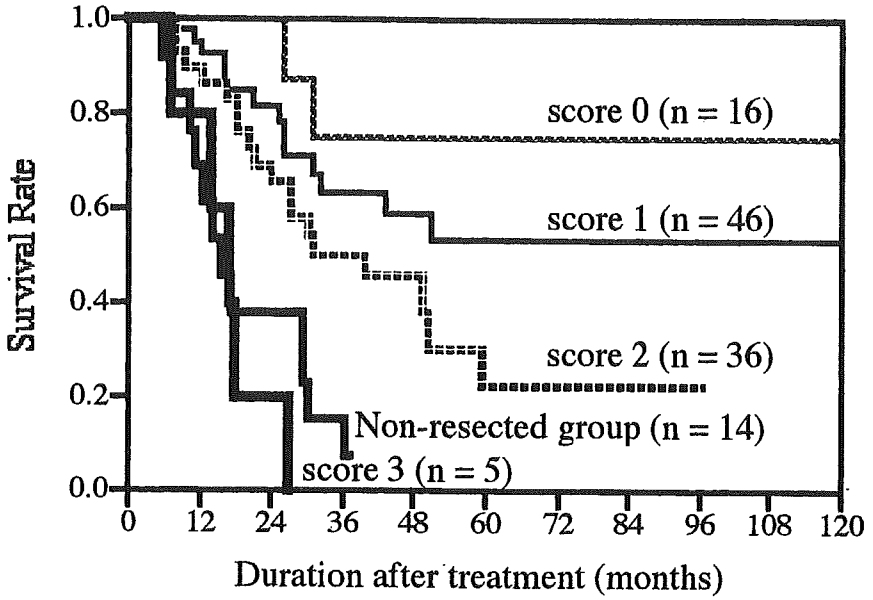

Fig. 1. Cumulative survival curves after admission according to risk factor scores (0–3). The 5-year cumulative survival rates after hepatic resection are 75% for score 0, 53.6% for score 1, 23.0% for score 2, and 0% for score 3 patients. Survival rates did not differ significantly between resection score 3 patients and nonresection patients.

Fortner et al.[11] proposed a three-stage system: stage I indicates hepatic tumor without invasion of major intrahepatic vessels or bile ducts; stage II, regional spread (tumor rupture, direct extension to adjacent organs, histologically positive resection margin) or direct invasion of major vessels or bile ducts; and stage III, presence of lymph node metastases and other intra-abdominal or distant metastases. Gayowski et al.[3] proposed a TNM staging system for colorectal liver metastases based on tumor distribution, number of metastases, tumor size, and presence of disease not confined to the liver. They also included invasion of

Table 3. Patient characteristics in the resection and nonresection groups

	RESECTION GROUPS (n = 103)				
	Score 0 (n = 16)	Score 1 (n = 46)	Score 2 (n = 36)	Score 3 (n = 5)	Nonresection group (n = 14)
Gender					
Male	12	26	16	2	7
Female	4	20	20	3	7
Mean age (yr)	63.4	61.9	65.3	69.8	62.1
Mean interval (mo)*	34.4	13.4	5.5	3.0	1.9
Mean No. of liver tumors	1.1	1.3	1.8	4.6	2.9
Mean CEA (ng/ml)	2.6	62.7	174.0	56.3	101.0
Mean tumor diameter (cm)	4.4	4.0	4.5	4.0	5.9
Primary site					
Colon	10	30	27	4	9
Rectum	6	16	9	1	5
Dukes stage					
A or B	9	22	12	1	4
C	7	24	24	4	10
Tumor differentiation					
Well	8	22	17	1	4
Nonwell	8	23	19	4	10

CEA = carcinoembryonic antigen.
*Interval between colorectal and hepatic surgery.

a major vessel or bile duct in the scoring. Nordlinger et al.[4] proposed a prognostic scoring system in which seven variables were considered adverse factors: age greater than 60 years, diameter of the largest lesion greater than 5 cm, extension of the primary cancer into the serosa, lymphatic spread of the primary cancer, disease-free interval less than 2 years, number of liver nodules of four or more, and resection margin less than 1 cm. Because this scoring system includes intraoperative or histologic factors (invasion to major vessels or bile ducts and surgical margin), [3,4,11] it cannot be used for preoperative assessment of hepatic metastasis. Other authors have proposed scoring systems that include only preoperative factors. Fong et al.[20] developed a preoperative clinical scoring system for predicting recurrence after hepatic resection. They listed five adverse preoperative factors: node-positive primary cancer, disease-free interval before the discovery of liver metastases less than 12 months, number of tumors greater than one, preoperative CEA level greater than 200 ng/ml, and diameter of the largest tumor greater than 5 cm. Ueno et al.[9] proposed prognostic staging before hepatectomy on the basis of three factors: primary site aggressiveness (marked tumor budding and/or extended nodal metastasis), time of diagnosis (synchronously or <1 year after the primary surgery), and number of liver metastases of three or more. However, this system was too complicated for clinical use. The three independent risk factors identified in our study, and the associated four-point scoring system, partly resemble the system of Fong and colleagues.[20] In studies incorporating a prognostic scoring system, the 5-year survival rate after hepatic resection was about 60% in the low-score group and about 20% in the high-score group.[3,9,20] The survival results in the equivalent preoperative score group in our study agree with those of the previous survival investigations.[3,9,20]

The indications for hepatic resection for colorectal liver metastasis have remained controversial. The previous studies of hepatic resection did not lead to strict criteria for hepatic resection. There are no established contraindications to resection of colorectal liver metastasis, but the procedure is not generally offered to patients with uncontrolled primary disease or such widespread hepatic involvement that residual liver function after resection would be inadequate.[16] Recent studies show that resection of multiple bilobar hepatic metastases or both liver and pulmonary metastases can result in long-term survival in selected patients.[17,18] Some investigators specify indications for hepatic resection such as good control of the primary tumor, no sign on preoperative images of disseminated disease, and expected complete resection of hepatic metastasis with acceptable postoperative hepatic function.[5,6,8,20] In the present study, the survival rate of score 3 patients did not differ from that of the selected (no extrahepatic metastasis and fewer than seven hepatic tumors) nonresection patients. Despite the small number of patients in our study, our results suggest that hepatic resection should not be offered to patients with three risk factors present.

