in rectal cancer led to an increase of blood loss and urinary and sexual dysfunction without any survival benefit. Since then, pelvic sidewall dissection has rarely been performed in Western countries. In addition, lateral pelvic lymph node metastasis was considered part of the systemic disease.

In 1982, Heald[5] proposed a new concept for resection of rectal cancer, total mesorectal excision. This technique decreased the rate of local recurrence in patients with rectal cancer. Total mesorectal excision with chemoradiotherapy has now become the standard treatment for advanced rectal cancer in Western countries. In Japan, pelvic sidewall dissection has been actively performed along with total mesorectal excision for rectal cancer since the late 1970s, pelvic sidewall dissection has been reported to be useful in advanced lower rectal cancer.[6] In past studies, the rates of positive lateral nodes have ranged from 10.6 percent to 25.5 percent.[7–13] However, there has been no randomized controlled study on the usefulness of pelvic sidewall dissection in patients with rectal cancer. Therefore, the definitive efficacy of pelvic sidewall dissection is still unclear.

The 6th edition of the AJCC cancer staging manual[14] designated both internal and external iliac lymph nodes as regional nodes in rectal cancer. However, details regarding lateral pelvic lymph nodes were not mentioned.

The aim of this retrospective multicenter study was to clarify the characteristics of lymph node metastasis located in the pelvic sidewall as well as in the mesorectum in patients with lower rectal cancer and to investigate the efficacy of pelvic sidewall dissection performed in addition to total mesorectal excision. We previously reported on the indications for pelvic sidewall dissection both in patients with upper and in those with lower rectal cancer from the database of the 12 member institutes of the Japanese Society for Cancer of the Colon and Rectum.[15] In the present study, we clarified details of the outcomes of surgery alone for lower rectal cancer with and without pelvic sidewall dissection.

PATIENTS AND METHODS

Patients

We reviewed records of 1,272 patients with lower rectal cancer enrolled in a database of patients who underwent curative resection at 12 institutions between 1991 and 1998. None of the patients received radiotherapy in this study. Lower rectal cancer was defined as the distal margin of tumor being located below the peritoneal reflection. All institutions were members of the Japanese Society for Cancer of the Colon and Rectum. This study was approved by the local Ethics Committee of each institution. All patients received total mesorectal excision.

The indications for pelvic sidewall dissection were T2-T4 in five institutions, T3-T4 in two, suspected positive lymph nodes in the mesorectum in one, and T3-T4 or suspected positive lymph nodes in the mesorectum in four. These criteria were determined at each institution based on risk analysis of lateral pelvic lymph node metastasis. Patients who underwent transanal local excision or endoscopic mucosal resection were excluded from this study. Other exclusion criteria were cancers associated with ulcerative colitis, Crohn's disease, or familial adenomatous polyposis.

Preoperative investigations included barium enema examination, colonoscopy, endoscopic ultrasonography, chest x-ray, ultrasonography (US) or computed tomography (CT) of the liver, and blood tests using carcinoembryonic antigen (CEA). Most institutions established a follow-up examination period of 5 to 10 years. The follow-up system consisted of serum tumor marker measurements every three months for the first three years and every six months for the next two years, hepatic imaging (US or CT) and chest x-ray every three to six months, pelvic CT every year, and colonoscopy every one to two years.

Statistical Analysis

We analyzed the risk factors for perirectal lymph node metastasis in all 1,272 patients who underwent total mesorectal excision and those for lateral pelvic lymph node metastasis in the 784 patients who had pelvic sidewall dissection in addition to total mesorectal excision. Prognostic factors were also analyzed.

Statistical analysis was performed using the StatView statistical package (StatView 5.0; Abacus Concepts, Inc., Berkeley, CA). Data are expressed as numbers of patients and percentages or means±standard deviation. The relationships between each parameter and lymph node metastasis or local recurrence were analyzed using the chi-squared test. Logistic regression analysis was used to determine independent risk factors for lymph node metastasis and local recurrence. The Kaplan-Meier method was used to calculate the actuarial survival of patients. Overall survival rates in all groups were compared by log rank test. Cox's proportional hazards model was used to determine independent prognostic factors in patients with lower rectal cancer. Statistical significance was established at $P < 0.05$ for all results.

RESULTS

Pelvic Sidewall Dissection

Of the 1,272 patients, 784 underwent pelvic sidewall dissection in addition to total mesorectal excision. Characteristics of patients with and without pelvic sidewall dissection are shown in Table 1. Pelvic sidewall dissection was more likely to be performed in younger than in older patients. Patients who had pelvic sidewall dissection were significantly more likely to have tumors ≥4 cm in size ($P < 0.0001$), not well differentiated adenocarcinoma ($P = 0.0006$), greater depth of tumor invasion ($P < 0.0001$),

TABLE 1. Characteristics of patients with and without pelvic sidewall dissection

	PSD (n = 784)		No PSD (n = 488)		
	n	(%)	n	(%)	P value
Gender					
Male	507	(64.7)	296	(60.7)	0.15
Female	277	(35.3)	192	(39.3)	
Age (yr)					
≥62	348	(44.4)	252	(51.6)	0.011
<62	436	(55.6)	235	(48.2)	
Unknown			1		
Size (cm)					
<4	246	(31.4)	299	(61.3)	<0.0001
≥4	535	(68.2)	182	(37.3)	
Unknown	3	(0.4)	7		
Histology					
Well or moderately differentiated adenocarcinoma	723	(92.2)	471	(96.5)	0.0006
Others	61	(7.8)	15	(3.1)	
Unknown	0		2	(0.4)	
T category					
T1	37	(4.7)	196	(40.2)	<0.0001
T2	207	(26.4)	127	(26.0)	
T3	497	(63.4)	157	(32.2)	
T4	43	(5.5)	8	(1.6)	
AJCC staging					
I	179	(22.8)	282	(57.8)	<0.0001
II	224	(28.6)	86	(17.6)	
III	381	(48.6)	120	(24.6)	

PSD = pelvic sidewall dissection.

and a more advanced stage of cancer ($P < 0.0001$) than those who did not receive pelvic sidewall dissection. For example, the proportion of patients with category T3 or T4 tumors or cancer stage III was approximately twice as high in patients who received pelvic sidewall dissection as in those who did not.

Lymph Node Metastasis

Perirectal lymph node metastasis was observed in 476 (37.4 percent) of all patients who underwent surgery, and lateral pelvic lymph node metastasis was observed in 117 (14.9 percent) of those who had pelvic sidewall dissection (Table 2). The rates of both types of metastasis increased significantly with depth of tumor invasion ($P < 0.0001$). Table 3 shows the distribution of patients with each type of node metastasis in relation to tumor category for the 784 patients with pelvic sidewall dissection. A total of 92 patients (11.7 percent) had both types of metastasis, 263 (33.5 percent) had only perirectal, 25 (3.2 percent) had only lateral pelvic, and 404 (51.5 percent) had no neither type of lymph node metastasis.

The lateral pelvic area was classified into 6 parts (Fig. 1): internal iliac areas both distal and proximal to superior vesical artery, obturator area, external iliac area, common iliac area, and aortic bifurcation area. Of the 117 patients with lateral pelvic lymph node metastasis, 55 (47 percent) had lymph node metastasis along the internal iliac artery distal to the superior vesical artery, 45 (38 percent) in the obturator area, and 30 (26 percent) along the internal iliac artery proximal to superior vesical artery. Only 9 patients (7.7 percent) had lateral pelvic lymph node metastasis found in other areas.

TABLE 2. Lymph node metastasis in patients with lower rectal cancer in relation to tumor invasion depth of tumor

	All patients			Patients with PSD		
		Perirectal LNM			Lateral pelvic LNM	
Tumor category	Total	n	(%)	Total	n	(%)
T1	233	19	(8.2)	37	2	(5.4)
T2	334	81	(24.3)	207	17	(8.2)
T3	654	347	(53.1)	497	82	(16.5)
T4	51	29	(56.9)	43	16	(37.2)
Total	1272	476	(37.4)	784	117	(14.9)

PSD = pelvic sidewall dissection; LNM = lymph node metastasis.

