TABLE 1. Characteristics of patients with colorectal cancer with or without cytology findings positive for free malignant cells in peritoneal lavage fluid

	Total N = 697	Cytology findings: Positive n = 15	Cytology findings: Negative n = 682	P value
Age (yrs)	59.8 ± 10.2	59.3 ± 12.6	59.8 ± 10.2	0.8659*
Gender				
Male	427 (61.3)	9 (2.1)	418 (97.9)	0.9192†
Female	270 (38.7)	6 (2.2)	264 (97.8)	
Tumor size (cm)	3.9 ± 2.2	4.8 ± 1.4	3.9 ± 2.2	0.1227*[a]
Tumor site				
Colon	391 (56.1)	8 (2.0)	383 (98.0)	0.8274†
Rectum	306 (43.9)	7 (2.3)	299 (97.7)	
Histologic grade				
Well	411 (59.0)	6 (1.5)	405 (98.5)	0.3198†
Mod	255 (36.6)	8 (3.1)	247 (96.9)	
Other	31 (4.4)	1 (3.2)	30 (96.8)	
Depth of invasion				
pTis, T1, T2	323 (46.3)	0 (0)	323 (100)	<0.0001‡
pT3	362 (51.9)	13 (3.6)	349 (96.4)	
pT4	12 (1.7)	2 (16.7)	10 (83.3)	
Regional lymph nodes				
pN0	490 (70.3)	3 (0.6)	487 (99.4)	<0.0001‡
pN1	150 (21.5)	6 (4.0)	144 (96.0)	
pN2	57 (8.2)	6 (10.5)	51 (89.5)	
pTNM stage				
0	68 (9.8)	0 (0)	68 (100)	0.0012‡
1	215 (30.8)	0 (0)	215 (100)	
2	208 (29.8)	3 (1.4)	205 (98.6)	
3	206 (29.6)	12 (5.8)	194 (94.2)	
Lymphatic invasion				
No	351 (50.4)	2 (0.6)	349 (99.4)	0.0036§
Yes	346 (49.6)	13 (3.8)	333 (96.2)	
Venous invasion				
No	385 (55.2)	3 (0.8)	382 (99.2)	0.0072§
Yes	312 (44.8)	12 (3.8)	300 (96.2)	

Well = well-differentiated adenocarcinoma; Mod = moderately differentiated adenocarcinoma; Other = poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma.
*Student *t* test; †chi-squared test; ‡chi-squared for linear trend; §Fisher's exact test.
Data are means ± SDs or numbers of patients with percentages in parentheses.

with those who had negative results for malignant cells on cytologic examination showed no significant differences between the 2 groups regarding age, gender, tumor size, tumor site, or histologic grade. Of patients with pTis, pT1, or pT2 tumors, none had cytology results positive for malignant cells, but the chance of malignant cells being present in the lavage fluid increased as the depth of tumor invasion increased ($P < 0.0001$). The likelihood of positive results on peritoneal cytology also increased with the number of affected regional lymph nodes ($P < 0.0001$), severity of pTNM stage ($P = 0.0012$), presence of lymphatic invasion ($P = 0.0036$), and presence of venous invasion ($P = 0.0072$).

Univariate Analyses of Factors Affecting Disease-Free and Cancer-Specific Survival

Results of peritoneal cytology and various clinicopathologic factors were evaluated for their impact on prognosis in univariate analyses of data from all 697 patients (Table 2). Tumor size, tumor site, histologic grade, depth of invasion, status of regional lymph nodes, status of lymphatic or venous invasion, and results of peritoneal cytology were all significantly associated with both disease-free and cancer specific survival at *P* values of <0.0001.

Kaplan-Meier disease-free and cancer-specific survival curves are shown for patients with and those without positive cytology results in Figure 1. Five-year disease-free survival (with 95% CI) was 46.7% (21.4–72.0%) in patients with positive results *vs.* 84.6% (81.9–87.3%) in those with negative results; five-year cancer-specific survival, 50.0% (23.7–76.3%) *vs.* 89.3% (81.9–91.7%). Ten-year disease-free survival was 37.3% (11.2–63.4%) in patients with positive results *vs.* 82.9% (80.0–85.8%) in those with negative results (Fig. 1A), and cancer-specific survival was 50.0% (23.7–76.3%) *vs.* 86.7% (84.0–89.4%, $P < 0.0001$) (Fig. 1B).