The prognosis of nonresection patients with colorectal liver metastasis is reportedly very poor. Wagner et al.[12] investigated the natural history of colorectal liver metastases and reported that the 3-year survival rate was 21% in patients with solitary lesions, 6% in patients with multiple unilateral lesions, and 4% in patients with multiple widespread lesions. Steele et al.[15] compared outcomes associated with curative resection, noncurative resection, and no resection and reported that noncurative resection provides no benefit to asymptomatic patients because patients who undergo noncurative resection have a life expectancy similar to that of patients treated nonsurgically. Wagman et al.[14] performed a randomized evaluation of the treatment of colorectal liver metastasis. In their study, patients with multiple surgically resectable liver metastases (<15 metastases, no involvement of portal structures, and <50% liver involvement) were randomized to complete resection with adjuvant chemotherapy or to chemotherapy only. The median survival time did not differ significantly between resection (19.8 months) and nonresection (22.4 months) patients. In their series, the mean number of hepatic tumors was greater in the nonresection group (mean, 2.9; range, 2–7) than in the resection group (mean, 4.5; range, 4–10). No other risk factors were described. In the present study, the survival rate after hepatic resection in patients with a risk score less than 3 was superior to that in resection patients with a score of 3 and in nonresection patients. All resection patients with a score of 3 died within 3 years after hepatic resection.

In conclusion, the three factors adversely affecting survival after hepatic resection for colorectal liver metastasis are a short interval between colorectal and hepatic surgery (<12 months), elevated preoperative CEA level (≥10 ng/ml), and more than four hepatic metastases. Therefore, hepatic resection may be appropriate for patients with fewer than three risk factors.

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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Liver metastasis and ICAM-1 mRNA expression in the liver after carbon dioxide pneumoperitoneum in a murine model

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Abstract
Background: Liver metastasis of colorectal malignancies is an important prognostic factor. Several studies have demonstrated that carbon dioxide (CO_2) pneumoperitoneum enhances liver metastasis in animal models. Little is known about intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor-alpha (TNF-(α) mRNA expression in the liver after CO_2 pneumoperitoneum.
Methods: Forty-five male BALB/c mice were randomly divided into three groups after intra-splenic tumor cell (colon 26) inoculation and the following procedures were performed: CO_2 pneumoperitoneum (n = 15), open laparotomy (n = 15), and anesthesia alone (n = 15). On day 7 after each procedure, the livers were excised and the number and diameter of the tumor nodules and the cancer index score were determined. Another 90 male BALB/c mice were randomly divided into three groups as described above, and they underwent each procedure (n = 30 each). After each procedure, the livers were excised on days 0, 1, 3, and ICAM-1 and TNF-α mRNA expression were examined by real-time RT-PCR using SYBR Green I.
Results: The number of tumor nodules and the cancer index score were larger in the CO_2 pneumoperitoneum group than in the control group ($p < 0.05$). The mean diameter of the tumor nodules was not different among the three groups. The expression of ICAM-1 in the CO_2 pneumoperitoneum group was higher than that in the other groups on day 1 ($p < 0.05$), and the TNF-α mRNA was higher than that in the control group on day 1 ($p < 0.05$).
Conclusions: CO_2 pneumoperitoneum enhances liver metastasis compared with anesthesia alone, and ICAM-1 expression in the liver after the pneumoperitoneum plays an important role in establishing liver metastasis in a murine model.

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Key words: pneumoperitoneum — Liver metastasis — Adhesion molecules — Murine model — Real-time RT-PCR — ICAM-1

The liver is the most frequent site of tumor metastasis in colorectal carcinoma, and liver metastasis is the most important prognostic factor in patients with primary colorectal cancer. Recently, the use of laparoscopic colorectal surgery has increased because it has become less invasive and because early recovery has become possible. Several randomized controlled trials (RCTs) showed better early short-term outcomes of laparoscopic colectomy [2, 26], but few RCT have been performed with regard to long-term outcomes [16, 17, 24], and the influence of CO_2 pneumoperitoneum on cancer progression is still controversial. In experimental studies, Ishida et al. and Gutt et al. have demonstrated that CO_2 pneurnoperitoneum enhances liver metastasis, and these researchers concluded that hepatic ischemia by CO_2 insufflations may be one of the causes of this phenomenon [7, 8, 10]. Furthermore, previous studies have demonstrated that CO_2 pneumoperitoneum reduces portal blood flow [11, 20, 21].

An important first step in establishing liver metastasis is for free tumor cells to adhere to the hepatic vascular endothelial surface. Yadav et al. have shown that ICAM-1 mediates reperfusion injury in the warm ischemic mouse liver [27]. Alexiou et al. have demonstrated that the serum level of ICAM-1 may reflect tumor progression and metastasis in colorectal cancer patients [1]. However, the expression of ICAM-1 and TNF-α mRNA in the liver after CO_2 pneumoperitoneum has not been clearly established.

In the present study, we investigated the effect of CO_2 pneumoperitoneum and the role of local ICAM–1 expression in establishing liver metastasis in an animal model.

Materials and methods

Animals

All animals were kept under standard laboratory conditions (temperature 20–24°C, relative humidity 50–60%, 12-h light/dark cycle) and were given a standard laboratory diet with free access to water *ad libitum* before and after surgery. All experiments were performed according to the guidelines for animal experimentation of Oita University. This study was performed using a murine pneumoperitoneum model [22]. A total of 135 male BALB/c mice, preserving T- and B-cell immunity, aged 6–8 weeks and weighting 20–24 g, were used. All surgical procedures were performed under ether anesthesia.

Tumor cell line

A mouse colon carcinoma cell line, colon 26 [13, 25], was maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum and penicillin-streptomycin at 1000 IU/ml and incubated in a humidified atmosphere of 95% air and 5% CO_2 at 37°C. For the establishment of liver metastases, tumor cell suspension of 1×10^6 cells/0.1 ml in PBS was used.

Operative procedure

All surgical procedures was done under general anesthesia induced by diethyl ether inhalation. A total of 135 BALB/c mice (including both experiments 1 and 2) were divided into three operative groups. In the pneumoperitoneum group (n = 45), mice were treated with CO_2 pneumoperitoneum at 8–10 mmHg for 60 min as previously reported [10]. Pneumoperitoneum condition was created by following procedure.

(a) A 22-gauge intravenous cannula was inserted into the left lower quadrant and used as an insufflation needle.
(b) A 20-gauge intravenous cannula was inserted into the right lower quadrant and used to measure intraperitoneal pressure.
(c) A disposable syringe to inject the gas was used as the insufflator. A syringe pump was used for continuous insufflation, and intraperitoneal pressure was measured as the distance between the right and left water levels in the U-shaped tube. In the laparotomy group (n = 45), a 3-cm abdominal midline incision was made, and the laparotomy condition was maintained for 60 min. In the control group (n = 45), only diethyl ether anesthesia was performed for 60 min.

Experiment 1 Induction of liver metastasis using a murine intra-splenic tumor cell inoculation model.