TABLE 3. Type of lymph node metastasis in relation to tumor category in 784 patients with pelvic sidewall dissection

	Perirectal + Lateral pelvic +		Perirectal + Lateral pelvic −		Perirectal − Lateral pelvic +		Perirectal − Lateral pelvic −		Total	
Tumor	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
T1	1	(2.7)	5	(13.5)	1	(2.7)	30	(81.1)	37	(100)
T2	11	(5.3)	41	(19.8)	6	(2.9)	149	(72.0)	207	(100)
T3	67	(13.5)	204	(41.0)	15	(3.0)	211	(42.5)	497	(100)
T4	13	(30.2)	13	(30.2)	3	(7.0)	14	(32.6)	43	(100)
Total	92	(11.7)	263	(33.5)	25	(3.2)	404	(51.5)	784	(100)

Risk factors for perirectal lymph node metastasis. Parameters such as gender, age, size of tumor, histology of tumor, T category, lymphatic invasion, and venous invasion were analyzed as potential risk factors for perirectal lymph node metastasis in the 1,272 patients undergoing total mesorectal excision for lower rectal cancer (Table 4). All of the above-mentioned variables had significant effects on perirectal lymph node metastasis in a univariate analysis. Multivariate analysis showed female gender (P = 0.0004), age under 62 years old (P = 0.0073), histology other than well or moderately differentiated adenocarcinoma (P = 0.0008), T category (T3 or T4, P < 0.0001), lymphatic invasion (P < 0.0001), and venous invasion (P = 0.037) to be independent risk factors for perirectal lymph node metastasis.

Risk factors for pelvic lymph node metastasis. In the 784 patients undergoing pelvic sidewall dissection in addition to total mesorectal excision for lower rectal cancer, univariate analysis showed significant effects of female gender, size of tumor, histology, T category, lymphatic invasion, venous invasion, and perirectal lymph node metastasis on lateral pelvic lymph node metastasis (Table 5). Only female gender (P = 0.0037), histology other than well or moderately differentiated adenocarcinoma (P = 0.0047), and the presence of perirectal lymph node metastasis (P < 0.0001) were independent risk factors for lateral pelvic lymph node metastasis on multivariate analysis.

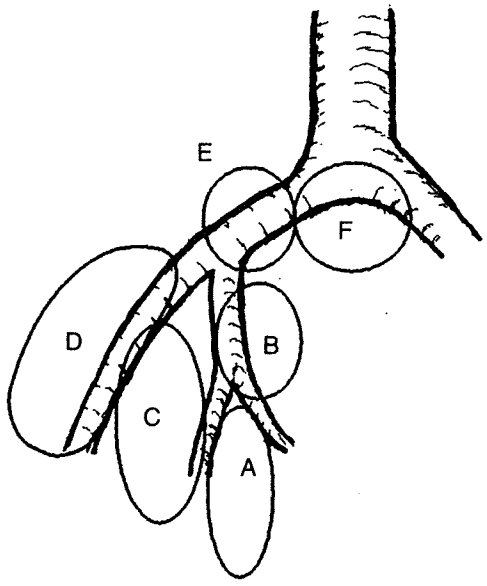

FIGURE 1. A schema of the lateral pelvic area: **(A)** internal iliac area distal to superior vesical artery and **(B)** proximal to superior vesical artery, **(C)** obturator area, **(D)** external iliac area, **(E)** common iliac area, and **(F)** aortic bifurcation area.

Local Recurrence of Cancer

Of all 1272 patients undergoing total mesorectal excision, 118 (9.3 percent) had a local recurrence of cancer. The mean follow-up was 3.3 ± 1.9 years in patients with and 5.1 ± 2.3 years in those without recurrence. As shown in Table 6, the rate of recurrence did not differ between patients who had pelvic sidewall dissection and those who did not (10.5 percent *vs.* 7.4 percent), regardless of the invasion depth of the tumor.

The rate of local recurrence was 4.1 percent in patients with stage I lower rectal cancer, 5.8 percent in those with stage II, and 16.1 percent in those with stage III. Of the 117 patients with lateral pelvic lymph node metastasis, 28 (23.9 percent) experienced local recurrence.

Risk factors for local recurrence. In the 784 patients who underwent pelvic sidewall dissection in addition to total mesorectal excision, univariate analysis showed significant effects of female gender, size of tumor, histology, tumor category, perirectal lymph node metastasis, and lateral pelvic lymph node metastasis local recurrence (Table 7). Multivariate analysis revealed that perirectal lymph node metastasis (P = 0.0016) and lateral pelvic lymph node metastasis (P = 0.0075) were independent risk factors for local recurrence.

Survival

No significant difference in overall five-year survival was seen between patients with pelvic sidewall dissection and those without pelvic sidewall dissection (75.8 percent *vs.* 79.5 percent) (Fig. 2). However, although no differences were seen between the two groups in patients with stage I or stage III cancer, patients with stage II lower rectal cancer who underwent pelvic sidewall dissection had a significantly better prognosis (87.0 percent five-year survival)

TABLE 4. Risk factors for perirectal lymph node metastasis in 1,272 patients with lower rectal cancer

		Perirectal LNM		Univariate analysis			Multivariate analysis		
	Total	n	(%)	OR	95% CI	P value	OR	95% CI	P value
Gender									
Male	803	278	(34.6)	1			1		
Female	469	198	(42.2)	1.38	1.09–1.74	0.007	1.63	1.25–2.13	0.0004
Age (yr)									
≥62	642	221	(46.4)	1			1		
<62	629	255	(53.6)	1.03	1.03–1.63	0.0244	1.43	0.54–0.91	0.0073
Unknown	1								
Size (cm)									
<4	545	136	(25.0)	1			1		
≥4	717	339	(47.3)	2.70	2.12–3.44	<0.0001	1.29	0.95–1.76	NS
Unknown	10								
Histology									
Well or moderately differentiated adenocarcinoma	1194	425	(35.6)	1			1		
Others	76	51	(67.1)	3.69	2.26–6.04	<0.0001	2.48	1.46–4.22	0.0008
Unknown	2								
T category									
T1–2	567	100	(17.6)	1			1		
T3–4	705	376	(53.3)	5.35	4.12–6.94	<0.0001	3.46	2.50–4.78	<0.0001
Lymphatic invasion									
Absent	343	46	(13.4)	1			1		
Present	922	430	(46.6)	5.64	4.03–7.90	<0.0001	3.50	2.42–5.06	<0.0001
Unknown	7								
Venous invasion									
Absent	493	120	(24.3)	1		<0.0001	1		
Present	772	356	(46.1)	2.66	2.07–3.41		1.36	1.02–1.82	0.037
Unknown	7								

OR = odds ratio; CI = confidence interval; LNM = lymph node metastasis.

than those who did not (67.1 percent five-year survival); $P = 0.0026$).

Prognostic factors. In Cox proportional hazard analyses of all 1,272 patients with lower rectal cancer, age ($P = 0.0015$), histology ($P = 0.0002$), T category ($P = 0.0002$), perirectal lymph node metastasis ($P < 0.0001$), and pelvic sidewall dissection ($P = 0.029$) were independent prognostic factors (Table 8). In the 784 patients with pelvic sidewall dissection, age ($P = 0.0017$), histology ($P = 0.0047$), T category ($P = 0.021$), perirectal lymph node metastasis ($P < 0.0001$), and lateral pelvic lymph node metastasis ($P < 0.0001$) were independent prognostic factors (Table 9). In patients with stage III lower rectal cancer, the five-year survival rate of those without lateral pelvic lymph node metastasis was 67.3 percent *vs.* 47.7 percent for patients with lateral pelvic lymph node metastasis.

DISCUSSION

In this study, 37.4 percent of patients with lower rectal cancer had perirectal lymph node metastasis and 14.9 percent of those who underwent pelvic sidewall dissection had lateral pelvic lymph node metastasis. The rates of lateral pelvic lymph node metastasis reported in previous studies vary from 10.6 percent to 25.5 percent, with most reporting rates around 15 percent.[7,8,11–13] Thus, our result was consistent with those of previous studies.

The rates of perirectal lymph node metastasis and lateral pelvic lymph node metastasis increased with the invasion depth of the tumor. A total of 16.5 percent of patients with T3 tumors and 37.2 percent of those with T4 tumors had lateral pelvic lymph node metastasis. Effective treatment of lateral pelvic lymph node metastasis would likely improve the prognosis of patients with T3 and T4 lower rectal cancer.

We investigated the risk factors for both perirectal lymph node metastasis and lateral pelvic lymph node metastasis and found that female gender and histology showing the main tumor to be not well or moderately differentiated were independent risk factors for both types of lymph node metastasis in lower rectal cancer. The reason why female gender was a risk factor was obscure. There is some possibility that a female hormone such as estrogen is associated with lymph node metastasis, as appears to be the case in breast cancer.[16] Further studies will be essential to clarify this issue.

