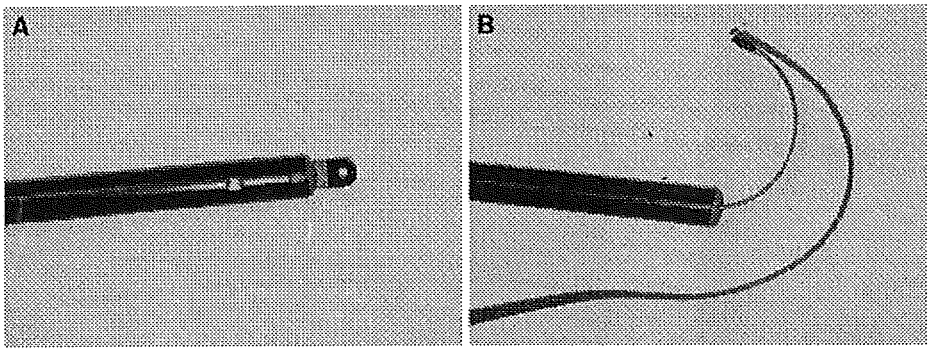

Fig. 1 (A) Endo Retract Maxi in closed position. (B) Endo Retract Maxi in activated position. Vessel tape has been preliminarily fixed to the tip of the metallic arch

of the liver, as described previously [4]. Laparoscopic encircling of the hepatoduodenal ligament usually is performed using an Endo Retract Maxi (United Surgical, a division of Tyco Healthcare Group LP, Norwalk, CT, USA) to which silicon tape (Vesseloops; Argon Medical Devices, TX, USA) is fixed preliminarily with suture securing vessel tape to the tip (Fig. 1). The lesser omentum is sectioned. Because a space exists between the hepatoduodenal ligament and the inferior vena cava, it is not necessary to divide any layers other than the lesser omentum.

The Endo Retract Maxi in closed position is inserted via a 12-mm trocar into the upper median or the left lumbar quadrant and advanced from an opening through the lesser omentum to Winslow's foramen. The metallic arch with vessel tape then is meticulously extended behind the hepatoduodenal ligament, allowing visualization of the tip with vessel tape at the right side of the hepatoduodenal ligament (Fig. 2).

Although the Endo Retract Maxi is blindly deployed between the hepatoduodenal ligament and the inferior vena cava, the tip can be delivered safely into the right side of the hepatoduodenal ligament because the blade is blunt. The vessel tape is grasped with laparoscopic forceps, divided with laparoscopic scissors, and separated from the Endo Retract Maxi. The Endo Retract Maxi then is pulled from the lesser omentum. Both ends of the vessel tape are pulled from the abdominal cavity to the upper median trocar and used as a tourniquet for complete interruption of blood inflow to the liver (Fig. 3). If hemihepatic inflow occlusion is necessary, the left or right Glissonean pedicles are encircled using an Endo Retract Maxi at the hepatic hilum, as described previously [4]. The Nelaton catheter (Terumo, Tokyo, Japan) through which both ends of the vessel tape are passed is inserted and pushed via the upper median 12-mm trocar and secured using the forceps to tighten the hepatoduodenal ligament down around the pedicle (Fig. 3).

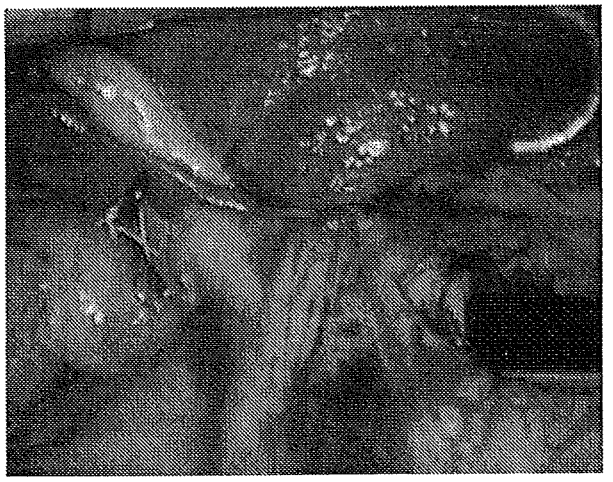

Fig. 2 The metallic arch of the Endo Retract Maxi is moved behind the hepatoduodenal ligament (HDL) so the tip with vessel tape is visualized at the right side of the HDL

A total of 32 consecutive patients who underwent laparoscopic or assisted hepatic resection at Chiba Cancer Center Hospital had the hepatoduodenal ligament encircled by vessel tape using an Endo Retract Maxi as a tourniquet for complete interruption of blood inflow to the liver if necessary. In all 32 patients, laparoscopic encircling of the hepatoduodenal ligament using an Endo Retract Maxi was easily and rapidly performed without any complications, even by surgeons with minimal or no laparoscopic experience.

Discussion

Recent technological developments and improved endoscopic procedures have further spread the application of laparoscopic liver resection. A major challenge with this procedure is to avoid massive hemorrhage from the transection plane. Pringle's maneuver has been widely used to reduce intraoperative blood loss because this technique is easily performed in conventional open surgery. However, this maneuver is not so easily performed under laparoscopic circumstances because the curve of the laparoscopic forceps usually is too obtuse to encircle the hepatoduodenal ligament. In addition, the tip of the laparoscopic forceps is sharp and hard, and thus has the potential to injure organs under blind manipulation. Although a biliary scope is very

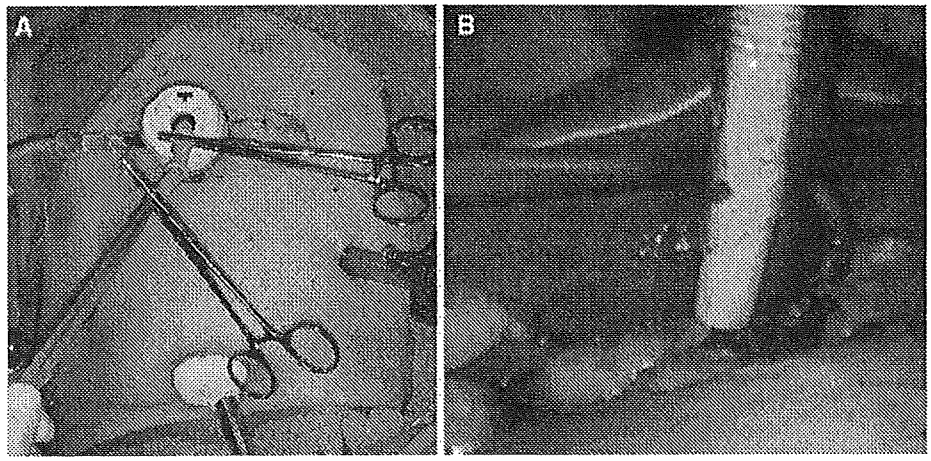

Fig. 3 Both ends of the vessel tape are pulled from the abdominal cavity to the upper median trocar (**A**) and used as a tourniquet for complete interruption of blood inflow to the liver (**B**)

useful for encircling the hepatoduodenal ligament [9], preparing and manipulating a biliary scope may be somewhat problematic and time consuming.

For the current procedure, no special instrument except an Endo Retract Maxi is necessary. Laparoscopic encircling of the hepatoduodenal ligament using an Endo Retract Maxi was performed in a few minutes without any of the 32 patients undergoing this approach experiencing any complications. Although our experience is limited, we believe that laparoscopic encircling of the hepatoduodenal ligament using an Endo Retract Maxi is easily performed for all patients undergoing laparoscopic liver resection.