Forty-five mice were used in this experiment. A 5-mm skin incision was made at the left back side, and the spleen was pulled out gently. Then, we injected intra-splenically 1×10^6 tumor cells/0.1 ml in PBS using a 30-gauage needle. At 2 min after the tumor-cell injection, the spleen was excised, and the skin was then closed in layers using nonabsorbable interrupted sutures. Immediately after this procedure, the mice were divided into three groups. In the pneumoperitoneum group (n = 15), we administered CO_2 pneumoperitoneum at 10 mmHg for 60 min. In the laparotomy group (n = 15), a 3-cm midline laparotomy was performed and maintained for 60 min. The skin incision was closed by interrupted sutures using 4-0 nylon. In the control group (n = 15), we administered general ether anesthesia for 60 min. All mice were killed on day 7 after each procedure, and we evaluated the numbers, diameter, and cancer index score [7] of metastatic nodules. Each cancer nodule on the liver surface was scored using the cancer index as shown in Table 1, and the total cancer index for each mouse was calculated as the sum of the cancer indices of each nodule.

Experiment 2 Expressions of ICAM-1 and TNF-α mRNA in the liver

Ninety mice were randomized and divided into three groups: the pneumoperitoneum group, the open laparotomy group, and the control group (n = 30 each). Each operative procedure was performed by the same methods used in Experiment 1. After each procedure, the animals' livers were excised on days 0, 1, and 3, snap-frozen in liquid nitrogen, and stored at −80°C until total RNA was extracted. Total mRNA was isolated from the liver by the acid guanidinium thiocyanate–phenol–chloroform extraction procedure [3]. The cDNA was synthesized by reverse transcription from 2.5 μg of total RNA. The cDNA specific for ICAM-1, TNF-α, was measured by PCR. The mRNA of β-actin was measured as the internal control. All PCR reactions were measured by a real-time PCR method using the Light Cycler System (Roche Diagnostics, Mannheim, Germany), and the detection was performed by measuring the binding of the fluorescent dye SYBR Green I to double-stranded DNA. The PCR reactions were set up in microcapillary tubes in a total volume of 20 μl. A master mix of the following reaction components for ICAM-1 and β-actin was prepared to the indicated final concentration: 8.6 μl water, 2.4 μl $MgCl_2$, 1 μl forward and reverse primers, and 2 μl Light Cycler Fast Start DNA Master SYBR Green I (Roche, Mannheim, Germany). A master-mix of the following reaction components for TNF-α was prepared to the indicated final concentration: 9.4 μl water, 1.6 μl $MgCl_2$, 1μl forward and reverse primers, and 2 μl Light Cycler Fast Start DNA Master SYBR Green I. Table 2 presents an overview of primer sequences and factor-specific amplification conditions with the single fluorescence measurement were used in this study. The following general real-time PCR protocol was used: a denaturation program (95 °C for 10 min), followed by an amplification program that was repeated 40 times (Table 2), a melting curve program (60–99°C with a heating rate of 0.1°C /sec and continuous fluorescence measurements), and finally a cooling program down to 40°C. The PCR product sizes for ICAM-1, TNF-α, and β-actin were 326 bp, 349 bp, and 189 bp, respectively. The relative fluorescence of each mRNA was normalized to that of β-actin for semiquantification.

Table 1. Cancer index scoring dependent on the diameter

Cancer index (score)	Diameter of nodule (mm)
1	< 5
2	5–10
3	> 10

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Differences between the mean of the control group and those of the treatment group were evaluated by analysis of variance (ANOVA) followed by the Tukey HSD multiple comparison test. The differences between the groups were regarded as significant when $p < 0.05$. All statistical calculations were performed using the Dr. SPSS (version 11.01) program for Windows computers.

Results

Experiment 1

The number of metastatic nodules was greater in the CO_2 pneumoperitoneum group than in the control group (15.82 ± 5.69 vs 8.80 ± 6.80, $p < 0.05$) (Fig. 1). However, the mean diameter of the tumor nodules was not significantly different among all groups (Fig. 2). The total cancer index in the CO_2 pneumoperitoneum group was higher than that in the control group (26.00 ± 9.76 vs 13.70 ± 11.26, $p < 0.05$) (Fig. 3). Both the number of metastatic nodules and the total cancer index were not significantly different between the CO_2 pneumoperitoneum group and the laparotomy group.

Table 2. Sequences of primers used for RT-PCR and amplification conditions with a single fluorescence measurement

Molecule		Primer sequence (5′–3′)	Real-time PCR cycling conditions (sec/°C)		
			Denaturation	Annealing	Elongation
β-actin	Sense	TGG-AAT-CCT-GTG-GCA-TCC-ATG-AAA-C	15/95	10/55	14/72
	Antisense	TAA-AAC-GCA-GCT-CAG-TAA-CAG-TCC-G			
ICAM-1	Sense	TGC-GTT-TTG-GAG-CTA-GCG-GAC-CA	15/95	10/60	13/72
	Antisense	CGA-GGA-CCA-TAC-AGC-ACG-TGC-CAG			
TNF-α	Sense	CCA-CGT-CGT-AGC-AAA-CCA-C	10/95	10/60	7/72
	Antisense	TGG-GTG-AGG-AGC-ACG-TAG-T			

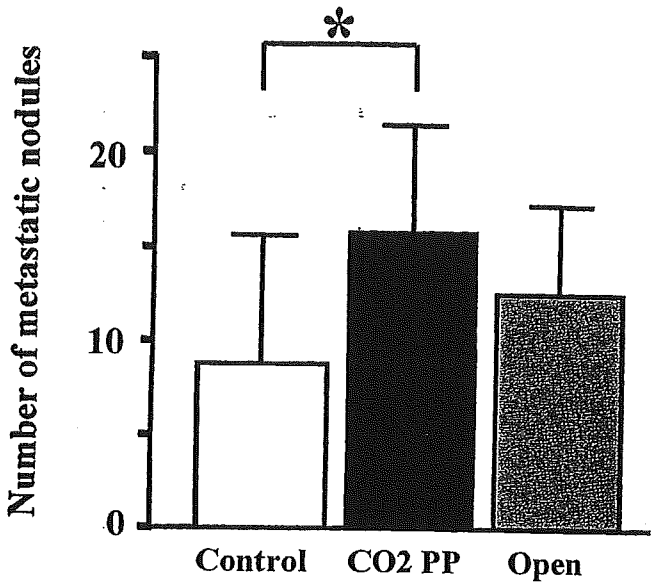

Fig. 1. The number of metastatic nodules on the liver surface was significantly greater in the CO_2 pneumoperitoneum group than in the control group. PP, pneumoperitoneum (*$p < 0.05$).