In our study, multivariate analysis revealed that, in addition to perirectal lymph node metastasis, lateral pelvic lymph node metastasis was an independent risk factor for local recurrence. Our patients with lateral pelvic lymph node metastasis had a local recurrence rate of 23.9

TABLE 5. Risk factors for lateral pelvic lymph node metastasis in 784 patients with pelvic sidewall dissection

		Lateral pelvic LNM		Univariate analysis			Multivariate analysis		
	Total	n	(%)	OR	95% CI	P value	OR	95% CI	P value
Gender									
Male	507	60	(11.8)	1			1		
Female	277	57	(20.6)	1.93	1.30–2.87	0.001	1.88	1.23–2.87	0.0037
Age (yr)									
≥62	398	54	(13.6)	1					
<62	386	63	(16.3)	1.24	0.84–1.84	0.279	...	...	...
Size (cm)									
<4	246	22	(8.9)	1			1		
≥4	535	95	(17.8)	2.20	1.35–3.59	0.0013	1.67	0.92–3.01	0.085
Unknown	3								
Histology									
Well or moderately differentiated adenocarcinoma	723	96	(13.3)	1			1		
Others	61	21	(34.4)	3.43	1.94–6.06	<0.0001	2.48	1.35–4.55	0.0047
T category									
T1–2	244	19	(7.8)	1			1		
T3–4	540	98	(18.1)	2.63	1.57–4.40	0.0002	1.18	0.63–2.24	0.60
Lymphatic invasion									
Absent	134	9	(6.7)	1			1		
Present	648	108	(16.7)	2.78	1.37–5.63	0.0033	1.42	0.66–3.05	0.36
Unknown	2								
Venous invasion									
Absent	232	22	(9.5)	1			1		
Present	551	95	(17.2)	1.99	1.22–3.25	0.0054	1.67	0.97–2.85	0.056
Unknown	1								
Perirectal LNM									
Absent	429	25	(5.8)	1			1		
Present	355	92	(25.9)	5.65	3.54–9.03	<0.0001	4.22	2.58–6.90	<0.0001

OR = odds ratio; CI = confidence interval; LNM = lymph node metastasis.

percent, compared with the overall rate of 9.3 percent in our series. In patients undergoing curative resection for T3 or T4 rectal tumors, Ueno *et al.*[13] found a local recurrence rate of 44.0 percent in patients with lateral pelvic lymph node metastasis and 11.7 percent in those without ($P < 0.001$).

Lateral pelvic lymph node metastasis was also an independent predictor of poor prognosis in our patients with pelvic sidewall dissection, as were age, histology, T category, and perirectal lymph node metastasis. In patients with stage III lower rectal cancer, the five-year survival rate of those without lateral pelvic lymph node metastasis was approximately 20 percentage points higher than that of patients with lateral pelvic lymph node metastasis. Therefore, adjuvant therapy for patients with lateral pelvic lymph node metastasis is important. Patients with stage III colorectal cancer usually receive adjuvant chemotherapy. However, more intensive chemotherapy might be recommended for those with lateral pelvic lymph node metastasis.

The definition of the lateral pelvic area in the 6th edition of AJCC cancer staging manual seems rather unclear. The present study showed that lymph node metastasis along the external iliac artery was very rare. More than 90 percent of metastatic lymph nodes were located in the obturator area and along the internal iliac

TABLE 6. Local recurrence of cancer in patients with and without pelvic sidewall dissection

	PSD			Non-PSD				All		
		Recurrence			Recurrence				Recurrence	
	Total	n	(%)	Total	n	(%)	P value	Total	n	(%)
T1	37	1	(2.7)	196	4	(2.0)	NS	233	5	(2.1)
T2	207	10	(4.8)	127	10	(7.9)	NS	334	20	(6.0)
T3	497	61	(12.3)	157	21	(13.4)	NS	654	82	(12.5)
T4	43	10	(23.1)	8	1	(12.5)	NS	51	11	(21.6)
Total	784	82	(10.5)	488	36	(7.4)	NS	1272	118	(9.3)

PSD = pelvic sidewall dissection; NS = not significant.

Table 4. Local recurrence of cancer in 784 patients with pelvic sidewall dissection

		Local recurrence		Univariate analysis			Multivariate analysis		
	Total	n	(%)	OR	95% CI	P value	OR	95% CI	P value
Gender									
Male	507	43	(8.5)	1			1		
Female	277	39	(14.1)	1.77	1.12–2.80	0.01	1.56	0.96–2.53	0.073
Age (yr)									
<62	436	45	(10.3)	1					
≥62	348	37	(10.6)	1.03	0.65–1.64	0.89	...	...	...
Size (cm)									
<4	246	16	(6.5)	1			1		
≥4	535	66	(12.3)	2.02	1.15–3.57	0.01	1.21	0.63–2.35	0.57
Unknown	3								
Histology									
Well or moderately differentiated adenocarcinoma	723	68	(9.4)	1			1		
Others	61	14	(23.0)	2.87	1.50–5.48	0.0009	1.78	0.89–3.55	0.10
T category									
T1–2	244	11	(4.5)	1			1		
T3–4	540	71	(13.1)	3.21	1.67–6.17	0.0003	1.99	0.93–4.25	0.077
Lymphatic invasion									
Absent	134	11	(8.2)	1					
Present	648	71	(11.0)	1.38	0.71–2.67	0.34	...	...	...
Unknown	2								
Venous invasion									
Absent	232	20	(8.6)	1					
Present	551	62	(11.3)	1.34	0.79–2.28	0.27	...	...	...
Unknown	1								
Perirectal LNM									
Absent	429	22	(5.1)	1			1		
Present	355	60	(16.9)	3.76	2.26–6.27	<0.0001	2.43	1.40–5.89	0.0016
Lateral pelvic LMN									
Absent	667	54	(8.1)	1			1		
Present	117	28	(23.9)	3.57	2.15–5.93	<0.0001	2.11	1.22–3.65	0.0075

OR = odds ratio; CI = confidence interval; LNM = lymph node metastasis.

artery. The lymph nodes in the internal iliac area distal to the superior vesical artery were most frequently involved. Almost half of the lateral pelvic lymph node metastases were located in this area. The next most frequent site of lateral pelvic lymph node metastasis was the obturator area. Canessa *et al.*[17] reported an anatomic study using cadaveric dissection, in which most of the metastatic lymph nodes found in the lateral pelvic area were located in the obturator area. Therefore, we believe that the next AJCC cancer staging manual should mention not the external iliac area but the obturator area as a site of regional lymph node metastasis in lower rectal cancer.

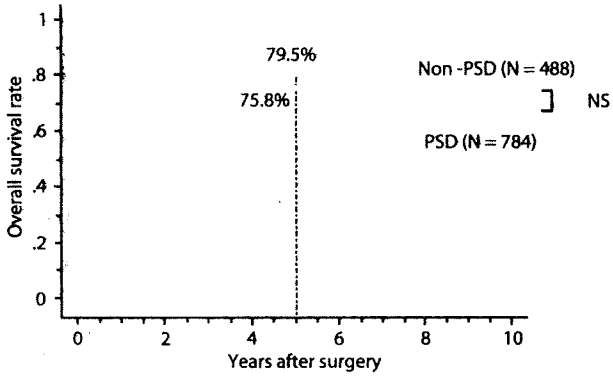

FIG. 3. The overall survival curve of patients with and without pelvic sidewall dissection. The 5-year overall survival rates in patients with and without pelvic sidewall dissection were 75.8 percent and 79.5 percent, respectively.

In many Western countries, the standard therapy for lower rectal cancer is total mesorectal excision with chemoradiotherapy.[18,19] In Japan, total mesorectal excision with pelvic sidewall dissection is accepted as a standard treatment, but the effectiveness of pelvic sidewall dissection has been controversial. We observed no differences in the rates of local recurrence between patients with and those without pelvic sidewall dissection. Because patients undergoing pelvic sidewall dissection tended to have more advanced disease, this finding may not be surprising. However, we found no difference in recurrence rates for any invasion depth of the tumor.