In addition, separate univariate analyses of clinical and pathologic factors were performed in patients with pT3 or pT4 tumors (Table 3). In these patients, both disease-free

TABLE 2. Univariate analysis of clinicopathologic factors for disease-free and cancer-specific survival in all patients

	No. of patients	*Disease-free 10-year survival*		*Cancer-specific 10-year survival*	
	n = 697	*% (95% CI)*	*P value**	*% (95% CI)*	*P value**
Age (years)					
< 60	331	80.4 (75.9–84.9)	0.6336	86.8 (82.9–90.7)	0.4674
≥ 60	366	83.2 (79.3–87.1)		85.1 (81.2–89.0)	
Gender					
Male	427	83.0 (79.3–86.7)	0.2123	85.7 (82.0–89.4)	0.9860
Female	270	80.0 (75.1–84.9)		86.4 (82.1–90.7)	
Tumor size					
< 4 cm	398	88.1 (84.8–91.4)	<0.0001	91.0 (88.1–93.9)	<0.0001
≥ 4 cm	299	73.5 (68.0–79.0)		79.1 (74.0–84.2)	
Tumor site					
Colon	391	89.2 (85.9–92.5)	<0.0001	90.9 (88.0–93.8)	<0.0001
Rectum	306	72.4 (67.1–77.7)		79.4 (74.5–84.3)	
Histologic grade					
Well	411	89.1 (85.8–92.4)	<0.0001	92.6 (89.9–95.3)	<0.0001
Mod/Other	286	71.4 (65.9–76.9)		76.0 (70.7–81.3)	
Depth of invasion					
pTis, 1, 2	323	95.7 (93.3–98.1)	<0.0001	96.8 (94.8–98.8)	<0.0001
pT3, 4	374	69.5 (64.4–74.6)		76.1 (71.4–80.8)	
Regional lymph nodes					
pN (-)	490	92.2 (89.7–94.7)	<0.0001	92.3 (89.8–94.8)	<0.0001
pN (+)	207	57.4 (50.1–64.7)		70.6 (63.9–77.3)	
Lymphatic invasion					
No	351	91.3 (88.2–94.4)	<0.0001	92.6 (89.5–95.7)	<0.0001
Yes	346	72.0 (66.9–77.1)		79.0 (74.5–83.5)	
Venous invasion					
No	385	89.0 (85.7–92.3)	<0.0001	92.0 (89.1–94.9)	<0.0001
Yes	312	72.9 (67.8–78.0)		78.1 (73.0–83.2)	
Peritoneal cytology					
Negative	682	82.9 (80.0–85.8)	<0.0001	86.7 (84.0–89.4)	<0.0001
Positive	15	37.3 (11.2–63.4)		50.0 (23.7–76.3)	

Well = well-differentiated adenocarcinoma; Mod/Other = moderately differentiated adenocarcinoma or poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma; 95% CI = 95% confidence interval.
*Log-rank test

survival and cancer-specific survival were significantly associated with tumor site, histologic grade, status of regional lymph nodes, and results of peritoneal cytology, but not with tumor size or venous invasion. Lymphatic invasion was associated with disease-free survival but not with cancer-specific survival.

Figure 2 shows the Kaplan-Meier survival curves for patients with pT3 or pT4 tumors (n = 374). In these pa-

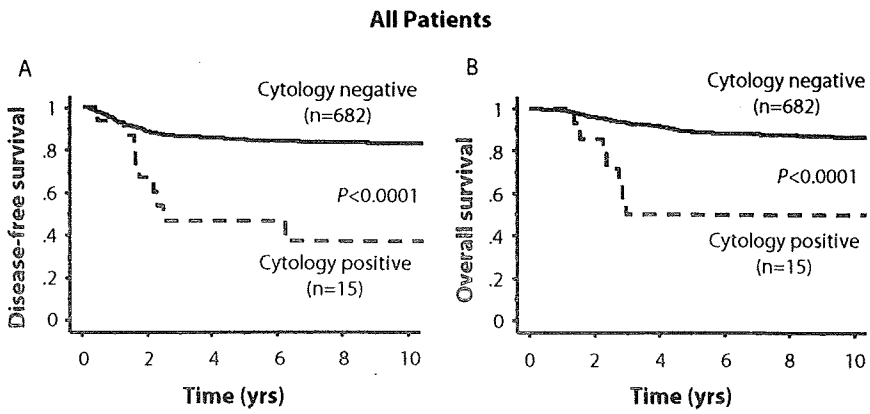

FIGURE 1. Kaplan-Meier curves for disease-free survival (A) and cancer-specific survival (B) in all 697 patients with colorectal cancer: positive *vs.* negative findings for malignant cells with peritoneal lavage cytology.