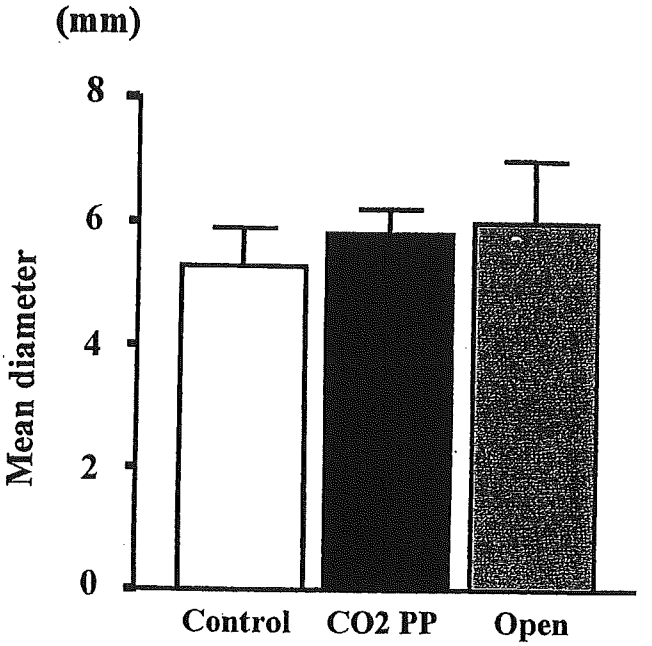

Fig. 2. The mean diameter of metastatic nodules was not significantly different among any of the groups.

Experiment 2

The expression of ICAM-1 mRNA in this study is shown in Fig. 4a. On day 0 (immediately after each procedure), the expression of ICAM-1 mRNA was not significantly different among the groups. On day 1, the expression of ICAM-1 mRNA was higher in the CO_2 pneumoperitoneum group than in the control and the open group (1.86 ± 0.56 vs 0.59 ± 0.42, 1.14 ± 0.40, $p < 0.05$). On day 3, the expression of ICAM-1 mRNA was higher in the CO_2 pneumoperitoneum and laparotomy groups than in the control group (2.03 ± 0.79, 1.62 ± 0.71 vs 0.74 ± 0.35, $p < 0.05$).

The expression of TNF-α mRNA in the CO_2 pneumoperitoneum group was higher than that in the control group on day 1 (0.177 ± 0.078 vs 0.025 ± 0.031, $p < 0.05$) (Fig. 4b). On days 0 and 3, there were no significant differences among any of the groups.

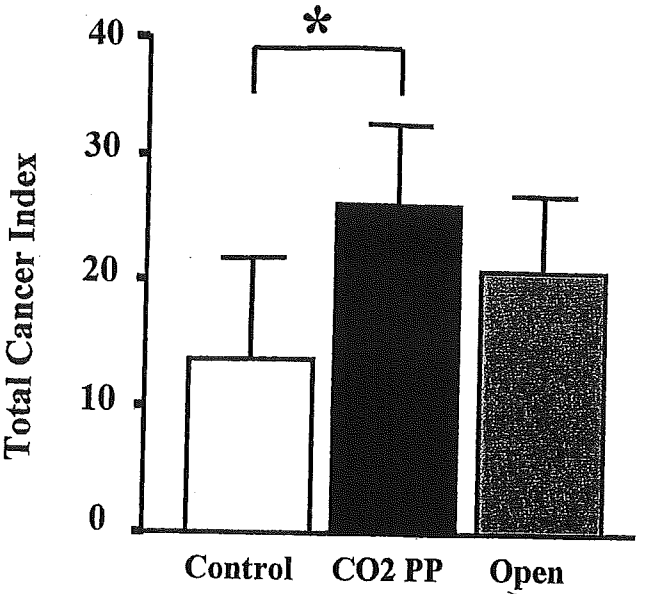

Fig. 3. The total cancer index score was significantly greater in the CO_2 pneumoperitoneum group than in the control group (*$p < 0.05$).

Discussion

In the present study, we examined the effect of CO_2 pneumoperitoneum on liver metastasis from the view-