A recent study in patients with stage II or stage III rectal cancer reported a higher rate of local recurrence

TABLE 8. Prognostic factors for overall survival in 1272 patients with lower rectal cancer

	Patients	*Cox proportional hazard model*		
	n	*HR*	*95% CI*	*P value*
Gender				
Male	803	1		
Female	469	0.88	0.69–1.13	0.32
Age (yr)				
≥62	642	1		
<62	629	1.47	1.16–1.87	0.0015
Size (cm)				
<4	545	1		
≥4	717	1.13	0.84–1.54	0.42
Unknown	10			
Histology				
Well or moderately differentiated adenocarcinoma	1194	1		
Others	76	2.01	1.39–2.90	0.0002
Unknown	2			
T category				
T1–2	567	1		
T3–4	705	1.90	1.35–2.67	0.0002
Lymphatic invasion				
Absent	343	1		
Present	922	1.33	0.94–1.88	0.11
Unknown	7			
Venous invasion				
Absent	493	1		
Present	772	1.18	0.90–1.56	0.23
Unknown	7			
Perirectal LNM				
Absent	796	1		
Present	476	2.26	1.75–2.93	<0.0001
Pelvic sidewall dissection				
Performed	784	1		
Not performed	488	1.36	1.03–1.78	0.029

HR = hazard ratio; CI = confidence interval; LNM = lymph node metastasis.

rate with pelvic sidewall dissection than with chemoradiotherapy.[20] However, that study was neither randomized nor case-matched. Watanabe *et al.*[21] found no differences in recurrence in patients with T3 or T4 rectal tumors who underwent radiation with or without pelvic sidewall dissection, but the number of subjects in that study was small. A randomized controlled study is essential to clarify the effect of pelvic sidewall dissection on local recurrence in patients with advanced lower rectal cancer.

We also found no difference in overall survival between patients with and those without pelvic sidewall dissection. Again, this may not be surprising because of the more advanced state of disease in the group receiving pelvic sidewall dissection. However, the Cox proportional hazards model showed that lack of pelvic sidewall dissection was a significant predictor of poor prognosis. In addition, patients with stage II lower rectal cancer who had pelvic sidewall dissection appeared to have a significantly better prognosis than those without pelvic sidewall dissection, although patients with stage I or III lower rectal cancer did not receive the same survival benefit. Thus, the indication for pelvic sidewall dissection may be potentially limited to those with stage II. However, the possibility exists that the better prognosis in patients with stage II cancer with pelvic sidewall dissection was a result of stage migration. Namely, patients with a diagnosis of stage II who did not undergo pelvic sidewall dissection may have actually had stage III disease that went undiagnosed because the nodes were not identified.

Fujita *et al.*[22] reported that pelvic sidewall dissection improved the prognosis of rectal cancer patients with a small number of lymph node metastases. In their study, the five-year disease-free survival rate was 73.3 percent in patients with N1 lymph node metastasis who underwent pelvic sidewall dissection, and 35.3 percent in those without pelvic sidewall dissection ($P = 0.013$). In contrast, Nagawa *et al.*[23] demonstrated that pelvic sidewall dissection was not necessary in patients with advanced lower rectal cancer who underwent preoperative radiotherapy. In their study, no difference was observed in either overall survival or disease-free survival between patients with and those without pelvic sidewall dissection in addition to preoperative radiotherapy. Their study was a randomized controlled trial, but the number of recruited patients was only 51. A large-scale randomized controlled study on the efficacy of pelvic sidewall dissection has not yet been

TABLE 5. Prognostic factors for overall survival in 784 patients with pelvic sidewall dissection

	Patients	Cox proportional hazard model		
	n	HR	95% CI	P value
Gender				
Male	507	1		
Female	277	0.80	0.59–1.08	0.15
Age (yr)				
<62	436	1		
≥62	348	1.59	1.19–2.11	0.0017
Size (cm)				
<4	246	1		
≥4	535	0.97	0.66–1.43	0.87
Unknown	3			
Histology				
Well or moderately differentiated adenocarcinoma	723	1		
Others	61	1.83	1.20–2.79	0.0047
T category				
T1–2	244	1		
T3–4	540	1.68	1.08–2.62	0.021
Lymphatic invasion				
Absent	134	1		
Present	648	1.50	0.90–2.51	0.11
Unknown	2			
Venous invasion				
Absent	232	1		
Present	551	1.25	0.88–1.78	0.22
Unknown	1			
Perirectal LNM				
Absent	429	1		
Present	355	2.47	1.78–3.45	<0.0001
Lateral pelvic LNM				
Absent	667	1		
Present	117	2.27	1.63–3.14	<0.0001

HR = hazard ratio; CI = confidence interval; LNM = lymph node metastasis.

reported. However, a phase III trial (JCOG 0212) of the effectiveness of pelvic sidewall dissection is ongoing in Japan and will recruit 600 patients in total.

In conclusion, we found no differences in the rates of local recurrence between the pelvic sidewall dissection group and the non-pelvic sidewall dissection group, although there might be a selection bias for pelvic sidewall dissection. Lateral pelvic lymph node metastasis is a risk factor for both local recurrence and overall survival. A randomized controlled trial will be essential to test the survival benefit of pelvic sidewall dissection in patients with advanced lower rectal cancer.

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【大腸癌肝転移切除成績の現状】

切除可能肝転移に対する術後補助化学療法

Adjuvant Chemotherapy after Potentially Curative Resection of Liver Metastases from Colorectal Cancer

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Summary

大腸癌肝転移完全切除後の補助化学療法について概説した。

肝転移切除後は残肝再発が多いが，抗がん剤の肝動注療法は生存率の向上に寄与しない。肝動注＋全身化学療法は無病生存期間の延長はみられるものの，全生存率の延長はみられない。全身化学療法のprospectiveな研究は少ないが，meta-analysisやpooled analysisの報告では，抗がん剤の術後投与は生存率を延長するとされている。EORTC40983の術前・術後にFOLFOX療法を行う治療法が現在有効な補助療法とみなされているが，EORTC40983の解析結果には問題があり，また切除可能な肝転移に対する術前投与にも問題が指摘されている。

切除可能肝転移に対する補助療法は肝切除後の全身化学療法が基本であり，投与regimenはFOLFOX療法が最もよいと考えられるが，単に進行癌に対するregimenを外挿するのではなく，肝切除という大きな手術侵襲が加わった患者に適した投与法の開発が望まれる。

● 大腸癌肝転移　● 術後補助化学療法　● 肝動注療法
● 全身化学療法　● FOLFOX療法

Key words

はじめに

大腸癌は日本人がん罹患の第1位を占め、2009年には138,000人が罹患すると予測されている。大腸癌症例の約20％に認められる肝転移に対する標準治療は肝切除であるが，その5年生存率は40％程度であり，残肝再発と肺転移再発とが主な再発形式である。肝転移切除後の再発予防を目的として補助療法が検討されてきたが，いまだに明らかな有効性が証明された補助療法はない。

本稿では大腸癌肝転移治癒切除例に対する補助化学療法について概説する。なお，補助化学療法とは肝転移完全切除後に行う化学療法とし，表にはprospectiveに行われた主なランダム化比較試験を採り上げた。

肝動注療法

肝転移切除後は残肝再発が約半数に起こり，残肝再発抑制のために肝局所療法，主に抗がん剤の肝動注療法が行われてきた。

抗がん剤の肝動注療法は腫瘍に高濃度の薬剤が長時間到達し，また主に使用されるFUDRや5-FUなどのフッ化ピリミジン系薬剤は肝で代謝・排泄されて全身への毒性が少ない利点がある。切除不能肝転移における奏効率は35～83%，meta-analysisでは奏効率は41%で全身化学療法よりも有意に高いが，生存率では全身化学療法との間に有意差はない[1]。

このような背景の下に肝動注療法は肝切除後の補助化学療法としても行われる。肝動注療法単独(表1)では残肝再発率は低下させ得たとしても肺転移を主体とする血行性転移を抑制できず，全生存率，無病生存率，残肝再発率ともに生存率の向上はみられていない。Lorenzら[2]の研究では中間解析の結果，治療群において治療を行った84例中治療関連死が8例にみられて試験を中止している。

肝動注に全身化学療法を加えた成績(表2)は，肝動注療法単独と比べると良好である。しかし，Kemeny Nら[5]の研究ではendpointである2年生存率は良好であるが，その後の解析[9]で動注群の無病生存率は有意に良好だったが，5年，10年の全生存率は変わらなかった。Kemeny MMら[8]は肝動注＋全身化学療法と全身化学療法を比較し，4年無病生存率は動注群でよかったが，4年生存率では有意差がなかった。この研究は症例集積に10年もかかった上に脱落例が多く，しかもITT解析でない。