TABLE 3. Univariate analysis of clinicopathologic factors for disease-free and cancer-specific survival in patients with pT3 or pT4 tumors

	No. of patients (n = 374)	Disease-free 10-year survival		Cancer-specific 10-year survival	
		% (95% CI)	P value*	% (95% CI)	P value*
Age (years)					
< 60	158	64.0 (55.8–72.2)	0.1053	75.0 (67.6–82.4)	0.7747
≥ 60	216	73.8 (67.7–79.9)		76.8 (70.5–83.1)	
Gender					
Male	222	68.4 (61.5–75.3)	0.8845	74.0 (67.3–80.7)	0.4269
Female	152	70.8 (63.4–78.2)		79.0 (72.4–85.7)	
Tumor size					
< 4 cm	126	71.2 (63.2–79.2)	0.9313	76.9 (68.9–84.9)	0.8670
≥ 4 cm	248	68.6 (62.3–74.9)		75.7 (69.6–81.8)	
Tumor site					
Colon	203	80.6 (74.7–86.5)	<0.0001	82.6 (76.9–88.3)	0.0035
Rectum	171	56.2 (48.2–64.2)		68.3 (60.5–76.1)	
Histologic grade					
Well	168	76.4 (69.3–83.5)	0.0022	84.3 (78.0–90.6)	0.0002
Mod/Other	206	64.0 (57.1–70.9)		69.2 (62.3–76.1)	
Regional lymph nodes					
pN (-)	208	83.6 (78.3–88.9)	<0.0001	84.0 (78.3–89.7)	<0.0001
pN (+)	166	52.1 (43.9–60.3)		66.2 (58.4–74.0)	
Lymphatic invasion					
No	115	76.6 (68.4–84.8)	0.0345	80.5 (72.3–88.7)	0.1113
Yes	259	66.3 (60.0–72.6)		74.5 (68.8–80.2)	
Venous invasion					
No	121	70.6 (62.0–79.2)	0.4540	78.1 (70.3–85.9)	0.5300
Yes	253	69.3 (63.2–75.4)		75.2 (69.3–81.1)	
Peritoneal cytology					
Negative	359	71.0 (65.9–76.1)	0.0094	77.1 (72.2–82.0)	0.0062
Positive	15	37.3 (11.2–63.4)		50.0 (23.7–76.3)	

Well = well-differentiated adenocarcinoma; Mod/Other = moderately differentiated adenocarcinoma or poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma, 95% CI = 95% confidence interval.
*Log-rank test

tients, five-year disease-free survival was 46.7% (21.4–72.0%) for patients with positive *vs.* 74.0% (69.5–78.5%) for those with negative results, and cancer-specific survival was 50.0% (23.7–76.3%) *vs.* 82.3% (78.2–86.4%). As in the entire patient collective, these differences were maintained at 10-year, with disease-free survival rates of 37.3% (11.2–63.4%) for the positive group *vs.* 71.0% (65.9–76.1%) for the negative group (Fig. 2A), and cancer-specific survival of 50.0% (23.7–76.3%) for the positive group *vs.* 77.1% (72.2–82.0%) for the negative group (Fig. 2B).

Multivariate Analysis of Factors Affecting Disease-Free and Cancer-Specific Survival

Multivariate Cox regression analyses of data from all patients demonstrated that tumor site in the rectum, histo-

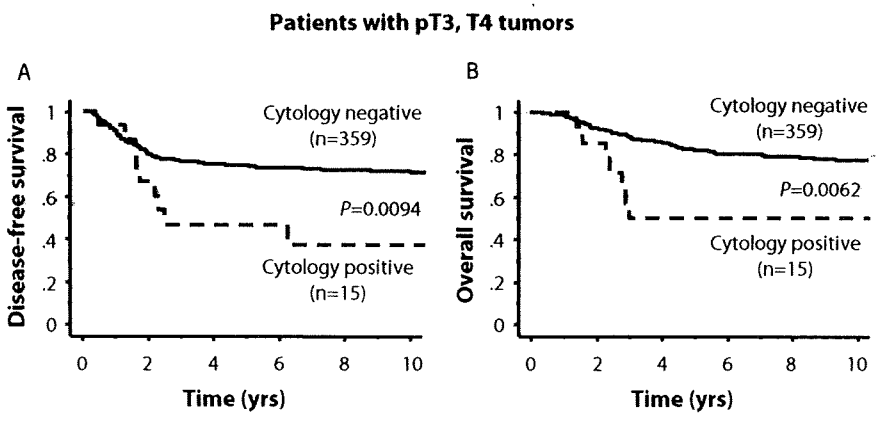

FIGURE 2. Kaplan-Meier curves for disease-free survival (A) and cancer-specific survival (B) in 374 patients with pT3 or pT4 colorectal tumors: positive *vs.* negative findings for malignant cells with peritoneal lavage cytology.