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Messenger RNA expression of COX-2 and angiogenic factors in primary colorectal cancer and corresponding liver metastasis

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Abstract. Several new drugs that are targeted towards various angiogenic factors have shown considerable potential for controlling tumor proliferation and metastases. Expression levels of the targeted genes in primary tumors and metastases should be understood to maximize the use of such drugs. The present study aimed to clarify associations between mRNA levels of cyclooxygenase 2 (COX-2) and angiogenic factors [vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8)] in primary colorectal cancer and in corresponding liver metastasis. We also compared these gene expressions of primary colorectal cancer between patients with and without liver metastasis. In 31 pairs of formalin-fixed and paraffin-embedded primary and metastatic liver tumors as well as 27 specimens of consecutive stage II patients without recurrence, mRNA was quantified by real-time reverse transcription-polymerase chain reaction following the laser capture microdissection. We found a significantly positive correlation in *IL-8* between primary tumors and matched liver metastases ($p=0.034$, $r_s=0.39$) and in VEGF ($p=0.0083$, $r_s=0.48$), but not in *COX-2*, which was associated with both *VEGF* ($p=0.044$, $r_s=0.37$) and *IL-8* ($p=0.0004$, $r_s=0.64$) in primary colorectal cancers. Multiple regression analysis revealed that *COX-2* was independently associated with *IL-8* ($p<0.0001$). There were no differences in mRNA levels between patients with and without liver metastasis. The mRNA levels of VEGF and IL-8 in liver metastasis can be predicted from those in primary colorectal cancer. COX-2 might exert angiogenic activity more through the IL-8, than the VEGF pathway. These angiogenic factors were sufficiently up-regulated before hematogenous metastasis. These preliminary data merit further validation studies.

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Key words: colon cancer, liver metastasis, cyclooxygenase-2, vascular endothelial growth factor, interleukin-8, reverse transcription-polymerase chain reaction, messenger RNA

Introduction

Colorectal cancer is a worldwide leading cause of cancer death (1,2). The most promising treatment for patients with colorectal cancer is curative resection, but this is sometimes impossible. Some patients with colorectal cancer constantly relapse despite curative resection (3). Molecular targeting therapy has recently been developed for advanced colorectal cancer. Various drugs targeting anti-angiogenesis have improved the survival of patients with metastatic colorectal cancer (4), because angiogenesis is essential for tumor growth (5).

Interleukin-8 (IL-8) is a pro-inflammatory chemotactic cytokine that stimulates the migration of cells including neutrophils, monocytes, lymphocytes, and fibroblasts (6-9). The angiogenic activity of IL-8 produced by monocytes and macrophages was originally demonstrated in 1992 (10). Several investigators have reported that IL-8 is also secreted by some human colorectal cancer cells. Studies have shown that the range of IL-8 expression is 45-74% in colorectal cancer (11,12). However, details of IL-8 messenger RNA (mRNA) expression in colorectal cancer and corresponding liver metastasis remain unclear.

Senger *et al* originally identified the vascular endothelial growth factor (VEGF), which promotes angiogenesis, in 1983 (13). Bevacizumab is a monoclonal antibody to VEGF that has improved the survival of patients with metastatic colorectal cancer when combined with other chemotherapies (4).

Cyclooxygenase (COX) is a key enzyme that is involved in the conversion of arachidonic acid to prostaglandins. The COX-2 isoform is expressed in most organs, but can be up-regulated by various factors including cytokines, growth factors and tumor promoters (14,15). Recent studies have demonstrated that COX-2 inhibitors exert angiogenic effects

in colorectal cancer (16,17). However, the association of mRNA between COX-2 and angiogenic factors in colorectal cancer remain unclear.

Several novel drugs that are targeted towards various angiogenic factors have shown considerable potential for controlling tumor proliferation and metastasis. To maximize the effects of such drugs, correlations between expression levels of targeted genes in primary tumors and metastases should be determined. The present study examines associations between the mRNA levels of COX-2 and angiogenic factors such as VEGF and IL-8 in primary colorectal cancer and in corresponding liver metastasis. We also evaluated the association between COX-2 and angiogenic factors.

Patients and methods

Patients. We enrolled 31 patients who had undergone surgical resection for both primary colorectal cancer and liver metastasis between April 1997 and June 2005 at Tokyo Medical and Dental University Hospital. Of these, 18 and 13 had metachronous and synchronous liver metastases, respectively. The median time from primary resection to hepatectomy was 20 months. We compared mRNA expression between primary colorectal cancer and corresponding liver metastases. We also enrolled 27 patients who had undergone curative resection for stage II colorectal cancer between January 1998 and August 2001 and who had not relapsed during a median follow-up of 4.8±1.1 years. We then compared mRNA expression between the 31 patients with liver metastasis (Group 1) and the 27 stage II patients without relapse (Group 2). Patients with ulcerative colitis, Crohn's disease, or familial adenomatous polyposis were excluded from this study, which was approved by the institutional review board of Tokyo Medical and Dental University, and all patients provided written, informed consent to participate. None of the patients had undergone prior radiotherapy or chemotherapy. Table I summarizes their clinical and histopathological data.

Laser capture microdissection. Formalin-fixed paraffin-embedded tumor tissue blocks were cut into 10-μm-thick slices, stained with nuclear fast red (American MasterTech Scientific, Lodi, CA) and then laser capture microdissection (P.A.L.M. Microlaser Technologies AG, Munich, Germany) was applied. This technique allows only tumor cells to be examined with stromal tissues removed.

RNA isolation and cDNA synthesis. After laser capture microdissection, RNA was isolated according to the proprietary procedure of Response Genetics (US patent no. 6,248,535) and then cDNA was prepared from each sample as described (18).

Quantitative reverse transcription polymerase chain reaction (RT-PCR). Genes of interest and an internal reference gene (ß-actin) were quantified using fluorescence-based real-time TaqMan detection (ABI PRISM 7900 Sequence Detection System; Applied Biosystems, Foster City, CA) as described (19) and the specific mRNA amplification primers and probes were listed in Table II. The PCR mixture comprised 1,200 nmol/l of each primer, 200 nmol/l probe, 0.4 U of AmpliTaq Gold Polymerase, 200 nmol/l each of dATP,

Table I. Clinicopathological characteristics.

	Group 1 (n=31 with liver metastasis)	Group 2 (27 stage II without relapse)	P-value
Age (years)	61±9	69±11	0.0035
Gender			
Male	24	15	NS
Female	7	12	
Primary site			
Cecum	1	0	NS
Ascending colon	3	4	
Transverse colon	3	5	
Descending colon	2	1	
Sigmoid colon	9	9	
Rectosigmoid	9	4	
Rectum	4	4	
Pathology (differentiation)			
Well	12	11	NS
Moderate	17	15	
Poor	1	1	
Mucinous type	1	0	
Depth of tumor			
T1	0	0	NS
T2	2	0	
T3	21	25	
T4	8	2	
Lymph node metastasis			
N0	9	27	<0.0001
N1	13	0	
N2	9	0	
Lymphatic invasion			
Absent	4	8	0.013
Minimal	13	17	
Moderate	12	2	
Severe	2	0	
Venous invasion			
Absent	0	5	NS
Minimal	13	11	
Moderate	11	8	
Severe	7	3	

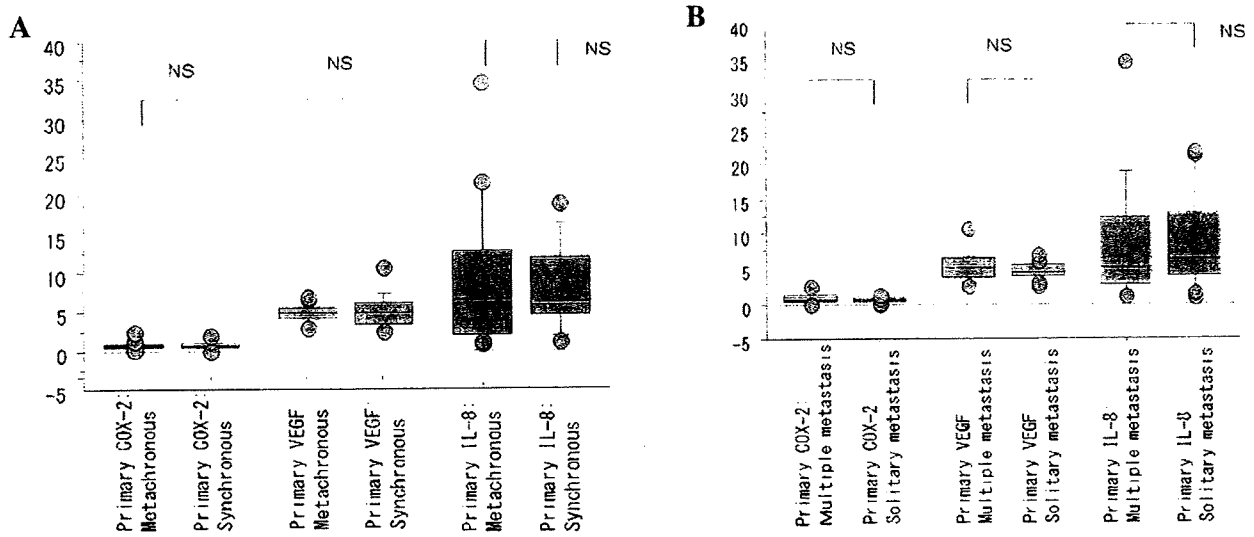

Figure 1. Messenger RNA expression in primary colorectal tumor of patients with liver metastasis according to: (A), timing of metastasis; and (B), number of metastatic tumors.