このように肝動注＋全身化学療法は無病生存率の向上はあるが，全生存率の向上はみられていない。すなわち再発時期は遅らせるが再発率は低下させえないということだろうか。

これらの研究は全身化学療法にオキサリプラチンやイリノテカンなどの新規抗がん剤は使われていないが，Houseら[10]のretrospectiveな検討では肝動注＋modern chemo(FOLFOXまたはFOLFIRI)を行った群の方がmodern chemoのみの群よりも5年生存率，5年肝無再発率，5年無再発率ともに有効だった。肝動注とFOLFOXやFOLRIRIとを併用することで予後の向上が期待できるかもしれない。

一方，最近の新規抗がん剤を用いた全身併用化学療法の成績はよく，奏効率の面でも肝動注療法と競うようになった。この肝動注＋全身化学療法の評価については，FOLFOXやFOLFIRIなどの全身化学療法のみで同等の成績が出るのではないかとの観点からの検討が要る。

肝動注における免疫化学療法の報告は少ないがLygidakisら[7]はインターロイキン2(IL-2)を肝動注した方が皮下注するよりも有意に副作用が少なく、延命効果が高いとする結果を報告した(表2)。同様にOkunoら[11]は18例と症例数は少ないが，肝切除後にIL-2の肝動注とMMC，5-FU全身化学療法を6ヵ月間行って75%もの5年生存率を報告しており，今後さらに多数症例で検討されるべき投与法と思われる。

肝動注は動注特有の肝毒性，カテー

表1　肝動注療法(HAI)

報告者	発表年	治療法 試験群 vs. 対照群	症例数	全生存率 (期間)	無病生存率／ 無再発生存期間	残肝再発率
Lorenz M et al.	1998	HAI：5-FU 1,000 mg/m²/d＋FA 200 mg/m² 5 days 6コース	108	全生存期間 34.5月	無再発生存期間 14.2月	18ヵ月再発率 33.3%
		vs. 手術単独	111	40.8月	13.7月	36.7%
				ns	ns	ns
Rudroff C et al.	1999	HAI：MMC 8 mg/m² d1＋5-FU 800 mg/m² d1-5 28日ごと4コース	13	5年生存率 31%	5年無病生存率 23%	
		vs. 手術単独	16	25%	15%	
				ns	ns	
兼武生 ほか	2001	HAI：5-FU 1,000 mg/m²/2週×16	71	5年生存率 44.7%	5年無病生存率 29.5%	5年無再発率 36.0%
		vs. 手術単独	66	47.9%	33.9%	34.0%
				ns	ns	ns

テルや動注ポートあるいは体内埋め込み型ポンプに関する技術的問題で制限され，表1，2に示したいずれの研究も動注中止が少ないサイクル数で起こり，治療完遂率は50%前後と低い。カテーテルやポート・ポンプのトラブルとしては血管撮影時のショック，カテーテルが設置できなくて治療が開始できない，カテーテル挿入後の出血(挿入部，腹腔内)，ポート・ポンプ周囲の感染、肝動脈血栓、カテーテル変位、肝動脈の仮性動脈瘤などである。総ビリルビン値＞3mg/dLの肝機能障害は18%にみられ[5]，胆管硬化症は時に致命的となる。

全身化学療法

全身補助化学療法について，相当数の症例を集積したprospectiveな研究は少ない(表3)。

FFCD9002 trial[12]は5-FU/ロイコボリン群が全生存率では差がないものの，5年無病生存率で有意の改善を示した。対照群に手術単独を置いたこの試験では，必要な症例集積に10年かかっている。Ychouら[13]は5-FU/ロイコボリンとFOLFIRIとを比較したが無病生存率，全生存率ともに差を認められなかった。FOLFIRIは進行癌では有効なのに，肝転移の補助化学療法としては有効とする報告が少ない。

EORTC40983試験[10]はFOLFOX4の術前・術後投与を導入した。対象を転移個数が1～4個と大腸癌取扱い規約の肝転移分類では進行度がH1に相当するものに限り，しかも実際に登録された症例のうち51%が転移個数1個と特に予後がよいものである。この試験については別項で解説されるので詳細は省くが，ITT解析では有意差はないものの適格例，切除例でFOLFOX4投与群の予後がよいと結論している。術前投与群では術後早期の再発率が低く，この差がその後も維持されているのであるが，これは術前化学療法を行っている3ヵ月の間に術後早期再発危険群が肝切除対象から除外されたためと推測できる。現在ではほかに有効

表2　肝動注(HAI)＋全身化学療法

報告者	発表年	治療法 試験群 vs. 対照群	症例数	全生存率 (期間)	無病生存率／ 無再発生存率	残肝再発率
Kemeny N et al.[6]	1999	5-FU 325mg/m²/d＋LV 200mg/m²/d 静注 5日間 2週後＋HAI：FUDR 0.25mg/kg/d ＋dexamethasone 20mg 14日間 1週間休薬 を6コース	74	2年生存率 86%	2年無病生存率 57%	2年無再発生存率 90%
		vs. 5-FU 325mg/m²/d＋LV 200mg/m²/d 静注 5日間 を4週ごと	82	72% p=0.03	42% p=0.07	60% p=0.001
Tono T et al.[9]	2000	HAI：5-FU 2,000mg 96時間で投与／週 ×6＋5-FU 200mg/d 経口	9	5年生存率 77.8%	3年無病生存率 66.7%	
		vs. 5-FU 200mg/d 経口	10	50.0% p=0.27	20.0% p=0.045	
Lygidakis NJ et al.[7]	2001	MMC 20mg/m² d1＋5-FU 750mg/m² ＋LV200mg/m² 静注 d1-5＋HAI：IL-2 18×106 IU d6-15 動注	62	5年生存率 73%	5年無病生存率 58%	5年無再発生存率 82%
		vs. MMC 20mg/m² d1＋5-FU 750mg/m² ＋LV200mg/m² 静注 d1-5＋IL-2 18×106 IU 皮下注 d6-15	60	60% p=0.04	34% p=0.006	49% p=0.00003
Kemeny MM et al.[8]	2002	HAI：FUDR 0.2mg/kg/d 14日間＋5-FU 300mg/m²/d 14日間 を4コース ＋5-FU 300mg/m²/d 静注 14日間 2週間休薬 を4コース	30	生存期間 63.7月	4年無再発生存率 45.7%	4年無再発生存率 66.9%
		vs. 手術単独	45	49.4月 p=0.60	25.2% p=0.04	43.0% p=0.03

表3　全身化学療法

報告者	発表年	治療法 試験群 vs. 対照群	症例数	全生存率	無病生存率／ 無再発生存率
Portier G et al.[14]	2006	5-FU 400 mg/m²/d＋LV 200 mg/m²	86	5年 51.1%	5年無病生存率 33.5%
		vs. 手術単独	85	41.9%	26.7%
				p=0.13	p=0.028
Ychou M et al.[13]	2009	LV 400 mg/m²＋5-FU 400 mg/m²＋5-FU 2,400 mg/m² 2週ごと12コース	153	3年 71.6%	2年無病生存率 46.2%
		vs. LV 400 mg/m²＋5-FU 400 mg/m²＋5-FU 2,400 mg/m² irinotecan 180 mg/m² 2週ごと12コース	153	72.2%	50.7%
				ns	ns
Nordlinger B et al.[12]	2008	術前FOLFOX4 6コース＋術後FOLFOX4 6コース	182		3年無再発生存率 35.4%
		vs. 手術単独	182		28.1%
					p=0.058

な治療法がないためにあたかもstandard治療のように扱われているがこれを疑問視する論文は少なくない[15-17]。

肝転移切除後の化学療法についてのprospectiveな研究は少ないが，meta-analysisやpooled analysisはいくつかある。

Parksら[18]はスコットランドのRoyal Infirmary of Edinburghと米国MSKCCの症例792例の解析から肝転移切除後の化学療法は多発肝転移例，予後不良因子が多いものによく効くとし，Mitryら[19]はともに5-FU/ロイコボリンの第Ⅲ相試験を行ったFFCD 9002試験[12]とカナダとEORTCの参加したENG試験の2つの試験のpooled analysisを行い，5-FU/ロイコボリン群の5年生存率，5年無病率ともに有意差はないけれども，術後の全身化学療法は有効であると報告した。Reddyら[20]は3施設の同時性肝転移499例のretrospective解析で肝転移完全切除後の生存期間中央値は化学療法なし39ヵ月，術前化学療法56ヵ月，術後化学療法99ヵ月，術前・術後化学療法97ヵ月で術後化学療法が独立した予後因子であり，術後化学療法の期間は6ヵ月以上が有意に有効とした。