TABLE 4. Multivariate Cox regression analysis of disease-free and cancer-specific survival in all patients

	Disease-free survival			Cancer-specific survival		
Factors	*HR*	*95% CI*	*P value*	*HR*	*95% CI*	*P value*
Tumor size (≥4 cm:<4 cm)	0.915	0.620–1.350	0.6545	1.034	0.657–1.626	0.8861
Tumor site (rectum:colon)	2.825	1.923–4.149	<0.0001	2.146	1.391–3.322	0.0006
Histologic grade (mod/other:well)	1.560	1.044–2.331	0.0301	2.288	1.412–3.704	0.0008
Depth of invasion (pT3–4:pTis-1–2)	4.412	2.393–8.137	<0.0001	4.215	2.035–8.729	0.0001
Regional lymph nodes (positive:negative)	3.802	2.494–5.814	<0.0001	2.506	1.580–3.968	<0.0001
Lymphatic invasion (yes:no)	1.153	0.694–1.916	0.5816	1.036	0.589–1.825	0.9021
Venous invasion (yes:no)	1.055	0.683–1.629	0.8112	1.087	0.651–1.815	0.7497
Peritoneal cytology (positive:negative)	1.709	0.853–3.425	0.1306	2.525	1.144–5.587	0.0218

Well = well-differentiated adenocarcinoma; mod/other = moderately differentiated adenocarcinoma or poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma; HR = hazard ratio; 95% CI = 95% confidence interval.

logic grade other than well-differentiated, depth of invasion pT3 or pT4, and positive involvement of regional lymph nodes were independent risk factors both for decreased disease-free and for decreased cancer-specific survival (Table 4). Positive peritoneal cytology was an independent risk factor for cancer-specific survival but not for disease-free survival.

In separate multivariate Cox regression analyses in patients with pT3 or pT4 tumors (Table 5), only tumor site in the rectum and positive involvement of regional lymph nodes were independent risk factors for both decreased disease-free and decreased cancer-specific survival. However, histologic grade other than well-differentiated and positive peritoneal cytology were independent risk factors for cancer-specific survival.

Factors Affecting Peritoneal Recurrence

Overall, peritoneal recurrence was observed in 12 patients, all of whom had pT3 or pT4 tumors. The impact of potential risk factors for peritoneal recurrence of cancer was therefore investigated in patients with pT3 or pT4 tumors. As shown in Table 6, of the various clinical and pathologic factors analyzed, only results of peritoneal cytology had a significant effect on peritoneal recurrence. Peritoneal recurrence was seen in 5 (33.3%) of 15 patients with positive peritoneal cytology results and in 7 (1.9%) of 359 patients with negative results. Patients with positive involvement of regional lymph nodes appeared to have a worse prognosis than patients without involvement of regional lymph nodes, but the difference was not statistically significant ($P = 0.0798$).

Kaplan-Meier analysis showed lower peritoneal recurrence–free survival rates in patients with positive cytology results (59.4%; 95% CI, 31.2–87.6%) compared with those who had negative cytology results (97.9%; 95% CI, 96.3–99.5%) (Fig. 3).

DISCUSSION

The major routes of metastatic spread in colorectal cancer are hematogenous metastasis to the liver and lung and regional lymph node metastasis. For lymph node metastases, standard surgical procedures for the radical treatment of colorectal cancer have generally been established. For liver metastases, hepatectomy has been aggressively used as a therapeutic modality. Peritoneal dissemination is less frequent and, therefore, considered less important prognostically than the other two routes.[29] However, peritoneal dissemination of colorectal cancer results in considerable morbidity and eventual mortality because it leads to intractable ascites, intestinal obstruction, and further tumor proliferation. Peritoneal dissemination may therefore indicate terminal stage disease, and most patients with peritoneal metastases have a very poor prognosis.[30] Surgery is usually impractical for peritoneal recurrence because of the multiplicity and microscopic size of the implants. No prognostic factors for peritoneal recurrence in colorectal cancer have been clarified. However, if well-defined risk

TABLE 5. Multivariate Cox regression analysis of disease-free and cancer-specific survival in patients with pT3 or T4 tumors

	Disease-free survival			Cancer-specific survival		
Factors	*HR*	*95% CI*	*P value*	*HR*	*95% CI*	*P value*
Tumor site (rectum:colon)	2.841	1.894–4.274	<0.0001	1.916	1.220–3.012	0.0048
Histologic grade (mod-other:well)	1.513	0.991–2.304	0.0551	2.257	1.357–3.759	0.0017
Regional lymph nodes (positive:negative)	3.401	2.198–5.263	<0.0001	2.342	1.453–3.774	0.0005
Lymphatic invasion (yes:no)	1.054	0.650–1.706	0.8322	1.074	0.629–1.834	0.7941
Peritoneal cytology (positive:negative)	1.786	0.891–3.571	0.1018	2.545	1.151–5.650	0.0210

Well = well-differentiated adenocarcinoma; Mod/other = moderately differentiated adenocarcinoma or poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma; HR = hazard ratio; 95% CI = 95% confidence interval.