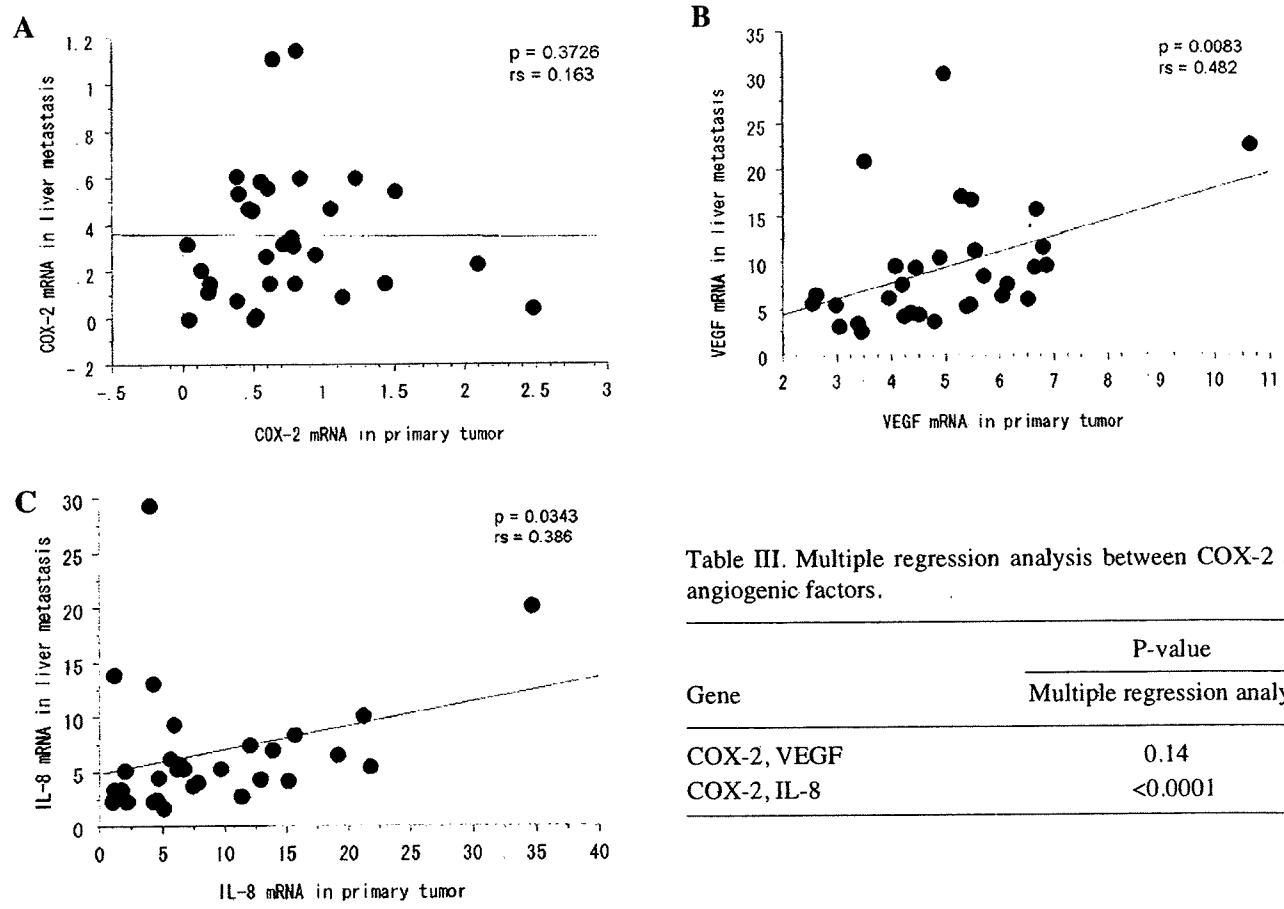

Figure 2. Correlation of messenger RNA expression between primary colorectal cancer and corresponding liver metastasis. (A), COX-2; (B), VEGF; and (C), IL-8.

and VEGF, 4.87±1.64 and 5.50±4.50, respectively. The COX-2 (p=0.55; Fig. 4A), IL-8 (p=0.61; Fig. 4B) and VEGF (p=0.22; Fig. 4C) mRNA levels did not differ between Groups 1 and 2.

Table III. Multiple regression analysis between COX-2 and angiogenic factors.

Gene	P-value Multiple regression analysis
COX-2, VEGF	0.14
COX-2, IL-8	<0.0001

Discussion

The present study demonstrated positive correlations between mRNA levels of IL-8 and VEGF, but not of COX-2 in primary

Table II. Primer and probe sequences of analyzed genes.

	Sequences
COX-2	
Forward primer	5'-GCTCAAACATGATGTTTGCATTC-3'
Reverse primer	5'-GCTGGCCCTCGCTTATGA-3'
Probe	5'-(FAM)TGCCCAGCACTTCACGCATCAGTT(TAMRA)-3'
IL-8	
Forward primer	5'-CAGCTCTGTGTGAAGGTGCAGTT-3'
Reverse primer	5'-GGGTGGAAAGGTTTGGAGTATGTC-3'
Probe	5'-(FAM)TGCACTGACATCTAAGTTCTTTAGCACTCCTTGGC(TAMRA)-3'
VEGF	
Forward primer	5'-AGTGGTCCCAGGCTGCAC-3'
Reverse primer	5'-TCCATGAACTTCACCACTTCGT-3'
Probe	5'-(FAM)ATGGCAGAAGGAGGAGGGCAGAATCA(TAMRA)-3'
ß-actin	
Forward primer	5'-TGAGCGCGGCTACAGCTT-3'
Reverse primer	5'-TCCTTAATGTCACGGACGATTT-3'
Probe	5'-(FAM)ACCACCACGGCCGAGCGG(TAMRA)-3'

dCTP, dGTP, dTTP, 3.5 mmol/l $MgCl_2$, and 1X TaqMan buffer A containing a reference dye in a final volume of 20 μl (all reagents were supplied by Perkin-Elmer Applied Biosystems). The cycling conditions comprised 50°C for 2 min and 95°C for 10 min followed by 46 cycles at 95°C for 15 sec and 60°C for 1 min. Gene expression is expressed as ratios (relative mRNA levels) between genes of interest and the internal reference ß-actin gene. All samples were amplified in triplicate.

Statistical analysis. Data were statistically analyzed using the StatView statistical package (StatView 5.0, Abacus Concepts, Inc., Berkeley, CA, USA). All data are expressed as median ± standard deviation. We compared the mRNA levels of genes of interest between primary colorectal cancer and corresponding liver metastasis using the Wilcoxon's signed-rank test. Spearman's rank correlation analysis determined correlations between mRNA levels of primary tumor and liver metastases and associations between mRNA levels of COX-2 and angiogenic factors. Associations between clinicopathological features and mRNA expression were assessed by the Mann-Whitney U test with two variables and by the Kruskal-Wallis test with three or more variables. Statistical significance was established at $p<0.05$ for all values.

Results

Table I shows the clinicopathological features of the patients. Those with stage II colorectal cancer whose cancer did not recur were older than those with liver metastasis (p=0.0035). The extent of lymph node metastasis and lymphatic invasion significantly differed between the two groups ($p<0.0001$ and p=0.013, respectively). The mRNA levels of each gene did not differ between patients with primary colorectal cancer accompanied by synchronous or metachronous liver metastasis (Fig. 1A). The mRNA levels of primary tumors also did not significantly differ between patients with solitary or multiple liver metastases (Fig. 1B).