全身化学療法についても適正な薬剤の組み合わせ，投与スケジュール，投与時期，投与期間などは解決していない。

投与時期について，切除可能肝転移に対する治療はまず肝切除を行い，その後に補助化学療法を行うのが原則であるとするものと[20-22]，2～3ヵ月間術前化学療法を行い，その時点で切除可能例を選別した上で適応例に肝切除を行うとする意見[15,23]とがある。術前化学療法には①抗がん剤の感受性を知ることができる，②化学療法中を待機することで遠隔転移の有無を知ることができる，③したがって切除不能肝転移例に対して早期に治療を開始できる，などの利点があげられているが，一方では術前化学療法による肝切除時の肝機能障害および術後合併症の増加が問題となっている[24-27]。Karakousisら[28]は術前化学療法の意義を示したevidenceはないので，術前化学療法をstandardとしてはならないと述べている。

また，術前化学療法例では切除後の全身化学療法は必須であるとする意見も多い。

肝切除後補助化学療法の至適投与期間は不明だが，多くのoncologistは4～6ヵ月の全身化学療法を行っている。

多くの論文で推奨されている化学療法はFOLFOXである。

FOLFOX療法(JCOG0603試験)

厚生労働省科学研究費補助金(H16-がん臨床-一般-032)による研究班では，完全切除例を対象に術後FOLFOX療法の有用性を検証する研究を計画した。本邦におけるオキサリプラチンの使用実績がなかったために，2005年に本邦でのオキサリプラチンの使用が許可されて，進行大腸癌に対す

るFOLFOX6の第Ⅱ相試験を行い[29,30]，奏効率は44%，無増悪生存期間は8.8ヵ月で欧米の報告と同様の結果が得られた。Grade3以上の好中球減少は33%，Grade2の末梢神経障害が8コース以上では56%に出現しオキサリプラチンの至適投与量を85mg/m²とした。すなわちmFOLFOX6である。

厚生労働省科学研究費補助金(H19-がん臨床-一般-024)の研究班では2007年から肝切除後にmFOLFOX6を12コース行う第Ⅱ相試験を行った(JCOG0603試験)[31]。治療完遂目標コース数を9コースに置いたのであるが，この試験では治療群に登録された39例中12例が有害事象のために9コースを完遂できなかった。有害事象の内訳は好中球減少：8，末梢神経障害：1，血栓症：1，胆嚢炎：1，悪心・嘔吐：1であり，2005年に行った進行癌に対する第Ⅱ相試験や文献上から，計画時点では末梢神経障害が最も多い中止理由となる有害事象であろうと想定していたが，実際には好中球減少が最も多い中止原因であった。肝切除後の補助化学療法としてのFOLFOX療法は手術を行わない進行大腸癌に対する場合と同じでよいものではなく，肝切除という過大な侵襲が伴う症例に適した補助化学療法が必要と考えられた。

最も問題となる投与コース数は，FOLFOX4が大腸癌術後補助化学療法としての有用性を示したMOSAIC試験でのオキサリプラチンの投与サイクル中央値は9.5サイクルである[32]。進行癌におけるFOLFOXの抗腫瘍効果出現をみるとFOLFOX4およびFOLFOX6ともに第4サイクルから腫瘍縮小効果は出現し，その出現率は9コースまで増加してplateauとなる(図)。したがって4コース以上行えれば効果が期待できると思われるが，安定した効果を期待するには9コース以上が必要と考えられる。

FOLFOX療法について，肝切除後の投与開始時期，有害事象出現時の投与延期期間，薬剤の減量規準や減量レベルを明らかにした報告はなく，解決すべき点である。

おわりに

肝転移切除の補助化学療法についてはevidenceがないのだから行うべきではないとする意見がある一方，StageⅢやStageⅣで有効なのだから肝切除後にも全身化学療法を行うべきとする意見がある。実際の臨床現場では，はっきりとしたevidenceがないにもかかわらず肝転移切除後には抗がん剤治療が行われることが多く，しか

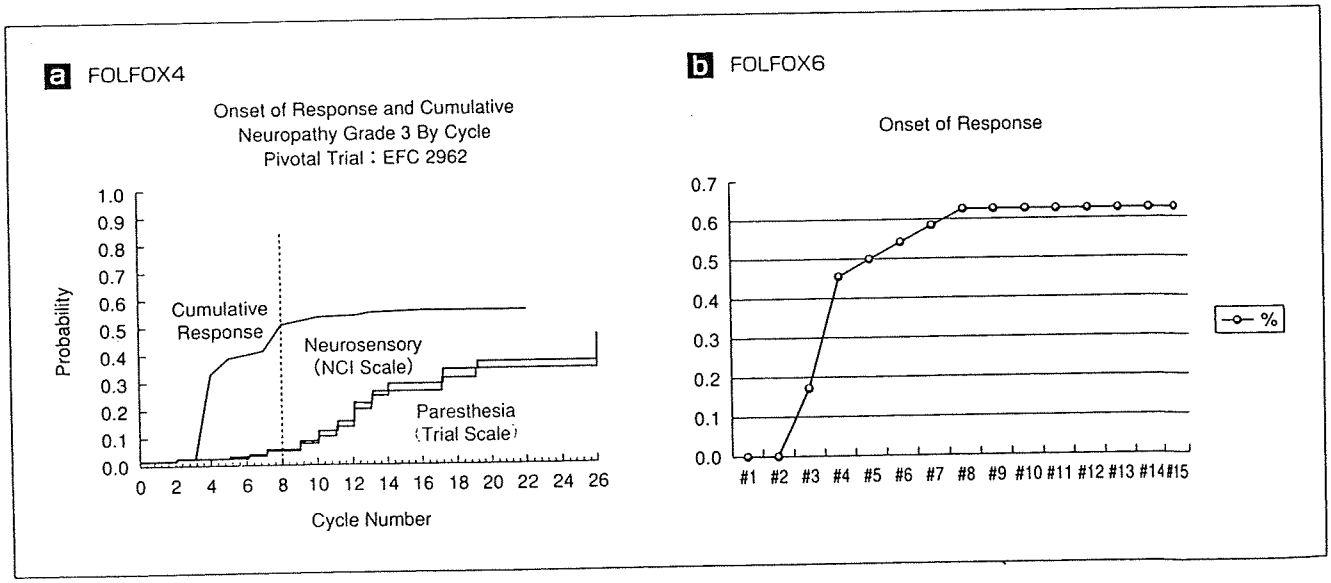

図　FOLFOX投与コース数と奏効率

a：米国FDAがELOXATINE(oxaliplatin)の承認にあたりde Gramontらの研究(J Clin Oncol18，2938，2000)のデータから作成したFOLFOX 4のコースごとの奏効率と神経毒性の発生率(NDA#21-063)

b：厚生労働省科学研究費補助金(H16-がん臨床-一般-032)によるFOLFOX6のコースごとの奏効率

抗腫瘍効果は3あるいは4コースからみられ，8～9コースでplateauになる

も術前化学療法が話題になれば術前化学療法を採り入れ，分子標的薬剤が使用可能になれば直ぐさまそれに飛びつく傾向がある。留意すべきはclinical trialとclinical practiceとは明確に分けなくてはならないことであり，肝切除という環境の下で進行癌に対する補助化学療法の結果を単に外挿するのには限界があることである。

実臨床で耐えうる安全で有効な肝転移切除後の補助化学療法の開発が望まれる。

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ORIGINAL ARTICLE

Effects of bevacizumab on plasma concentration of irinotecan and its metabolites in advanced colorectal cancer patients receiving FOLFIRI with bevacizumab as second-line chemotherapy

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Abstract
Purpose Bevacizumab (BV) prolongs the survival of colorectal cancer patients when combined with irinotecan (CPT-11)-based regimens. In the AVF2107g study, the area under the curve (AUC) ratio for bolus CPT-11/5-fluorouracil (5-FU)/leucovorin (LV) (IFL) with the BV arm to bolus IFL with placebo indicated that SN-38 concentrations may have been increased in subjects receiving BV. However, the mechanism underlying such increase remains unclear, and the difference might be caused by an imbalance between the two arms and a possible inter-subject variability of CPT-11 metabolism. Within-subject comparisons were used to evaluate the effect of BV on advanced colorectal cancer patients when administered with the FOLFIRI regimen as second-line chemotherapy.
Methods Ten advanced colorectal cancer patients received the FOLFIRI regimen every 2 weeks. At cycle 1, BV was administered following FOLFIRI administration to allow baseline pharmacokinetic (PK) analysis of CPT-11 and its metabolites. From cycle 2, BV was administered just before FOLFIRI administration. Plasma samples were collected under the same condition (at cycle 3).
Results There were no significant differences in the C_{max} and $AUC_{0-\infty}$ of CPT-11, SN-38, and SN-38G between cycle 1 (without BV) and cycle 3 (with BV). PK parameters of CPT-11, SN-38, and SN-38G were not significantly affected by BV. There were no significant differences in the changes in the AUC ratio of CPT-11 to SN-38 between cycles 1 and 3, as well as in the ratio of SN-38 to SN-38G.
Conclusion BV does not affect the plasma concentration of CPT-11 and its metabolites on FOLFIRI regimen.