TABLE 6. Univariate analysis of clinicopathological factors for peritoneal recurrence-free survival in patients with pT3 or pT4 tumors

	No. of patients N = 374	*Peritoneal recurrence-free 10-year survival % (95% CI)*	*P value**
Age (years)			
< 60	158	96.0 (92.5–99.5)	0.9760
≥ 60	216	96.5 (94.0–99.0)	
Gender			
Male	222	97.1 (94.7–99.5)	0.5495
Female	152	95.3 (91.6–99.0)	
Tumor size			
< 4 cm	126	97.5 (94.8–100.0)	0.5281
≥ 4 cm	248	95.7 (92.8–98.6)	
Tumor site			
Colon	203	95.5 (92.4–98.6)	0.4500
Rectum	171	97.3 (94.8–99.8)	
Histologic grade			
Well	168	97.5 (95.0–100.0)	0.3350
Others	206	95.1 (91.6–98.6)	
Regional lymph nodes			
pN (-)	208	97.6 (95.2–100.0)	0.0798
pN (+)	166	94.5 (90.8–98.2)	
Lymphatic invasion			
No	115	98.2 (95.8–100.0)	0.2438
Yes	259	95.3 (92.4–98.2)	
Venous invasion			
No	121	98.3 (95.9–100.0)	0.2133
Yes	253	95.2 (92.3–98.1)	
Peritoneal cytology			
Negative	359	97.9 (96.3–99.5)	<0.0001
Positive	15	59.4 (31.2–87.6	

Well = well-differentiated adenocarcinoma; 95% CI = 95% confidence interval.
*Log-rank test

factors for peritoneal recurrence in colorectal cancer could be identified, then high-risk patients could be treated with more frequent postoperative follow-up and possibly with adjuvant chemotherapy.

It has been suggested that malignant cells spontaneously rubbed free from the serosal part of the tumor may disseminate within the peritoneal cavity.[31] Free malignant cells may also leak from the colon lumen[32] or from cut lymphatics.[6] Therefore, in the current study, all samples for cytologic examination were taken before any manipulation of the tumor or opening of the colon.

The viability of exfoliated cancer cells has been investigated.[32] Viable tumor cells showing the characteristic morphology and dye exclusion in preparations stained with trypan blue were recovered from 14 of 19 colorectal lavage fluids. These cells may implant and proliferate in the peritoneum.

We identified 4 characteristics of tumors that are prone to exfoliate cells into the peritoneal cavity: 1) depth of tumor invasion, 2) regional lymph nodes, 3) lymphatic invasion, and 4) venous invasion. In a multivariate analysis reported by Hase *et al.*,[18] an annular or semiannular shape of the tumor was the most important factor in patients who underwent a curative resection, whereas the depth of tumor invasion was not associated with positive cytology. Kanellos *et al.*[20] evaluated 113 patients with colorectal cancer who underwent a curative resection and found a significant relationship between tumor penetration and cytology findings. Similarly, we found that advanced tumor invasion was associated with positive cytology findings; none of our patients with pTis, pT1, or T2 tumors had cytology results positive for malignant cells.

Some authors have used immunocytochemistry[16,24] or RT-PCR.[3,25,26] to detect disseminated tumor cells in peritoneal lavage fluid in patients with colorectal cancer. In these studies, the detection rates of free cancer cells in peritoneal lavage fluid were comparatively high, ranging from 12% to 47%. However, their significance for survival was unclear. Although immunohistochemical and RT-PCR techniques are more sensitive than conventional cytology in detecting cancer cells, ability to estimate amount of cancer cells might be more clinically useful than simply detecting their presence or absence. Thus, conventional cytology might be more useful clinically than immunohistochemical or RT-PCR techniques. Furthermore, conventional peritoneal cytology is a practical means of detecting cancer cells because it is a universal and inexpensive method that can be easily performed at any institution worldwide.[33]

Studies using conventional cytology to evaluate abdominal washing fluid specimens have found malignant cells in 3% to 28% of patients with colorectal cancer.[14,17–23] The wide range may be due to differences in patient pop-

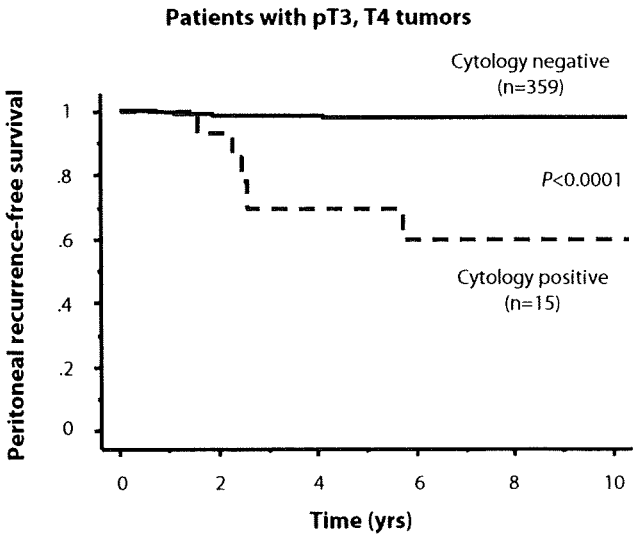

FIGURE 3. Kaplan-Meier curves for peritoneal recurrence-free survival in 374 patients with pT3 or pT4 colorectal tumors: positive *vs.* negative findings for malignant cells with peritoneal lavage cytology.