Correlation in mRNA expression between primary colorectal cancer and corresponding liver metastasis. The expression of COX-2 mRNA did not significantly differ between primary colorectal cancer and corresponding liver metastasis from 31 patients (Group 1; Fig. 2A). On the other hand, VEGF values were significantly associated between primary tumor and matched liver metastasis (Fig. 2B; p=0.0083, r_s=0.482) and IL-8 (Fig. 2C, p=0.034, r_s=0.39).

Correlation in mRNA expression between COX-2 and angiogenic factors in primary colorectal cancer. The mRNA expression of COX-2 significantly correlated with that of VEGF in primary tumors from Group 1 patients (Fig. 3A; p=0.044, r_s=0.37) and IL-8 (Fig. 3B; p=0.0004, r_s=0.64). Multivariate analysis revealed that IL-8 mRNA and COX-2 mRNA expression was independently associated (Table III; $p<0.0001$).

Comparison of mRNA levels between patients with stage II colorectal cancer without recurrence and those with colorectal cancer with liver metastasis. The mRNA levels of primary tumors in Group 1 and 2 patients were as follows: COX-2, 0.61±0.55 and 0.59±0.78; IL-8, 6.17±7.68 and 6.27±13.43

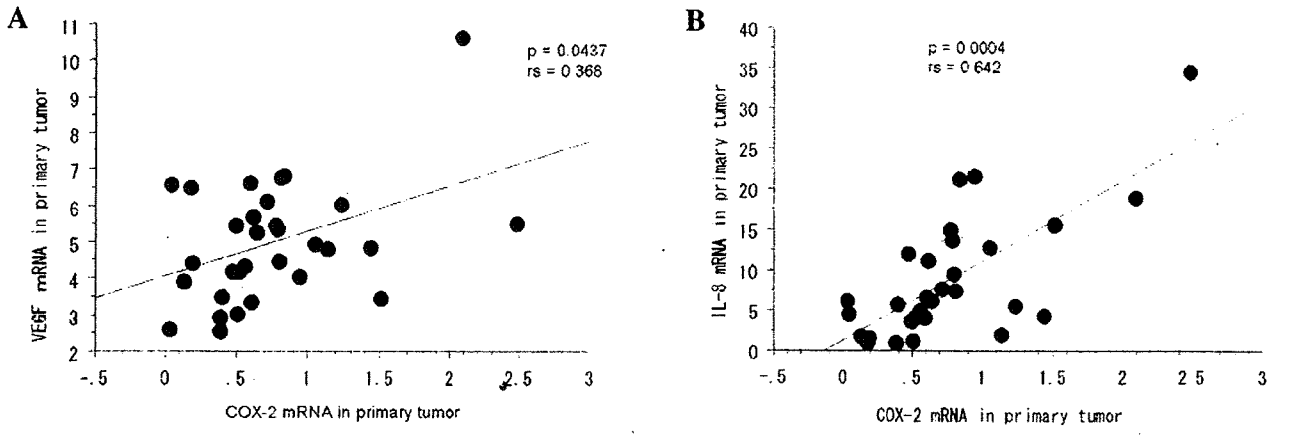

Figure 3. Correlation of messenger RNA expression between COX-2 and: (A), VEGF; or (B), IL-8 in primary tumors.

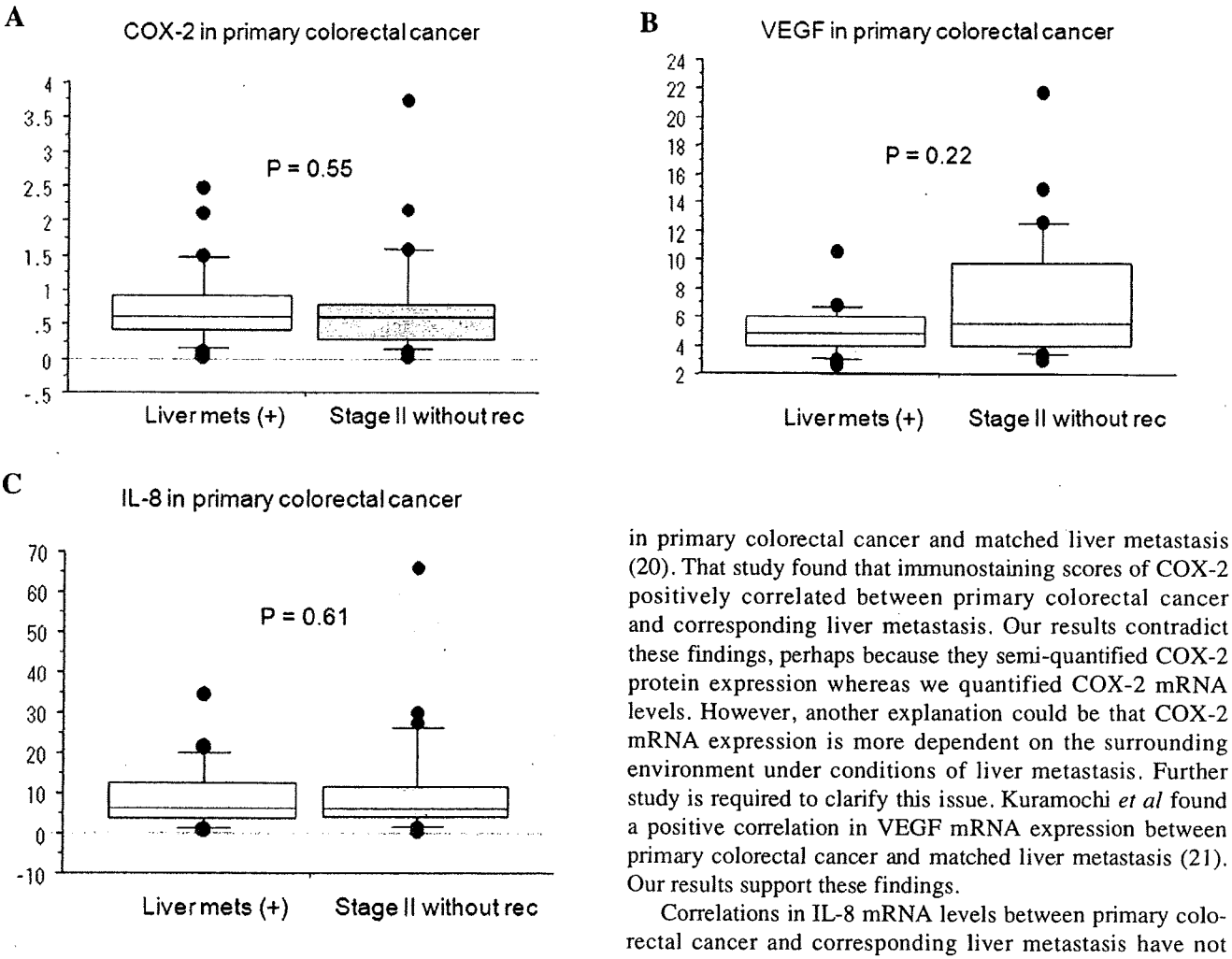

Figure 4. Comparison of messenger RNA expression between primary colorectal cancer with liver metastasis and stage II tumor without recurrence. (A), COX-2; (B), VEGF; and (C), IL-8.

colorectal cancer and corresponding liver metastases. The expression of COX-2 in primary colorectal cancer and liver metastasis has not been examined in detail. Only one immunohistochemical study has compared COX-2 expression in primary colorectal cancer and matched liver metastasis (20). That study found that immunostaining scores of COX-2 positively correlated between primary colorectal cancer and corresponding liver metastasis. Our results contradict these findings, perhaps because they semi-quantified COX-2 protein expression whereas we quantified COX-2 mRNA levels. However, another explanation could be that COX-2 mRNA expression is more dependent on the surrounding environment under conditions of liver metastasis. Further study is required to clarify this issue. Kuramochi *et al* found a positive correlation in VEGF mRNA expression between primary colorectal cancer and matched liver metastasis (21). Our results support these findings.

Correlations in IL-8 mRNA levels between primary colorectal cancer and corresponding liver metastasis have not been reported. Rubie *et al* reported that IL-8 mRNA and protein expression is up-regulated in colorectal cancer compared with adjacent normal tissues (22). Anti-angiogenic therapy for colorectal cancer targeting IL-8 might be developed soon, and the present results should be applicable at that time.