Keywords Bevacizumab (BV) · Irinotecan · Pharmacokinetics · Colorectal cancer

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Introduction

Bevacizumab (BV) is a humanized monoclonal antibody against vascular endothelial growth factor, an important regulator of physiologic and pathologic angiogenesis [1]. A large, randomized, controlled Phase III clinical trial (AVF2107g) has demonstrated that BV addition to standard chemotherapy with the bolus irinotecan (CPT-11)/5-fluorouracil (5-FU)/leucovorin (LV) (IFL) regimen improves survival of patients with previously untreated metastatic colorectal cancer [2]. Subsequently, CPT-11/bolus 5-FU/continuous 5-FU/LV (FOLFIRI) + BV conferred a significant survival benefit compared with IFL + BV in the BICC-C study [3]. Thus, CPT-11 with BV demonstrated significant survival benefits in patients with colorectal cancer. CPT-11 has a complex metabolism requiring activation into SN-38 by carboxylesterase [4, 5] and glucuroconjugation for catabolism [6]. As shown in the AVF2107g study, SN-38 concentrations were on average 33% higher in patients receiving bolus IFL in combination with BV compared with bolus IFL alone [7]. However, the underlying mechanism of such increase remains unclear, and the difference might be caused by an imbalance between the two arms and a possible inter-subject variability of CPT-11 metabolism. Thus, we investigated the potential pharmacokinetic (PK) interaction between CPT-11 and BV in advanced

colorectal cancer patients when administered with the FOLFIRI + BV regimen as second-line chemotherapy.

Methods

Inclusion and exclusion criteria

Patients meeting the following inclusion criteria were eligible: histologically proved colorectal cancer (e.g., adenocarcinoma, mucinous carcinoma, and signet-ring cell carcinoma); failure of first-line treatment containing 5-FU-based chemotherapy (almost an adjuvant setting and recurrence were found in the chemotherapy period or after the end of chemotherapy within 24 weeks) or oxaliplatin-based chemotherapy (all FOLFOX regimens) without BV and CPT-11; Eastern Cooperative Oncology Group performance status of 0–2; age: 20–74-year-old; no previous exposure to BV or CPT-11; adequate bone marrow function (leukocyte count $\geq$3,000 and $\leq$12,000/μl, hemoglobin $\geq$8.0 g/dl, and platelet count $\geq 10 \times 10^4$/μl); serum creatinine level $\leq$1.5 mg/dl; total bilirubin level $\leq$1.5 mg/dl; AST and ALT $\leq$100 IU/l; qualitative urine protein $\leq$(1+); measurable disease according to response evaluation criteria for solid tumors (RECIST); and written informed consent.

Patients were excluded if they had the following: known central nervous system metastasis; other active double cancer; inadequately controlled hypertension, diarrhea, diabetes, or heart disease; severe peritoneal metastasis; interstitial pneumonia or pulmonary fibrosis; previous history of vascular thromboembolism or severe drug hypersensitivity; bleeding tendency; hepatic B or C virus infection; underwent any form of surgery within 4 weeks before study enrollment; pregnant or lactating.

Study design

Ten patients were treated with the FOLFIRI regimen preceded by BV every 2 weeks. At cycle 1, CPT-11 was administered before BV to allow baseline PK analysis of CPT-11 and its metabolites. At cycle 3, plasma samples were collected for PK analysis of CPT-11 when administered in combination with BV. The PK investigations were used intra-patients comparison.

Pretreatment and follow-up examination

Complete medical history evaluation, physical examination, laboratory tests (complete blood count, creatinine, serum electrolytes, calcium, uric acid, total protein, albumin level, hepatic, and coagulation tests) and urinalysis were performed to obtain baseline data and repeated biweekly.

Toxicity was evaluated biweekly and graded using the National Cancer Institute's Common Toxicity Criteria, version 3.0. Tumor responses were evaluated and measured as baseline data and reassessed every 4 cycles using RECIST.

Drug administration

The FOLFIRI regimen consisted of CPT-11 (180 mg/m^2 IV over 90 min), *l*-LV (200 mg/m^2 IV over 2 h), and 5-FU (400 mg/m^2 IV bolus), followed by 5-FU (2,400 mg/m^2 IV over a 46-h infusion), and repeated every 2 weeks. BV was administered as a 30-min intravenous infusion at a biweekly dose of 10 mg/m^2 before the FOLFIRI regimen (only in the cycle 1, BV was administered after the FOLFIRI regimen for PK analysis of the non-BV phase) (Fig. 1).

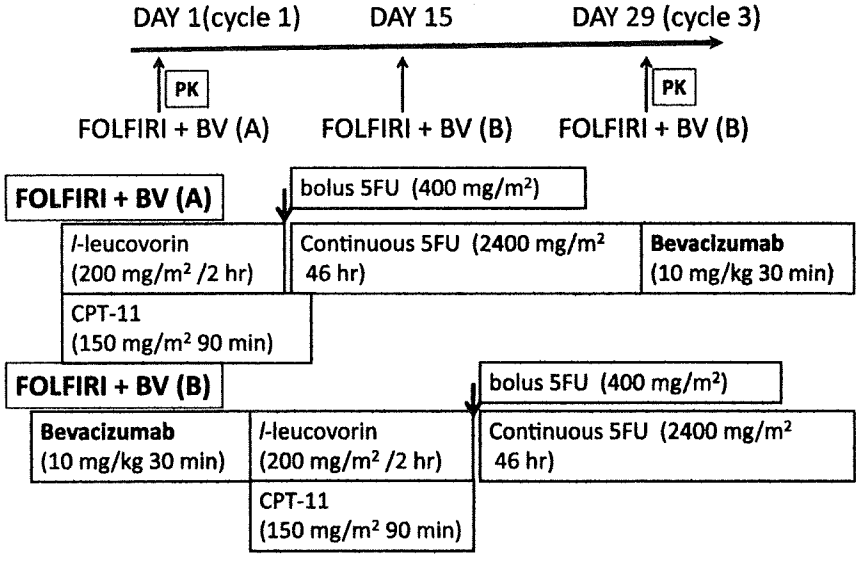

Fig. 1 At cycle 1, CPT-11 was administered before BV to allow baseline pharmacokinetic (PK) analysis of CPT-11 and its metabolites. At cycle 3, plasma samples were collected for PK analysis of CPT-11 when administered in combination with BV

Table 1 Patient characteristics

Age (years)	
Range	38–74
Median	60
Gender	
Male	9
Female	1
Previous chemotherapy	
5-FU-based regimen[a]	5
FOLFOX	5
Total cycles of treatment	
Range	7–19
Median	11

[a] As adjuvant chemotherapy

Pharmacokinetic analysis

Plasma samples were collected at cycles 1 and 3 before the start of chemotherapy, and 0, 1, 2, 4, 7, and 24 h after CPT-11 infusion. Whole blood (4.0 ml) samples were collected in heparinized tubes and centrifuged at 3,000 rpm for 10 min at 4°C. Then, 2.0 ml of plasma was transferred into tubes with 2.0 ml of phosphate buffer (0.1 M) and stored at −80°C before analysis. Thereafter, quantitative analysis of CPT-11 and its metabolites was performed using high-performance liquid chromatography [8]. The lower limit of quantification was 0.002 μg/ml for CPT-11 and its metabolites. Maximum plasma concentration (Cmax), area under the plasma/serum concentration time curve (AUC) and terminal half-life were determined. The AUC calculation is limited up to 24 h of to infinite (∞). Changes in the ratios of CPT-11 to SN-38 and SN-38 to SN-38G were estimated as $AUC_{SN\text{-}38}/AUC_{CPT\text{-}11}$ and $AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$, respectively.