ulations, lavage methods, or the criteria used for assessment. Fluid collected from peritoneal washing contains not only exfoliated cancer cells but also mesothelial cells, histiocytes, and other nonmalignant cells. Furthermore, floating cancer cells usually vary in degree of degeneration. In the present study, among the 697 patients examined, 15 (2.2%) were found to be positive for intraperitoneal cancer cells on cytologic evaluation. This positive rate is low because only patients undergoing curative surgery were studied and the strict definition used for identification of cancer cells excluded suspicious or borderline malignant cells. None of our patients with pTis, pT1, or pT2 tumors had positive cytology results. Thus, peritoneal lavage cytology appears to be unnecessary in patients with tumors in these categories. In our patients with pT3 or pT4 tumors, the positive rate was 4.0% (15 of 374).

The inconsistent findings in previous studies of the prognostic value of intraperitoneal cytology may be due to small numbers of patients and short follow-up periods. The current study investigated the usefulness of conventional peritoneal cytology as a prognostic tool in a large number (N = 697) of patients undergoing curative resection of colorectal cancer, with a long follow-up period (mean, 90.5 months). Univariate analyses showed that 10-year disease-free and cancer-specific survival rates were significantly lower for positive than for negative cytology results. In multivariate analyses using the Cox proportional hazards model in all 697 patients and in the subgroup of 374 patients with pT3 or pT4 tumors, peritoneal cytology status remained an independent prognostic factor for cancer-specific survival.

We also investigated the value of peritoneal cytology in predicting peritoneal recurrence in our 374 patients with pT3 or T4 tumors. Overall, 3.2% of these patients had peritoneal recurrence. Whereas only 1.9% of patients with negative cytology results had peritoneal recurrence, 33.3% of those with positive peritoneal cytology results had peritoneal recurrence. Univariate analysis of various potential risk factors showed that only peritoneal cytology results represented a prognostic factor for peritoneal recurrence–free survival in patients with pT3 or T4 tumors; 10-year peritoneal recurrence–free survival was also significantly lower in patients with positive than in those with negative cytology results.

In conclusion, the present data suggest that conventional peritoneal cytology is an important tool for predicting cancer-specific survival in all patients operated with curative intent, and may be particularly useful in patients with pT3 or T4 tumors. Furthermore, of the variables studied, only peritoneal cytology was related to risk of peritoneal recurrence of cancer. We therefore consider peritoneal cytology to be a useful prognostic tool which may help in making decisions whether to select intraperitoneal or systemic chemotherapy.

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Clinical Trial Note

Preventive Effect of Goshajinkigan on Peripheral Neurotoxicity of FOLFOX Therapy: A Placebo-controlled Double-blind Randomized Phase II Study (the GONE Study)

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We conducted a controlled double-blind randomized study in patients with advanced/recurrent colorectal cancer to investigate the efficacy of Goshajinkigan (GJG) for peripheral neurotoxicity induced by FOLFOX therapy. The primary endpoint is the incidence of peripheral neurotoxicity ≥Grade 2 after eight cycles of chemotherapy. The secondary endpoints are the incidence of peripheral neurotoxicity of each grade after each cycle, the psychometric properties of the FACT/GOG-Ntx, time to occurrence of neurotoxicity, time to treatment failure, progression-free survival, response rate and toxicity. Eighty patients are required in the study (40 patients per group).

Key words: colorectal cancer – Japanese herbal medicine – oxaliplatin – Goshajinkigan – neurotoxicity

INTRODUCTION

At present, oxaliplatin (L-OHP) + infusional 5-fluorouracil (5-FU)/leucovorin (LV) (FOLFOX therapy) or irinotecan (CPT-11) + infusional 5-FU/LV (FOLFIRI therapy) combined with molecular-targeting agents such as bevacizumab or cetuximab are considered the standard chemotherapy regimens for advanced colorectal cancer (1,2). However, the quality of life of patients and continuation of treatment are greatly influenced by peripheral neuropathy, which is the dose-limiting toxicity of FOLFOX therapy, and thus establishment of countermeasures for neuropathy is required in clinical practice worldwide. Kono et al. (3) reported the preventive effect of a traditional Japanese herbal medicine [Goshajinkigan (GJG)] against peripheral neurotoxicity. Ninety patients with advanced colon cancer receiving FOLFOX4 or mFOLFOX6 therapy were also treated with GJG alone, calcium gluconate (Ca) and magnesium sulfate (Mg) alone (Ca/Mg), combined GJG + Ca/Mg or no concomitant treatment, and the incidence of peripheral neurotoxicity was assessed. It was reported that the GJG group showed improvement of peripheral neurotoxicity and that patients in the GJG group tended to receive more L-OHP before peripheral neurotoxicity developed. Because GJG is an oral Japanese herbal medicine and does not require intravenous infusion unlike Ca/Mg, it is considered to be more convenient both for patients and healthcare workers. However, Kono et al. performed a retrospective study and the number of patients varied between the groups, so further evaluation of GJG by prospective studies is necessary. Accordingly, we conducted a placebo-controlled double-blind randomized Phase II study of GJG to evaluate its

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efficacy against peripheral neurotoxicity induced by FOLFOX therapy.