Multiple regression analysis revealed a significant correlation between mRNA levels of IL-8 and of COX-2 in advanced colorectal cancer. To our knowledge, the association

between COX-2 and IL-8 mRNA expression in colorectal cancer has not yet been reported. However, details of interactions between COX-2 and IL-8 were not clarified in the present study. Singh *et al* reported that COX-2 expression led to IL-8 induction in breast cancer cells (23). A similar mechanism might exist in colorectal cancer, because we found a close correlation between the mRNA levels of COX-2 and IL-8. Details of the mechanism between COX-2 and IL-8 in colorectal cancer require further investigation using various strategies.

Since Tsujii *et al* reported that COX-2 regulates angiogenesis in colon cancer cells (24), several studies have shown an association between COX-2 expression and angiogenesis (16,17). However, our univariate analysis found that COX-2 mRNA expression in primary colorectal cancer positively correlated with VEGF mRNA levels, whereas multivariate analysis did not. One reason for this finding might be that several factors other than COX-2 affect VEGF and thus, angiogenesis.

The present study found no differences among COX-2, VEGF, and IL-8 mRNA levels in primary colorectal cancer between patients with synchronous and metachronous liver metastases. The mRNA levels of each factor did not differ between primary tumors from patients with solitary liver or multiple liver metastases, suggesting that these genes are already sufficiently up-regulated by the time liver metastases develop from colorectal cancer. Therefore, the mRNA levels of these genes might not change with further tumor advances.

We found no difference in the IL-8 mRNA levels between TNM stage II and IV primary colorectal cancer. There were no differences in the COX-2 and VEGF mRNA levels between two groups, either. These findings suggest that the IL-8 as well as COX-2 and VEGF mRNA levels in colorectal cancer are already sufficiently up-regulated at stage II. Anti-angiogenic therapy targeting these genes may exert their effect for patients with stage II colorectal cancer as well as for those with stage IV. To maximally exclude bias, we examined samples from consecutive patients with stage II cancer who had not developed recurrence for at least 3 years. Terada *et al* reported that the IL-8 levels were lower in T1, than in T2-4 colorectal cancer (25). Therefore, IL-8 might become up-regulated early. They found higher IL-8 levels in patients with, than without liver metastases. One explanation for the difference in the results between their study and ours might be that they measured IL-8 levels using an ELISA in only 9 patients with liver metastasis. Further large-scale investigations are required to clarify this issue.

In conclusion, the present study found no association between mRNA expression of angiogenic factors and liver metastasis. The mRNA expression of these angiogenic factors in colorectal cancer might already be sufficiently up-regulated before hematogenous metastasis. The angiogenic activity of COX-2 might be exerted more through the IL-8 than the VEGF pathway. The mRNA levels of VEGF and IL-8 in liver metastasis can be predicted from those in primary colorectal cancer. These findings will be useful when considering anti-angiogenic therapy for patients with colorectal cancer, although further studies are required to validate these preliminary data.

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Timing of Relapse and Outcome after Curative Resection for Colorectal Cancer: A Japanese Multicenter Study

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Key Words
Colorectal cancer · Treatment for relapse · Curative resection · Time to relapse · Recurrence

Abstract
Background: The aim of this multicenter study was to clarify the influence of timing of relapse after curative resection for colorectal cancer on prognosis. ***Methods:*** We enrolled 5,230 consecutive patients who underwent curative resection for colorectal cancer at 14 hospitals from 1991 to 1996. All patients were intensively followed up. Time to relapse (TR) was classified into three groups as follows: group A, TR ≤1 year; group B, TR >1 year and ≤3 years, and group C, TR >3 years. The prognoses after relapse were compared among the three groups. ***Results:*** Of the 5,230 patients, 906 experienced relapse (17.3%). The curative resection rates for recurrent tumors were 35.2% in group A, 46.6% in group B, and 45.1% in group C ($p = 0.0045$). There were significant differences in the prognoses after relapse among the three TR groups in patients with relapse to the liver ($p = 0.0175$) and in those with local relapses ($p = 0.0021$), but not in those with pulmonary or anastomotic recurrence. There were no differences in prognoses after relapse in any recurrence site among the three groups in patients who underwent curative resection for relapse. ***Conclusion:*** If patients can undergo curative resection for relapse, they receive a survival benefit regardless of the timing of relapse.

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Introduction

Colorectal cancer is the second most common cause of cancer death in both the USA and Japan, and is one of the most rapidly expanding diseases in Japan [1, 2]. Although the most promising treatment for colorectal cancer is curative resection, some of the patients with curative resection for colorectal cancer develop relapse [3]. Therefore, it is important to improve the outcome of treatment for relapse of colorectal cancer.

Recent remarkable advances of multiagent chemotherapies, including those using molecular target drugs, have improved the prognosis of metastatic colorectal cancer [4–6]. However, the complete resection of metastatic tumors is still the best treatment for this disease. There have been many studies investigating the outcome of resection for metastatic tumors of colorectal cancer. The 5-year survival rates after resection for hepatic and pulmonary metastases ranged from 27 to 58% and from 29 to 64%, respectively [7–17]. Most of the relapses occur within 5 years after curative resection for colorectal cancer [3]. However, it remains uncertain whether there is an association between the timing of relapse and the outcome. Kornprat et al. [18] demonstrated that the disease-free interval from colorectal surgery to liver metastases was not associated with the prognosis after hepatectomy. On the other hand, it has been reported that the disease-free survival after hepatectomy in patients with metachronous liver metastasis is better than that in patients with synchronous liver metastasis [19].

The relationship between the time to relapse (TR) and the rate of resection after relapse remains unclear. Further, the association between the outcome in patients treated with resection for relapse and the TR is also obscure.

The aim of this retrospective multicenter study was to clarify the association between TR after resection for colorectal cancer and prognosis after relapse.

Patients and Methods

The study group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) on postsurgical surveillance of colorectal cancer collected data on 5,230 consecutive patients who underwent curative resection at 14 member institutions from January 1991 to December 1996. The patients with T1 cancers which were removed by endoscopical or transanal resection were excluded from this study. The patients with cancers associated with familial adenomatous polyposis, ulcerative colitis or Crohn's disease were also excluded. Treatment of recurrent tumors was decided according to the criteria of each institution. The local ethics committee of each institution approved this study. Recurrence sites were classified into liver, lung, local, anastomosis, and others. Other recurrence sites consisted of bone, brain, ovary, distant lymph node, and so on. Peritoneal carcinomatosis was also classified into others.

Table 1. A Cox proportional hazards model for prognosis after relapse

	n	p value	Hazard ratio	95% CI
Age				
<63 years	456	NS	1	
≥63 years	450		1.15	0.99–1.33
Histologic grade				
Well- or moderately differentiated adenocarcinoma	835	0.012	1	
Poorly differentiated adenocarcinoma or mucinous carcinoma	70		1.40	1.08–1.82
Unknown	1			
Direct invasion of the primary tumor to other organs				
Absent	840	0.0010	1	
Present	65		1.58	1.20–2.07
Unknown	1			
TNM stage				
Stage I	51	NS	1.14	0.81–1.60
Stage II	255		0.85	0.72–1.01
Stage III	600		1	
Time to relapse (TR)				
A	358	NS	1.16	0.93–1.46
B	395		1.07	0.86–1.34
C	153		1	
Resection for relapse with curative intent				
Absent	527	<0.0001	1	
Present	379		0.26	0.22–0.31

CI = Confidence interval. A = TR ≤ 1 year; B = 1 year < TR ≤ 3 years; C = 3 years < TR.

Follow-Up Examination

All patients had intensive prospective follow-up after surgery according to the follow-up protocols of each institution. Most institutions established a follow-up examination period of 5–10 years. The standard follow-up protocol was as follows: measurement of a serum tumor marker and hepatic imaging (ultrasonography and/or computed tomography) every 3 months for the first 3 years and every 6 months for the next 2 years, and chest X-ray every 6 months, pelvic CT for rectal cancer every year, and colonoscopy every 1–2 years.

Timing of Relapse

Patients were classified into three groups according to the TR: group A, TR ≤ 1 year; group B, 1 year < TR ≤ 3 years, and group C, 3 years < TR. The prognosis after relapse was compared among the three groups, and between group A and a combined group including groups B and C. The resection rates for metastatic tumors were also compared among the three groups.