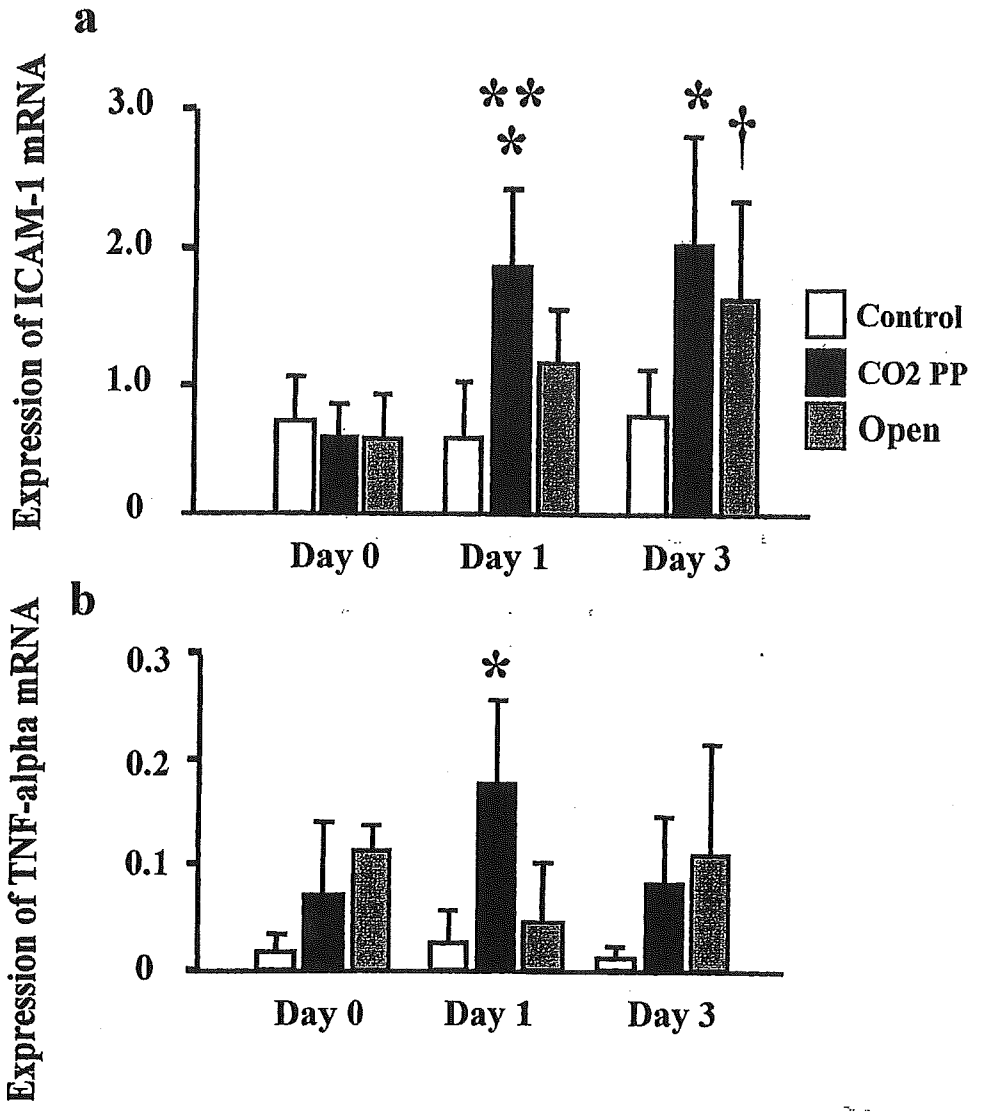

Fig. 4. a Expression of ICAM-1 mRNA and b TNF-α-mRNA in the liver measured by real-time RT-PCR. The relative expression of each mRNA is normalized to the expression of β-actin for semi-quantification. $p < 0.05$ CO_2 pneumoperitoneum versus control group, $^{**}p < 0.05$ CO_2 pneumoperitoneum versus open group, $\dagger p < 0.05$ laparotomy versus control group.)

points of intrahepatic adhesion molecule expression using a murine liver metastasis model. Our results showed that both the number of tumor nodules on the liver surface and the cancer index score were higher in the CO_2 pneumoperitoneum group than in the control group. The intrahepatic expression of ICAM-1 was higher in the CO_2 pneumoperitoneum group than in the other groups. Thus, in a murine model, CO_2 pneumoperitoneum enhanced liver metastasis, and the induction of ICAM-1 after CO_2 pneumoperitoneum may play an important role in the establishment of liver metastasis.

The first step in the establishment of liver metastasis is the adherence of free tumor cells to the hepatic vascular endothelium. Several studies have previously demonstrated that intrabdominal insufflation of CO_2 causes a marked and rapid decrease (35% to 84%) in portal blood flow [11, 20, 21]. In this study, portal blood flow may decrease because of the high pressure of CO_2 pneumoperitoneum, which was used in the previous study [10]. Doi et al. demonstrated that the condition of the ischemic lobe is favorable for liver metastasis [5], and the expression of adhesion molecules located in the vascular endothelium may play a crucial role in the establishment of liver metastasis. Our results showed an enhancement of liver metastasis and an increase of ICAM-1 and TNF-α after CO_2 pneumoperitoneum. It is possible that CO_2 pneumoperitoneum causes damage to the hepatic vascular endothelium by inducing liver ischemia.

ICAM-1 is a member of the immunoglobulin supergene family of adhesion molecules. Previous studies have demonstrated that ICAM-1 mediates hepatic reperfusion injury in the ischemic mouse liver [15, 27, 28]. Taketomi et al. demonstrated that the enhancement of inflammation in the liver is related to intrahepatic recurrence through ICAM-1 in patients with hepatocellular carcinoma [23]. The expression of ICAM-1 can be upregulated by inflammatory cytokines such as TNF-α and interleukin-1 [4, 18]. TNF-α is one of the most effective cytokines for inducing the expression of ICAM-1 on the endothelial cells [14, 19]. Gulubova et al. concluded that the enhanced expression of adhesion molecules in the liver sinusoids could direct the adhesion of new circulating tumor cells to the sinusoidal endothelium [6]. Kamei et al. demonstrated that TNF-α mRNA expression in the liver is higher 3-24 h after air pneumoperitoneum than after anesthesia alone [12]. In the

present study, we demonstrated the increases of ICAM-1 and TNF-α mRNA expression in the liver after CO_2 pneumoperitoneum. Also, the peak of TNF-α mRNA expression appeared earlier than that of ICAM-1 after CO_2 pneumoperitoneum. These results suggested that CO_2 pneumoperitoneum caused liver ischemia, and enhanced the expression of ICAM-1 induced by inflammatory cytokines such as TNF-α on the hepatic endothelium. Furthermore, the possibility that new circulating tumor cells adhered to the sinusoidal endothelium via ICAM-1 was shown.

Recently, in a clinical setting, randomized controlled trials regarding the long-term outcome after laparoscopic colorectal cancer surgery were reported [16, 17, 24]. A Spanish trial showed that the cancer-related survival rate in patients with stage III tumors was higher in the laparoscopic group than in the open group [16]. On the other hand, trials in the United States and Hong Kong showed that there were no significant differences in the survival rate between these two groups [17, 24]. In this experimental study, there were no significant differences in the incidence of liver metastasis between the CO_2 pneumoperitoneum group and the laparotomy group. However, we demonstrated that CO_2 pneumoperitoneum enhanced liver metastasis in comparison with the control group, and also that this effect might be associated with the induction of ICAM-1 and TNF-α in establishing liver metastasis. For the inhibition of liver metastasis after CO_2 pneumoperitoneum, it may be necessary to prevent portal blood flow depression by means of a gasless procedure or lower insufflation pressure [9, 10].

In conclusion, in a murine model, CO_2 pneumoperitoneum increased the expression of ICAM-1 and TNF-α in the liver and enhanced liver metastasis compared with anesthesia alone. Further investigation is necessary to clarify the mechanism and established a prevention method of liver metastasis after CO_2 pneumoperitoneum.

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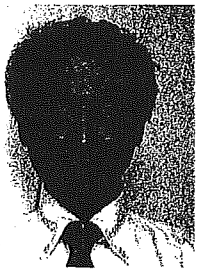
大腸がん化学療法
——あらたな標準治療体系
Chemotherapy for colorectal cancer



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Junichi MATSUBARA and Yasuhiro SHIMADA
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◎大腸がんの化学療法は，1990年代前半までの5-fluorouracil(5-FU)しかなかった時代からイリノテカン(irinotecan)，オキサリプラチン(oxaliplatin)，さらに分子標的治療薬としてcetuximab，bevacizumabという大腸がんに対し有効な薬剤がつぎつぎと開発され，大きく様変わりしてきた．これまですでに5-FU(+LV)，イリノテカン，オキサリプラチンの3剤を順次組み合わせて治療することが生存期間の延長に寄与するということが証明されている．それに分子標的治療薬も加わり，さらなる生存期間の延長が期待されるが，今後は患者ごとの腫瘍遺伝子解析の結果をもとに，もっとも効果のある組合せを最初に選択するテイラーメイド医療が望まれる時代になるであろう．