Statistical analysis

Correlation between related species were all carried out using the paired *t* test (Microsoft Excel 2000 SP-3), and *P* values <0.05 with a two-tailed distribution were considered significant.

Results

Patient characteristics

Ten patients received the treatment regimens (Table 1), and all the patients completed the PK program and were assessable for drug safety and anti-tumor activity. A total of 120 cycles of treatment was administered (median number of cycles: 11 (range 7–19)).

Pharmacokinetic analysis

Analysis of the PK parameters showed no significant difference between the parameters of cycle 1 (non-BV phase) and cycle 3 (BV phase) (Table 2). This indicates that BV had no effect on the pharmacokinetics of CPT-11. The mean AUCs for CPT-11 were 12.2 ± 2.3 μg h/ml at cycle 1 and 12.8 ± 1.7 μg h/ml at cycle 3. The half-lives of CPT-11 were 6.0 ± 0.6 h at cycle 1 and 5.7 ± 0.6 h at cycle 3. Mean CPT-11 concentrations versus time profiles either alone or in combination with BV were nearly superimposed (Fig. 2).

The mean SN-38 PK parameters showed no significant differences between cycles 1 and 3 (Table 2). The mean AUCs for SN-38 were 0.40 ± 0.44 μg h/ml at cycle 1 and 0.22 ± 0.16 μg h/ml at cycle 3. Mean SN-38 concentrations versus time profiles either alone or in combination with BV were nearly superimposed (Fig. 3). In SN-38G, significant differences in the PK parameters were also not found between cycles 1 and 3 (Table 2), and mean SN-38G concentrations versus time profiles either alone or in

Table 2 Pharmacokinetic parameters

Analyte		C_{max} (mg/ml)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (mg h/ml)	$MRT_{0-\infty}$ (h)	Vd (L)	CL (L/h)
CPT-11	BV (−)	2.1 (0.3)	1.5 (0)	6.0 (0.6)	12.2 (2.3)	6.1 (0.6)	185 (43.3)	21.6 (5.6)
	BV (+)	2.1 (0.3)	1.5 (0)	5.7 (0.6)	12.8 (1.7)	6.1 (0.5)	164 (34.6)	19.7 (3.0)
SN-38	BV (−)	0.024 (0.013)	2.0 (0.7)	14.3 (16.6)	0.40 (0.44)	–	–	–
	BV (+)	0.022 (0.012)	2.8 (0.8)	8.3 (7.6)	0.22 (0.16)	–	–	–
SN-38G	BV (−)	0.14 (0.030)	2.4 (0.3)	12.9 (4.7)	1.98 (0.70)	–	–	–
	BV (+)	0.14 (0.030)	2.6 (0.6)	11.4 (3.5)	1.81 (0.26)	–	–	–

Values are expressed as mean (±SD). There are no significant differences in the C_{max} and $AUC_{0-\infty}$ of CPT-11, SN-38, and SN-38G between cycle 1 (BV-) and cycle 3 (BV+); paired *t* test

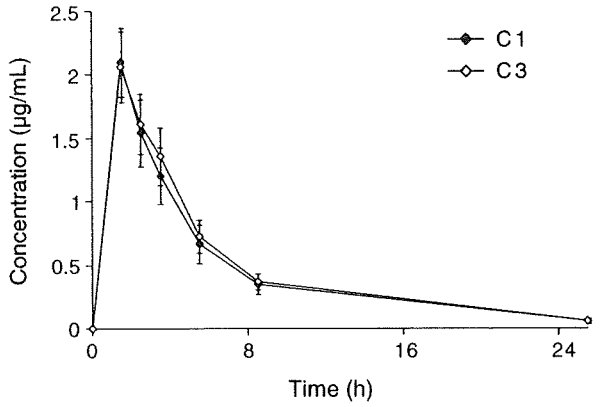

Fig. 2 Mean CPT-11 concentrations versus time profiles either alone or in combination with BV were superimposed

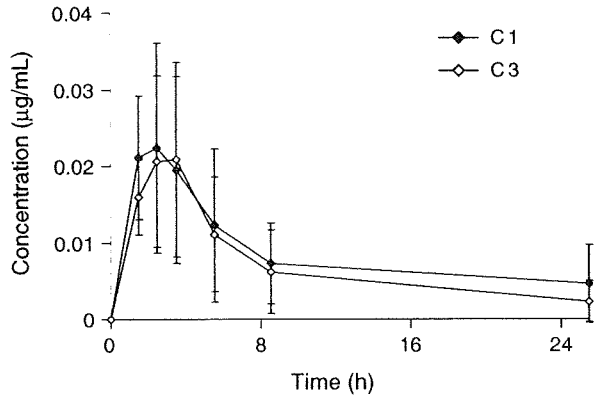

Fig. 3 Mean SN-38 concentrations versus time profiles either alone or in combination with BV were nearly superimposed

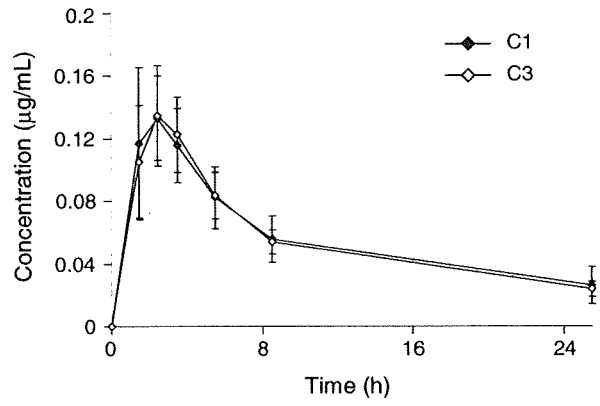

Fig. 4 Mean SN-38G concentrations versus time profiles either alone or in combination with BV were superimposed

combination with BV were also nearly superimposed (Fig. 4).

There were no significant differences in the changes in the ratio of CPT-11 to SN-38 between cycles 1 and 3 (Table 3), as well as in the ratio of SN-38 to SN-38G.

Table 3 Changes in ratio of CPT-11 to SN-38 and SN-38 to SN-38G

Patient No.	AUC ratio of SN-38/CPT-11(%)		AUC ratio of SN-38G/SN-38	
	BV (−)	BV (+)	BV (−)	BV (+)
1	3.1	4.1	3.8	3.9
2	2.2	2.2	7.9	5.9
3	2.5	1.8	8.7	8.0
4	9.2	1.8	2.3	7.7
5	0.6	0.7	23.1	22.3
6	0.3	0.3	51.7	76.0
7	4.4	1.4	3.5	8.8
8	1.0	0.5	13	23.8
9	1.0	0.8	13.5	14.6
10	5.6	4.3	2.3	3.2

There were no significant differences in the AUC ratios of SN-38/CPT-11 and SN-38G/SN-38 between cycle 1 (BV-) and cycle 3 (BV+); paired *t* test

The results indicate that the CPT-11 and BV combination had no effect on the extent of conversion of CPT-11 into its metabolites SN-38 and SN-38G.

We also observed a larger inter-patient variability for the changes in the ratios of CPT-11 to SN-38 and SN-38 to SN-38G (Table 3).

Discussion

In the present study, we found no significant differences in the mean AUCs, C_{max} and CPT-11 clearance after BV addition. Our results demonstrate that BV addition to CPT-11 (in the FOLFIRI regimen) showed no effect on the drug disposal of CPT-11 and its metabolites. This is the limited sample size study, but this is the first report clarifying the effect of BV on CPT-11 metabolism in humans.

Gaudreault et al. previously reported on the effect of BV on CPT-11 metabolism and safety using cynomolgus monkeys as subjects. Their report was the only published study available in the literature search regarding the effect of BV on CPT-11 metabolism. In their study, monkeys received bolus IFL with or without BV, and blood samples were collected for PK analysis of CPT-11 and 5-FU. They concluded that BV had no effect on the metabolism of either agent, although the number of animals tested in each group was small [with BV ($n = 5$); without BV ($n = 4$)] and no statistical comparison between groups was performed [9].

As previously shown, in the AVF2107g study, CPT-11 metabolism was characterized in a small PK study (results are presented only in the package insert of BV