Table 2. Characteristics of patients

	Patients with relapse	Patients without relapse	p value
Gender			
Male	559 (18.0)	2,546 (82.0)	NS
Female	347 (16.3)	1,778 (83.7)	
Age	62 ± 11	63 ± 11	NS
Primary tumor site			
Colon	506 (14.1)	3,077 (85.9)	<0.0001
Rectum	400 (24.3)	1,247 (75.7)	
TNM stage			
Stage I	51 (3.7)	1,316 (96.3)	<0.0001
Stage II	255 (13.3)	1,657 (86.7)	
Stage III	600 (30.8)	1,351 (69.2)	
First recurrence site			
Liver	373		
Lung	250		
Local	209		
Anastomosis	22		
Others	199		
Follow-up period	3.5 ± 2.9	7.1 ± 3.1	<0.0001

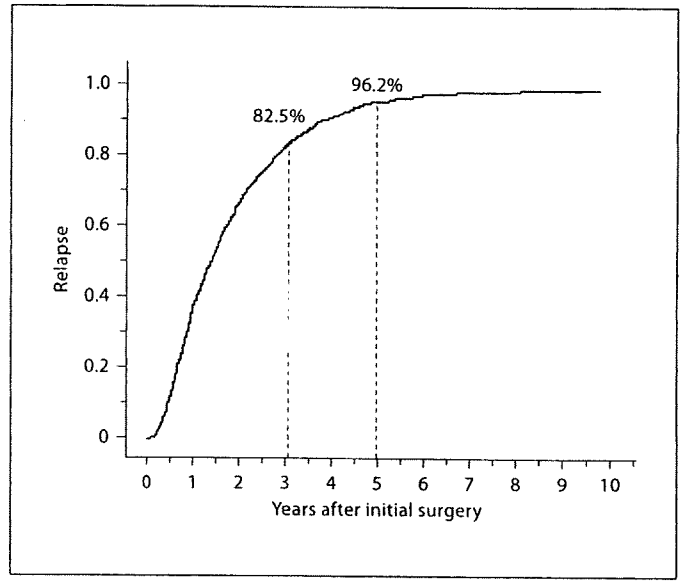

Fig. 1. Curve showing the accumulated relapse rate of patients who underwent curative resection for colorectal cancer. More than 80% of the relapses occurred within 3 years, and 96.2% occurred within 5 years after curative resection for colorectal cancer.

Prognostic Factors after Relapse

Age, gender, location of tumor, histologic grade, direct invasion of the primary tumor to other organs, TNM staging, lymphatic invasion, venous invasion, TR, and resection for relapse with curative intent were analyzed as risk factors for overall survival after relapse (table 1).

Statistical Analysis

Statistical analysis was performed with the StatView statistical package (StatView 5.0; Abacus Concepts, Inc., Berkeley, Calif., USA). All data are expressed as the median ± SD. The χ^2 test for independence was used to investigate the frequency of resection in relapsed cases for each of the three TR groups. We used the Kaplan-Meier method to calculate the actuarial survival of patients. Overall survival rates for each of the three patient groups were assessed by log-rank test. A Cox proportional hazards model was used to determine which risk factors had an independent effect on survival after relapse. Differences in results were considered significant at $p < 0.05$.

Results

Relapse

Of the 5,230 patients, 906 (17.3%) had relapse after curative resection for colorectal cancer during the median follow-up time of 6.6 ± 3.1 years. Among them, 39.5% developed recurrence within 1 year (group A), 82.5% within 3 years, and 96.2% within 5 years (fig. 1). There were no differences in gender or age between patients with relapse and those without (table 2). Relapse was significantly more frequent in patients with rectal cancer than in those with colon cancer. The more advanced the stage, the more frequent the relapse. The most common recurrence site was the liver, followed in order by the lungs and local recurrence sites.

Overall Survival after Initial Colorectal Surgery according to Timing of Relapse

There was a significant difference in overall survival after colorectal surgery in patients with liver, lung, and local relapse, but not in those with anastomotic relapse (table 3). The later the relapse occurred, the better the prognosis was after initial colorectal surgery.

Overall Survival after Relapse according to the Timing of Relapse

There was a significant difference in overall survival after relapse in patients with liver or local relapse (table 3) according to the timing of relapse ($p = 0.0175$ and $p = 0.021$, respectively). The survival after relapse in group A patients with liver metastasis was worse than that in group B or group C patients, but there was no difference

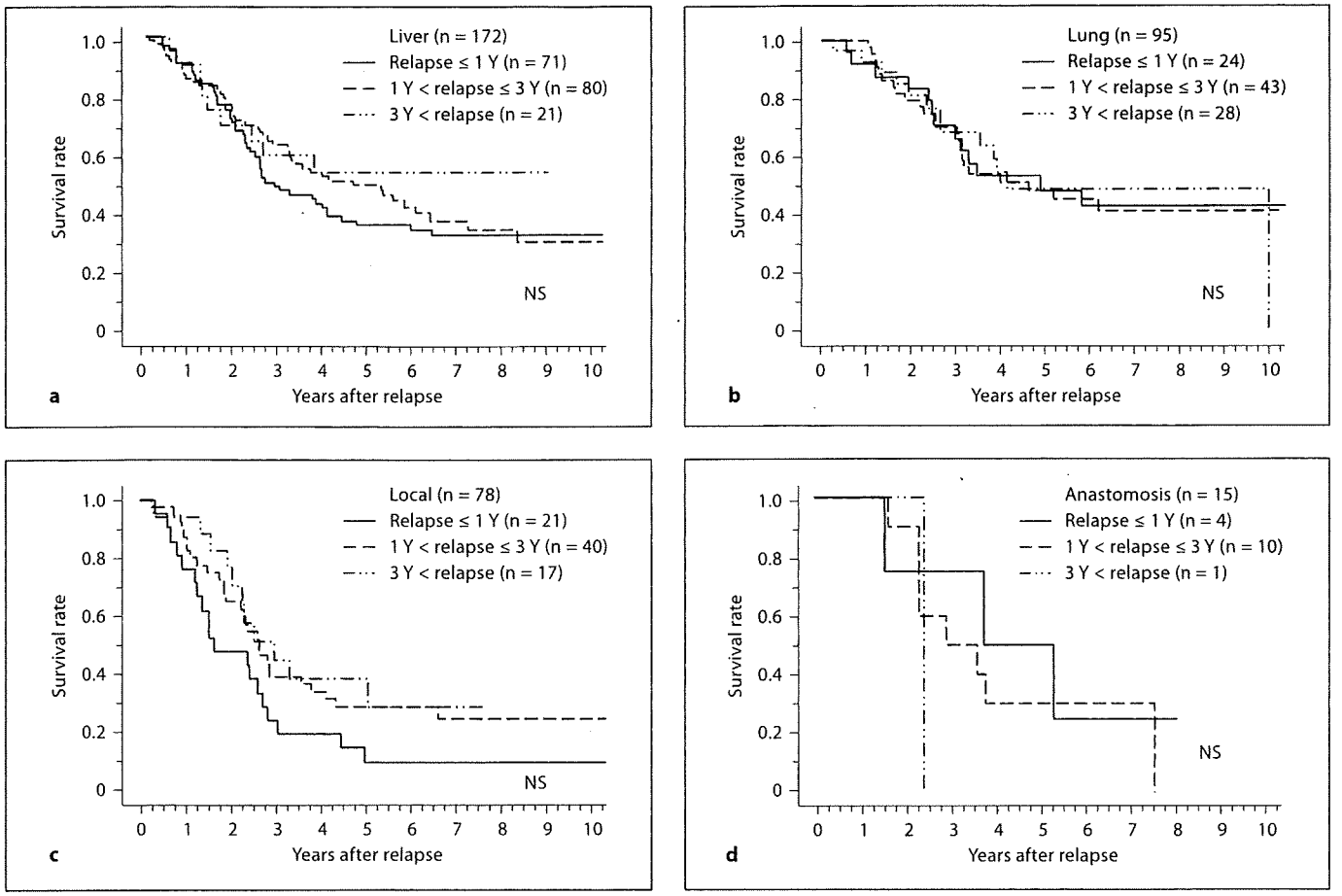

Fig. 2. There were no differences in the prognosis after curative resection for relapse among the three TR groups for patients with (**a**) liver, (**b**) lung, (**c**) local, or (**d**) anastomotic recurrence.

between group B and group C patients. There were no significant differences in survival after relapse among the three TR groups for patients with pulmonary or anastomotic relapse (table 3).