PROTOCOL DIGESTS OF THE STUDY

Objective

The GONE study is a double-blind, randomized, placebo-controlled, multicenter Phase II trial that is performed in adult patients with advanced/recurrent colorectal cancer in order to investigate the preventive effect of GJG for peripheral neurotoxicity induced by L-OHP.

Resources

Research grant from a non-profit organization: Epidemiological and Clinical Research Information Network (ECRIN).

Endpoints

The primary endpoint is the incidence of peripheral neurotoxicity $\geq$Grade 2 after eight cycles of chemotherapy. The secondary endpoints are the incidence of each grade of peripheral neurotoxicity after each cycle, the psychometric properties of the FACT/GOG-Ntx, time to occurrence of neurotoxicity, time to treatment failure, progression-free survival, response rate and toxicity.

Eligibility Criteria

Inclusion Criteria

i) Histologically confirmed colorectal cancer.
ii) No prior chemotherapy. However, patients with recurrence >4 weeks after completion of adjuvant chemotherapy with an oral pyrimidine fluoride derivative or 5-FU/L-LV were also eligible.
iii) ECOG PS of 0 or 1.
iv) Age of at least 20 years at registration.
v) A life expectancy of >12 weeks.
vi) Adequate function of vital organs, including normal hematopoietic function, normal liver function and normal renal function as evidenced by the following data within 7 days before registration:
a) White blood cell count $\geq$3000 and $\leq$12 000/mm^3.
b) Neutrophil count $\geq$1500/mm^3.
c) Platelet count $\geq$100 000/mm^3.
d) Aspartate aminotransferase and alanine aminotransferase levels <2.5 times the institutional upper limit of normal.
e) Total bilirubin level <1.5 times the institutional upper limit of normal.
f) Serum creatinine level below the institutional upper limit of normal.
vii) All patients provided written informed consent before initiation of study-related procedures.

Exclusion Criteria

i) Patients who had received blood transfusion, blood products or hematopoietic growth factors such as granulocyte colony-stimulating factor within 7 days prior to registration.
ii) Patients who had used Japanese herbal (Kampo) medicines within 4 weeks before registration.
iii) History of severe hypersensitivity (allergy) to any medicines.
iv) Prior or current therapy for neuropathy or sensory dysfunction.
v) Other active malignancies or a history of other malignancies within the past 5 years.
vi) Uncontrolled pleural effusion or ascites.
vii) Pericardial effusion.
viii) A systemic inflammatory condition or serious infection.
ix) Symptomatic brain metastasis.
x) Significant electrocardiographic abnormality.
xi) Clinically problematic cardiac disease (congestive heart failure, symptomatic coronary artery disease, uncontrolled arrhythmia or myocardial infarction within the past 12 months).
xii) Severe pulmonary disease (interstitial pneumonia, pulmonary fibrosis, pulmonary emphysema etc.).
xiii) Gastrointestinal bleeding that requires medication or transfusion.
xiv) Diarrhea (watery) or diarrhea that interferes with daily activities for patients with a stoma.
xv) Ileus or bowel obstruction.
xvi) Central nervous system disorders.
xvii) Senile dementia.
xviii) Serious psychological disease.
xix) Uncontrolled diabetes mellitus with or without diabetic neuropathy.
xx) Pregnant or lactating women.
xxi) Any other medical condition that makes the patient unsuitable for inclusion in the study according to the opinion of the investigator.

Registration

An eligibility report form is sent to the registration center at ECRIN. Eligible patients are centrally randomized to either Arm A (FOLFOX with GJG) or Arm B (FOLFOX with placebo). Information regarding the necessary follow-up tests is then sent from the registration center at ECRIN.

Treatment Methods

Arm A

Patients receive GJG with either FOLFOX4 or mFOLFOX6 therapy. Cycles of chemotherapy are given every 2 weeks until progressive disease (PD) or unacceptable toxicity occurred.

GJG therapy. GJG is given orally at a dose of 2.5 g three times a day for 26 weeks starting on the day of L-OHP

infusion. To avoid a possible influence on the assessment of neurotoxicity, infusion of Ca or Mg is not allowed during administration.

FOLFOX4 therapy. Infusion of L-LV at 100 mg/m^2 over 2 h is followed by 5-FU as a bolus (400 mg/m^2) and a 22 h infusion (600 mg/m^2), with infusion of L-OHP at 85 mg/m^2 over 2 h on day 1. This regimen is repeated every 2 weeks.

mFOLFOX6 therapy. Infusion of L-LV at 200 mg/m^2 over 2 h is followed by 5-FU as a bolus (400 mg/m^2) and a 46 h infusion (2400 mg/m^2) with infusion of L-OHP at 85 mg/m^2 over 2 h on day 1. This regimen is repeated every 2 weeks.