Key word：大腸がん，5-FU，イリノテカン，オキサリプラチン，分子標的治療薬

厚生労働省の統計において平成15年(2003年)度に日本では年間約3.9万人が大腸がんで亡くなり，悪性新生物による死因のうち第3位(男性では第4位，女性では第1位)を占めている．また，日本において大腸がんはここ数年増加傾向にあるがんのひとつである．

大腸がんの化学療法は1990年代前半までの5-Fluorouracil(5-FU)しかなかった時代からイリノテカン，オキサリプラチン，cetuximab(C-225, Erbitux®)，bevacizumab(Avastin®)と大腸がんに対し有効な薬剤がつぎつぎと開発され，大きく様変わりしてきた．すなわち，大腸がんに対し抗がん剤治療を行う意義を問う時代から，それらを有効に組み合わせて治療を行い，腫瘍縮小効果を高め，かつより効果を長く維持していかに生存期間を延ばしていくかが問われる時代になった．

本稿では欧米および日本における大腸がんの治療体系をマイルストーンとなったエビデンスに触れながら，進行・再発大腸がんの全身化学療法と術後補助化学療法に大別して述べていくこととする．

進行・再発大腸がんの化学療法

1. 細胞傷害性薬剤(cytotoxic agents)の進歩

5-FUは40年以上前に開発され，いまもなお大腸がん化学療法の基本となる薬剤である．その開発以来，長期にわたりロイコボリン(LV)を併用した5-FU急速静注療法がアメリカでは標準治療とされてきた．日本においても急速静注療法のひとつであるRosewell-Park Memorial Institute regimen(RPMI regimen，表1)がごく最近まで頻用されていた．ヨーロッパでは1997年にフランスのde Gramontら[1]が持続静注療法(表1)のほうが急速静注療法より効果も安全性も優れていると発表してからは，持続静注療法がより好まれてきた．

続いてイリノテカンが開発され，5-FUが無効となった大腸がん症例の二次治療として単剤での有効性が示された[2]．その後，アメリカでは5-FU急速静注療法と組み合わせたレジメン(IFL，表1)で，ヨーロッパでは5-FU持続静注療法と組み合わせたレジメン(FOLFIRI，表1)で，いずれも5-FU+LV療法に比べ約2倍の奏効率(約40%)と2〜3カ月の生存期間延長が得られるというエビ

表 1　代表的な大腸がん化学療法レジメン

5-FU+LV療法

1．Rosewell-Park Memorial Institute (RPMI) regimen
LV 500 mg/m^2 (l-LV 250 mg/m^2) over 2 hrs, 5-FU (600 mg/m^2) IV bolus 1 hr after start of LV, days 1, 8, 15, 22, 29, and 36. Repeat every 8 weeks.

2．de Gramont regimen
l-LV 200 mg/m^2 over 2 hrs followed by 5-FU IV bolus 400 mg/m^2 plus 5-FU 600 mg/m^2 over 22 hrs, days 1 and 2. Repeat every 2 weeks.

5-FU+LV+CPT-11療法

1．IFL regimen
CPT-11 100 mg/m^2 over 90 minutes, and 5-FU 500 mg/m^2 IV bolus, and l-LV 20 mg/m^2 IV bolus, days 1, 8, 15, 22. Repeat every 6 weeks.

2．FOLFIRI regimen
・CPT-11 180 mg/m^2 over 2 hrs, day 1.
l-LV 200 mg/m^2 over 2 hrs followed by 5-FU IV bolus 400 mg/m^2 plus 5-FU 600 mg/m^2 over 22 hrs, days 1 and 2. Repeat every 2 weeks (Douillard regimen).
・CPT-11 180 mg/m^2 over 90 minutes, and l-LV 200 mg/m^2 over 2 hrs during CPT-11 infusion, day 1.
Followed by 5-FU IV bolus 400 mg/m^2 plus 5-FU 2,400～3,000 mg/m^2 over 46 hrs.
Repeat every 2 weeks.

5-FU+LV+oxaliplatin療法

1．FOLFOX4 regimen
oxaliplatin 85 mg/m^2 over 2 hrs, day 1.
l-LV 100 mg/m^2 over 2 hrs followed by 5-FU IV bolus 400 mg/m^2 plus 5-FU 600 mg/m^2 over 22 hrs, days 1 and 2. Repeat every 2 weeks.

2．FOLFOX6 regimen (mFOLFOX6 は oxaliplatin 85 mg/m^2)
oxaliplatin 100 mg/m^2 over 2 hrs, and l-LV 200 mg/m^2 over 2 hrs during oxaliplatin infusion, day 1.
Followed by 5-FU IV bolus 400 mg/m^2 plus 5-FU 2,400～3,000 mg/m^2 over 46 hrs.
Repeat every 2 weeks.

3．FOLFOX7 regimen
oxaliplatin 130 mg/m^2 over 2 hrs, and l-LV 200 mg/m^2 over 2 hrs during oxaliplatin infusion, day 1.
Followed by 5-FU 2,400 mg/m^2 over 46 hrs.
Repeat every 2 weeks.

デンス[3,4]が示され，初回標準治療として広く受け入れられてきた．ただしその後の検討から，IFL は FOLFIRI などの 5-FU 持続静注を用いるレジメンより骨髄抑制や下痢などの副作用が強く出やすく，注意深い経過観察と適切な減量やスケジュール調整が必要なやや毒性の強いレジメンであることが示唆された[5,6]．

イリノテカンと並んで重要な新規抗がん剤が，日本では 2005 年 4 月にようやく保険承認となったオキサリプラチンである．シスプラチン (cisplatin) やカルボプラチン (carboplatin) が大腸がんに無効なのに対し，高い効果が期待できる第三世代の白金系抗がん剤で，毒性についても末梢神経障害が特徴的で，腎障害，脱毛，内耳神経障害はまれである．オキサリプラチンは単剤で投与された場合の抗腫瘍活性はやや弱いが，5-FU 持続静注療法と併用 (FOLFOX，表 1) することで高い相乗効果を有することが示された[7,8]．そこでヨーロッパでは初回治療例において FOLFOX6 (表 1) と FOLFIRI のランダム化比較試験が行われたが[9]，両群に生存期間の有意差はなかった．一方，アメリカでは初回治療例で IFL，FOLFOX4 (表 1)，CPT-11＋オキサリプラチン (IROX) の 3 群ランダム化比較試験が行われ[10]，無増悪生存期間，奏効率，生存期間の総合的観点から FOLFOX4 が標準的な初回治療法になりうると結論された (ただし各群の二次治療法で大きな偏りがあり，その解釈には注意を要するという意見もある)．

その後欧米では初回治療として FOLFOX を中心に治療法開発が進められているが，オキサリプラチンに特徴的な末梢神経障害により FOLFOX 治療を継続できない症例が問題となっている．