Resection Rate in Relapsed Cases

Curative resection for recurrent tumors was performed in 46.1% of cases of liver metastasis, 38.0% of cases of lung metastasis, 37.3% of cases of local recurrence, and 68.2% of cases of anastomotic recurrence. There were significant differences in the resection rates for the patients with liver ($p = 0.0023$) and pulmonary ($p = 0.038$) relapse among the three TR groups (table 4, while no differences were observed in resection rates for patients with local or anastomotic relapse among the three TR groups. The resection rate for other recurrence sites was 40.2% in total.

Survival after Curative Resection for Recurrent Tumors

Of the 906 patients with relapse, 379 (41.8%) underwent curative resection for recurrent tumors. The 5-year survival rates after resection for recurrent tumors of the liver, lungs, local sites, and anastomotic sites were 45, 48, 27, and 33%, respectively.

There was no difference in survival after relapse in patients who underwent curative resection for any relapse sites according to the timing of relapse (fig. 2). However, group A patients who received resection for local relapse showed significantly worse survival than the combined group of patients from groups B and C who received resection for local relapse ($p = 0.040$). In other recurrence sites, there were no differences in prognosis between group A, group B and C. Of the 379 patients who received resection for recurrent tumors, 240 (63.3%) experienced

Table 3. Overall survival rate after initial colorectal surgery and relapse according to timing of relapse

Recurrent site	TR (patients)	5-Year overall survival rate after initial colorectal surgery, %	p value	5-Year overall survival rate after relapse, %	p value
Liver	A (188)	18	<0.0001	14	0.018
	B (140)	39		31	
	C (45)	69		32	
Lung	A (82)	18	<0.0001	15	0.34
	B (113)	29		21	
	C (55)	72		26	
Local	A (74)	12	<0.0001	9	0.0021
	B (95)	26		16	
	C (40)	83		26	
Anastomosis	A (7)	29	0.22	29	0.95
	B (14)	36		21	
	C (1)	100		0	

A = TR ≤ 1 year; B = 1 year < TR ≤ 3 years; C = 3 years < TR.

re-relapse. Among them, 24 remained disease-free after surgery for re-relapse. Finally, 163 of the 906 patients with relapse (18.0%) remained disease-free.

Prognostic Factors after Relapse

In the 906 patients, age ($p < 0.0001$), histologic grade ($p < 0.0001$), direct invasion of the primary tumor to other organs ($p = 0.0075$), TNM staging of the primary tumor ($p = 0.0014$), timing of relapse ($p = 0.0035$), and the performance of curative resection for relapse ($p < 0.0001$) had effects on survival after relapse based on the log-rank test. Among them, histologic grade ($p = 0.012$), direct invasion of the primary tumor to other organs ($p = 0.0010$), and the performance of curative resection for relapse ($p < 0.0001$) were independent prognostic factors (table 1).

Discussion

This study demonstrated that, in patients who underwent curative resection for relapse of colorectal cancer, the timing of relapse did not affect the survival time after relapse. There were no differences in overall survival after hepatectomy for liver metastases according to timing of relapse in our series. Kornprat et al. [18] reported the outcome after hepatectomy for multiple colorectal metastases. In their study, there was no difference in survival between patients with a disease-free interval after colorectal surgery of <12 months and those with an interval of ≥12 months. On the other hand, Tsai et al. [19] demonstrated that synchronicity of liver metastasis is associated with disease-free survival after hepatectomy. In their study, the disease-free survival after hepatectomy in patients with metachronous liver metastasis was better than that in those with synchronous liver metastasis. Their multivariate analysis revealed that both synchronicity and primary tumor stage were independent prognostic factors that influenced disease-free survival.

In pulmonary metastases, we showed that there were no differences in prognoses after curative metastasectomy among the three different TR groups. That is, the survival curves after pulmonary resection were very similar among the three TR groups in this study. Lee and coworkers [17] demonstrated an association between timing of relapse and prognosis after pulmonary resection for metastases from colorectal cancer. In their study, the prognoses after pulmonary resection did not differ between the patients with a TR of <24 months and those with a TR of >24 months. Our study supports their results. On the other hand, a recent German study [20] showed that a disease-free interval of >36 months was a prognostic factor in a group of 153 patients. A large-scale study will be needed to clarify the association between timing of relapse and survival after pulmonary resection.

As for local relapse, the patients who underwent curative resection for recurrent tumors within 1 year after the initial colorectal resection had worse outcomes after relapse than those who underwent such resection after 1 year. In contrast, Wanebo et al. [21] demonstrated that there was no difference in prognosis between patients undergoing an abdominosacral resection for recurrent rectal cancer within 1 year and those undergoing this procedure after 1 year. One of the reasons for this discrepancy may be the difference in the populations of the two studies. That is, only patients with advanced recurrent rectal cancer were evaluated in the study of Wanebo et al.

In this study, we showed that the curative resection rates differed according to the timing of relapse for patients with liver or lung recurrence, but not for those with local or anastomotic recurrence. In other words, there were significant differences in the resection rates for distant metastases according to the timing of relapse after curative resection for colorectal cancer. In our series, the

Table 4. TR and curative resection rate

Recurrence site	TR	Patients with curative resection for relapse	Patients without resection for relapse	Total number of relapses %	Resection rate, %	p value
Liver		172	201	373 (7.1)	46.1	
	A	71	117	188	37.8	0.0023
	B	80	60	140	57.1	
	C	21	24	45	46.7	
Lung		95	155	250 (4.8)	38.0	
	A	24	58	82	29.3	0.038
	B	43	70	113	38.1	
	C	28	27	55	50.9	
Local		78	131	209 (4.0)	37.3	
	A	21	53	74	28.4	NS (0.14)
	B	40	55	95	42.1	
	C	17	23	40	42.5	
Anastomosis		15	7	22 (0.4)	68.2	
	A	4	3	7	57.1	NS (0.63)
	B	10	4	14	71.4	
	C	1	0	1	100.0	

The total number of patients in this study was 5,230. A = TR ≤ 1 year; B = 1 year < TR ≤ 3 years; C = 3 years < TR.

resection rates for hepatic relapse were 37.8% in group A and 54.6% in the combined group that included groups B and C. In a French population-based study, the curative surgery rate was 7.2% in synchronous liver metastases and 19.8% in metachronous ones [22]. The authors of this previous study indicated that the synchronous presence of liver metastasis with primary colorectal cancer was associated with a lower curative resection rate than metachronous liver metastasis. On the other hand, we could not find any previous study on the association between timing of relapse and the resection rates of lung metastasis from colorectal cancer. As for local relapse, several studies reported that there were no significant associations between timing of relapse and curative resection rate, which are consistent with the findings of the present study [17, 23, 24].

This study also demonstrated that the overall survival after relapse differed according to the timing of relapse in patients with hepatic and local relapse after curative resection for colorectal cancer. One of the reasons for this phenomenon may have been the differences in the resection rate according to the timing of relapse, because the prognoses after the resection with curative intent for relapse did not differ according to the timing of relapse.

At the present time, surgery with curative intent seems to be the only way to achieve the long-term survival of patients with colorectal cancer relapse. During the period of the present study, chemotherapies such as FOLFOX or FOLFIRI were not available in Japan. Chemotherapy for colorectal cancer has improved remarkably in recent years. To cure patients with relapse of colorectal cancer, it is necessary to increase the rate of curative resection for recurrent tumors. Recent studies have demonstrated that neoadjuvant chemotherapy can render nonresectable liver metastases resectable [25, 26]. Therefore, advances in chemotherapy may contribute to the improvement of surgical resection for metastases from colorectal cancer.

In conclusion, the timing of relapse after curative resection for colorectal cancer may affect the rate of curative resection for recurrent tumors. However, if patients can undergo curative resection for recurrent tumors, they may receive a survival benefit regardless of the timing of relapse. Further studies will be needed to validate our results in the era of multiagent chemotherapy.

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未来の消化器医療を探る

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今月のアプローチ

特集：未来の消化器医療を探る

アジュバント/ネオアジュバント化学療法の進歩と未来

石川　敏昭*　植竹　宏之*　杉原　健一**
いしかわ　としあき　うえたけ　ひろゆき　すぎはら　けんいち

- 補助化学療法の有用性は無作為比較試験における予後改善の有無により検証される．近年，有効な抗癌剤の開発とそれを用いた大規模無作為化比較試験の成果により補助化学療法の有用性の実証と標準治療の確立が進んでいる．
- わが国と欧米では手術術式や治療成績に違いがある．欧米の臨床試験の結果を合理的に導入しつつ，わが国の癌治療に適した標準治療の確立を進めることが重要である．
- 現在の補助化学療法では手術単独で治癒する患者も対象に含まれている．治療効果の向上だけでなく，副作用や経済的負担の軽減も重要である．適切な患者に有効かつ副作用の少ない薬剤を投与する個別化治療の確立が求められている．
- 個別化治療には指標となるバイオマーカーが必要である．実用性の高いバイオマーカーの同定を試みるトランスレーショナル研究が進められており，今後は，同定したバイオマーカーを用いた個別化治療の有用性を検証する無作為比較試験が重要になる．

Key Words　補助療法，標準治療，個別化治療，バイオマーカー，トランスレーショナル研究

消化器癌の治療では，手術治療が唯一，治癒の期待できる治療方法である．しかし，進行例では治癒切除後であっても再発する場合があり，再発例の予後は不良である．補助療法の目的は治癒切除後の再発を抑制し，予後を向上させることである．今までも補助化学療法による予後の改善が期待されてきたが，科学的根拠は十分ではなかった．近年，有効な抗癌剤の開発と大規模無作為化比較試験の成果により，補助化学療法の有用性の実証と標準治療の確立が進んでいる．本稿では，消化器癌に対する補助化学療法の進歩と標準化の現状およびその将来として個別化治療の展望を概説する（**図1**）．

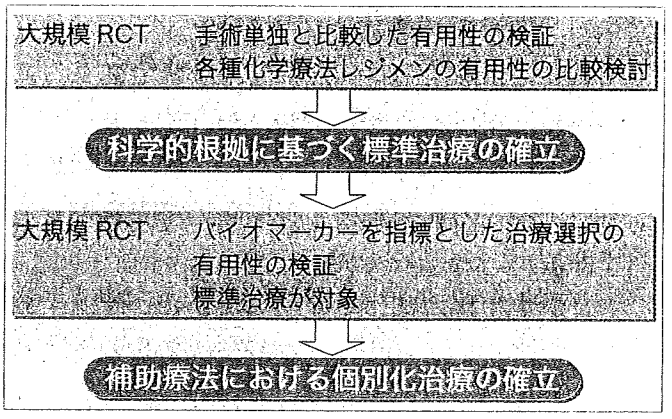

図1　補助化学療法の進歩と将来

□ 補助化学療法とは

一般に腫瘍量が少ないほど抗癌剤耐性細胞が少なく，抗腫瘍効果も高いと考えられており，治癒切除術後に遺残している可能性がある癌細胞の根絶が補助化学療法に期待されてきた．

1．ネオアジュバント/アジュバント化学療法

ネオアジュバント化学療法は，治癒手術が計画されている症例に術前に行う補助療法を意味し，切除不能進行癌に対する化学療法が奏効して結果的に根治切除が可能になった場合とは区別される．術前補助化学療法の利点は，病期の改善による機能温存手術の可能性があることや切除検体の組織学的検索により薬剤感受性の判定が可能であることがあげられる．不利な点としては，無効であった場合病期が進行し，手術の根治性が損なわれる危険性や手術合併症が増加する可能性がある．一

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表 1　消化器癌に対する補助化学療法の標準治療

標準治療が確立している補助化学療法

対　象	化学療法レジメン
Stage Ⅲ結腸癌	術後 5-FU＋LV 静注療法， UFT＋LV 療法， カペシタビン療法
Stage Ⅱ，Ⅲ胃癌	術後 S-1 療法

標準治療の確立が予想される補助化学療法

対　象	化学療法レジメン
Stage Ⅱ，Ⅲ胸部食道癌	術前 CDDP＋5-FU 療法
根治切除術後膵癌 (T1-4，N0-1，M0)	術後ゲムシタビン療法

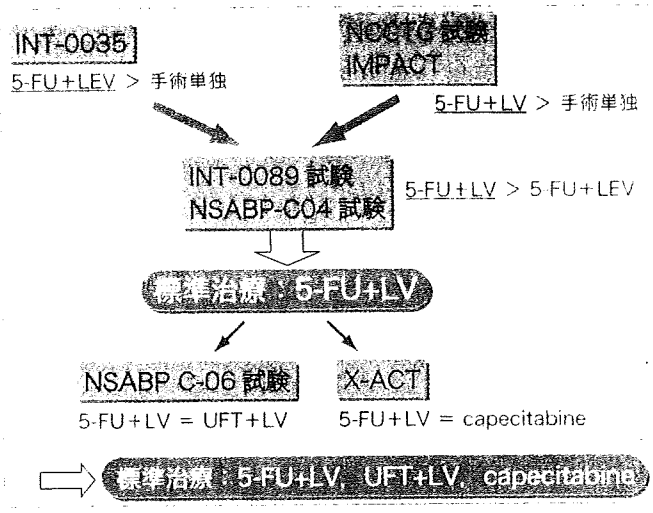

図 2　Stage Ⅲ結腸癌の術後補助化学療法の標準治療の変遷

方，術後補助（アジュバント）化学療法は，術後の病期判定に応じた治療が可能であるが，評価可能病変がないため効果判定が困難である．

術前補助化学療法に用いるレジメンは奏効率が高く，手術への影響が少ないことが条件である．消化器癌治療が外科主導で行われてきた本邦では，術後補助化学療法を中心に進歩してきた．

2．標準治療の確立の重要性

補助化学療法の目的は予後の改善であり，その有効性は無作為化比較試験における 5 年生存率や無病生存率などで評価するため，科学的根拠を得るには多くの症例集積と長期間の経過観察が必要である．

科学的根拠に基づく標準治療がない場合，無効な化学療法により副作用や経済的負担などの患者の不利益が生じたり，逆に有効な化学療法が必要な患者に行われない可能性がある．

Ⅱ　消化器癌の補助化学療法

本邦における標準治療を中心に消化器癌の補助化学療法を概説する（**表 1**）．詳細は，おのおのの治療ガイドラインに記載されているので，参照していただきたい．

1．大腸癌

Stage Ⅲ結腸癌に対する術後補助化学療法として 5-fluorouracil（FU）＋leucovorin（LV）静注療法および UFT＋LV 療法，カペシタビン療法が標準治療としてコンセンサスを得ている．**図 2** に標準治療の変遷を示した．手術単独に対する有用性が示された 5-FU＋levamisole 療法と 5-FU＋LV 静注療法の比較試験の結果[1]5-FU＋LV 静注療法が標準治療となり，さらに同法と UFT＋LV 療法および capecitabine 療法の同等性が示された[2,3]．

Stage Ⅱ結腸癌に対する補助化学療法の有効性は明らかでなく，手術単独群と UFT 術後補助化学療法群を比較する臨床試験（SACURA trial）が本邦で進行中である．

直腸癌に対する補助療法では標準治療は確立されていないが，本邦では Stage Ⅲ直腸癌に対する UFT の術後 1 年間投与の有用性が報告されている[4]．

2．胃　癌

手術単独群と S-1 を投与する術後補助化学療法の比較試験（ACTS-GC）により，Stage Ⅱ，Ⅲ胃癌に対する S-1 術後補助化学療法が標準治療として認められた[5]．現在，JCOG0501 において S-1＋CDDP 療法による術前補助化学療法の有用性の検証が行われている．

3．食道癌

手術単独群と 5-FU＋CDDP 療法による術後補助化学療法の比較試験（JCOG9204）において術後補助化学療法の有用性が示された[6]．その後行われた Stage Ⅱ，Ⅲ胸部食道癌に対する 5-FU＋CDDP 療法による術前補助化学療法と術後補助化学療法の無作為化比較試験（JCOG9907）において術前補助化学療法が術後補助化学療法よりも