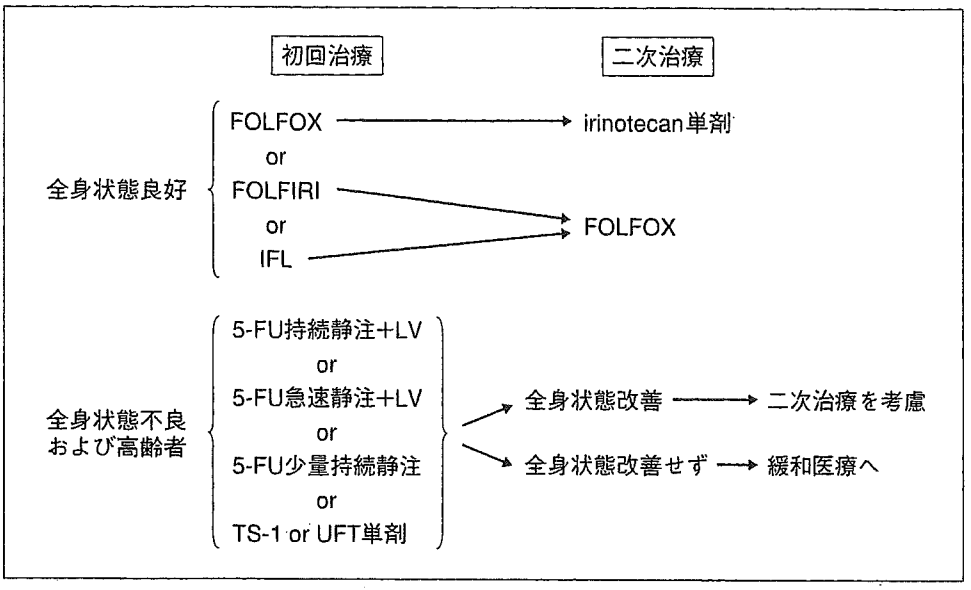

図 1　日本における進行・再発大腸がん標準治療体系

Grothey[11]は，オキサリプラチン総投与量が 800 mg/m^{2}になると全症例の 15％で，1,200 mg/m^{2}になると約 50％で機能障害をきたす末梢神経障害が発現すると報告した．そこで現在，欧米では FOLFOX7(表 1)を 6〜8 サイクル行い，その後 8〜12 サイクルはオキサリプラチンを休薬して 5-FU 持続静注＋LV で行い，その後また FOLFOX7 を再開するという治療スケジュールがいくつかのランダム化比較試験(OPTIMOX Study in Europe，CONcePT Study in USA)で検証されている途中である．末梢神経毒性は可逆性[11]であるため，この治療スケジュールはオキサリプラチン総投与量をより増やすことができると考えられ，今後分子標的薬剤と組み合わせていく世界的標準治療法になると期待されている．

以上より，現状では標準的な初回治療法は未確定であるが，次項で述べる分子標的治療薬がまだ承認されていない日本においては，FOLFOX4，mFOLFOX6，FOLFIRI，IFL のいずれかを患者の全身状態，担当医の経験および利便性などから選択していくべきである(図 1)．Grothey ら[12]は，初回治療が何であれ，5-FU(＋LV)，イリノテカン，オキサリプラチンの 3 剤を順次組み合わせて治療することが生存期間の延長に寄与することを示した．Tournigand ら[9]の報告では生存期間中央値が約 20 カ月と selection bias があるにしても 1990 年代の約 2 倍にまで延長しており，大腸がん化学療法の成績は飛躍的に進歩しているといえる．

一方，利便性という点で優れている経口フッ化ピリミジン系薬剤については UFT＋LV 療法と capecitabine 単独療法(日本では未承認)が 5-FU＋LV 静注療法と有効性が同等であるということが複数のランダム化比較試験[13-16]において証明されている．現在では経口フッ化ピリミジン系薬剤はイリノテカンやオキサリプラチンなどとの併用療法での有効性が検討されているが，いまだ十分なエビデンスは得られていない．

また，前述のような積極的な治療レジメンに耐えられない高齢者や全身状態不良例では図 1 にあるように TS-1® または UFT 単剤療法や 5-FU 持続または急速静注＋LV 療法，5-FU 少量持続静注療 法(Lokich regimen：5-FU 300 mg/m^2/day，連日 24 時間持続静注)により治療されるのが一般的である．

2. 分子標的治療薬(molecular targeted agents)の登場

現在，大腸がん領域において臨床応用されている分子標的治療薬は大きく 2 つの種類に分けられる．抗 EGFR 抗 体(epidermal growth factor receptor monoclonal antibody)と抗 VEGF 抗体(vascular endothelial growth factor antibody)である．どちらの種類もすでにいくつかの薬剤が臨床応用されているが，アメリカですでに承認されているものは抗 EGFR 抗体では cetuximab(Erbitux®，C-225)で

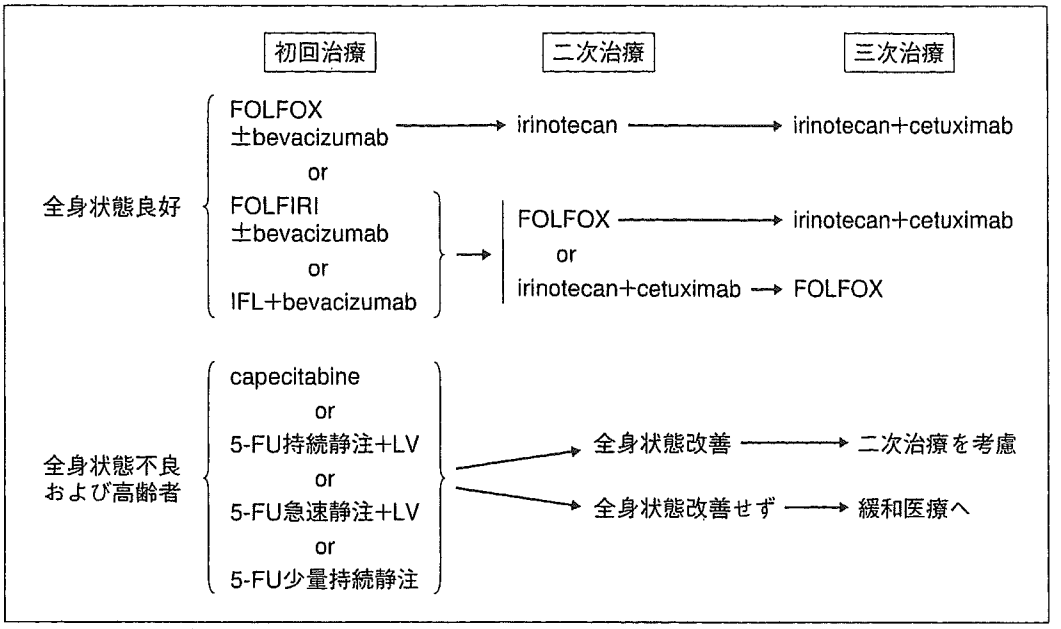

図 2　アメリカにおける進行・再発大腸がん治療ガイドライン(NCCN Practice Guidelines 2005より改変)

つかのランダム化比較試験が欧米を中心に行われている(ただし日本においてはイリノテカンもオキサリプラチンも補助化学療法における保険承認はされていない).

IFL 療法はすでにその毒性と比較試験(CALGB C89803 Study)[22]の結果から補助療法としては行うべきでないとされた. FOLFIRI 療法にしては2005 年アメリカ臨床腫瘍学会総会で 2 つの試験結果(ACCORD-02 Study[23], PETACC-3 Study[24])が報告されたが, "有意差なし"と"T 因子調整後に有意差あり"の結果であり, FOLFIRI 有用性についての結論はまだ出ていない.

オキサリプラチンの補助療法における有用性については, 2005 年アメリカ臨床腫瘍学会総会でつぎの 2 つの試験結果が発表された. StageⅡ/Ⅲ症例を対象とした NSABP C-07 Study[25]と MOSAIC Study[26]である. NSABP C-07 Study は 5-FU+LV weekly bolus regimen と, それに隔週でオキサリプラチン 85 mg/m^{2}を加えた FLOX regimen の比較試験であり, 6 カ月間投与で 3 年無病生存率が FLOX 群は 76.5% と 5-FU+LV bolus 群より 5% 上まわり, 有意によかったと報告された. MOSAIC Study は, 5-FU+LV の de Gramont regimen と FOLFOX4 regimen の比較試験であり, 6 カ月間投与で 3 年無病生存率が FOLFOX4 群は 78.2% と 5-FU+LV 群より 5% 上まわり, 有意に優れていた. すなわち, 術後補助療法におけるオキサリプラチン投与の際の併用療法は 5-FU+LV の急速静注でも持続静注でもどちらでも効果が期待できるということが示されたわけである. ただし生存期間についてはまだ経過観察期間中であり, 本当にオキサリプラチンが補助化学療法に有用かどうかの最終結論は出ていない. また, オキサリプラチンによる末梢神経障害は補助化学療法においては大きな問題であり, 今後投与スケジュールに工夫が必要になるであろう.

分子標的治療薬も, すでに欧米では補助化学療法の比較試験に組み込まれており, 使用が検討されている. Bevacizumab については NSABP C-08 (mFOLFOX6), MOSAIC-2〔FOLFOX4 or capecitabine+オキサリプラチン(XELOX) or FOLFOX7 3 カ月〕, AVANT(FOLFOX4 or XELOX)などの study で, Cetuximab については INT-N0147 Study(mFOLFOX6 6 カ月 or 3 カ月)で, それぞれの治療法に分子標的治療薬が on/off されて比較試験が行われている.

補助化学療法の対象として, stageⅢ症例については有用性が確立されている. しかし, stageⅡ症例に関しては十分なエビデンスがなく, 補助化学療法が必要かどうかのコンセンサスも得られておらず, 今後の課題のひとつである.

直腸がんの補助化学療法については最初に述べたように欧米とは開発の方向性が異なり，データも参考にはできない．現時点で日本においてはUFTなどの経口フッ化ピリミジン系薬剤か5-FU＋LV静注療法が推奨される．

今後の課題

前述したように，大腸がんの化学療法においては5-FU(＋LV)，イリノテカン，オキサリプラチンの3剤を順次組み合わせて治療することが生存期間の延長に寄与するということがすでに証明されている[12]．今後は患者ごとに，もっとも効果のある組合せを最初に選択するテイラーメイド医療が望まれる．すでにthymidylate synthase(TS)やdihydropyrimidine dehydrogenase(DPD)など5-FUの代謝酵素を測定し，効果予測をする試みがなされているが，いまだ結論は得られていない．これからも5-FUのみならずイリノテカンやオキサリプラチンの代謝経路にかかわる酵素の遺伝子多型や変異を研究し，また分子標的治療薬の標的分子の発現量や遺伝子多型と副作用や効果との関連をさらに研究していくことがテイラーメイド医療の実現には必要であろう．

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シンポジウム

S2-01 JCOG0205 Stage III 治癒切除大腸がんに対する術後補助療法のランダム化第III相比較臨床試験：5FU/l-LV 対 UFT/LV

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Stage III 治癒切除大腸がんを対象とした術後補助療法として，国際標準である静注療法 5FU/l-LV を対照群として，経口抗がん剤 UFT/LV の臨床的有用性を検証するために，非劣性デザイン RCT を 2003 年 2 月から全国 43 施設の共同研究として開始している．

主評価項目は無再発生存期間（DFS），副評価項目は生存期間（OS），有害事象割合である．投与スケジュールは，5FU/l-LV は RPMI の 5FU：500mg/m2，l-LV：250mg/m2 を週 1 回投与，6 週連続/2 週休薬，8 週を 1 コースとして 3 コース投与． UFT/LV は UFT：300mg/m2/日，LV：75mg/日を 28 日間内服，7 日間休薬，5 週間を 1 コースとして 5 コース投与．症例選択条件は，組織学的根治度 A の手術症例，75 歳以下，化学療法および放射線治療未施行例，主要臓器機能が保持されている，術後 9 週以内に術後補助化学療法が開始できる，患者本人から文書同意が得られているなどである．

対照群の 5 年 DFS を 75—85%，経口群を＋0～1% と設定して，経口群において許容される 5 年 DFS を－5%（5% 以上下回らない）条件で必要症例数を設定した（片側 $\alpha=0.05$）．予定症例数は 2 群合わせて 1,100 例であり，登録期間 3 年，追跡期間は登録終了後 5 年である．2005 年 5 月時点で 640 例の症例登録が行われ，月 25～30 例の症例登録が継続されている．有害事象に関しても，下痢，食欲不振などの消化器毒性，肝機能異常が認められているが重篤な例はなく，試験継続可能である．

本試験により，経口抗がん剤の術後補助療法の意義が国際的標準治療との比較において評価することができ，同時に静注療法の日常診療への導入も可能となると期待している．将来的に，FOLFOX などの併用療法が術後補助療法において評価されると考えられるが，本臨床試験グループではその大規模試験の基盤整備に大きな貢献をするものと確信する．術後補助療法に要する医療費は極めて莫大であり，このような大規模試験によりエビデンスを積み重ねることが，適正な治療選択/医療費分配への重要な検証プロセスである．