Arm B

Patients receive placebo with either FOLFOX4 or mFOLFOX6 therapy. Cycles of chemotherapy are given every 2 weeks until PD or unacceptable toxicity occurred.

Placebo therapy. Placebo is given orally at a dose of 2.5 g three times a day for 26 weeks starting on the day of L-OHP infusion.

Follow-up

Neurological toxicity and other adverse reactions are assessed at baseline, every 2 weeks until Cycle 8, and every 4 weeks thereafter until the 26th week according to CTCAE and FACT/GOG-Ntx. The follow-up period is 1 year after registration of the last patient.

Study Design and Statistical Analysis

This study was designed to evaluate the efficacy of GJG for preventing L-OHP-induced neuropathy.

In Japan, when approval of L-OHP for post-operative adjuvant therapy is obtained in the future, it is expected to be administered with the target of 12 consecutive courses of treatment. However, preliminary results from the drug use investigation conducted in Japan (4) indicate that the median onset of Grade 3 neurological symptoms associated with dysfunction occurs in Cycle 8, indicating that this cycle is pivotal for continuation of treatment in the actual clinical setting.

Based on the clinical trial and the post-marketing surveillance performed in Japan (preliminary results) and the large-scale trial performed overseas, the estimated incidence of neurological symptoms of Grade 1 or worse is ~70–80% and that of Grade 2 or worse symptoms is ~30–50% when the cumulative dose of L-OHP exceeds 680 mg/m^2 (equivalent to about eight cycles at 85 mg/m^2/cycle) (4–8). In addition, Kono et al. reported that the estimated incidence of Grade 2 or worse neurotoxicity in patients concomitantly receiving GJG is ~10–30% when the cumulative dose of L-OHP exceeds 680 mg/m^2, whereas it is ~50% in patients not receiving GJG, showing a difference of ~30% between patients treated or not treated with GJG after the cumulative dose of L-OHP exceeds 500 mg/m (2,3).

Therefore, taking into account the exacerbation of peripheral neurotoxicity due to a higher total dose of L-OHP and spontaneous improvement after discontinuation of L-OHP, it was assumed that the incidence of neurological symptoms of Grade 2 or worse would be 15% in the study group (Arm A) and that in the control group (Arm B) would be 45% from the start of L-OHP treatment until completion of Cycle 8. In order to achieve a power of 80% with a two-sided significance of $P < 0.05$ for detecting the superiority of concomitant treatment with GJG by the χ^2 test, the number of patients required per group was calculated to be 36. In consideration of possible dropouts, the target number of patients was therefore set at 40 per group (80 in total).

Randomization is done by using three strata: use of bevacizumab, the institution and the presence of target lesions evaluated by RECIST. Adequate statistical methods will be used for the final statistical analysis.

PARTICIPATING INSTITUTIONS

Approximately 37 Japanese institutions and hospitals are participating in this trial.

Funding

Research grant from a non-profit organization:

Conflict of interest statement

None declared.

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Original Paper

Multicenter Phase II Study of FOLFOX for Metastatic Colorectal Cancer (mCRC) in Japan; SWIFT-1 and 2 study

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KEY WORDS: Chemotherapy; FOLFOX4 and mFOLFOX6 regimens; Metastatic colorectal cancer; Phase II study

ABBREVIATIONS: Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD); Not Evaluable (NE); Eastern Cooperative Oncology Group (ECOG); Granulocyte-Colony Stimulating Factor (G-CSF)

ABSTRACT

Background/Aims: This study assessed the efficacy and toxicity of the FOLFOX4 (SWIFT1) and mFOLFOX6 (SWIFT2) regimens in Japanese patients with metastatic colorectal cancer (mCRC).

Methodology: Patients with mCRC were required to have ECOG performance status of 0 to 1, and to have adequate organ function. Two multicenter Phase II studies (SWIFT1 /SWIFT2) were conducted in chemotherapy naïve patients with mCRC.

Results: 112 patients were enrolled in these studies (SWIFT1: 54 patients / SWIFT2: 58 patients). The disease sites for each study were the colon in 27 patients and 28 patients, and the rectum in 27 patients and 30 patients, respectively. All patients received a median of 8 courses. After a median follow-up period of 35 months, 54 patients and 58 patients were evaluable in the respective studies, and the overall response rate was 50.0% (CR:3/PR:53). The response rate according to the sites of metastasis were as follows: liver, 54.1% (46/85); lung, 17.4% (4/23); and lymph node, 23.3% (7/30). Grade 3/4 neutropenia occurred in 14 patients (12.5%), while Grade 3/4 non-hematological toxicities were observed in 16 patients (31.0%) and Grade 3 neurotoxicity was observed in 6patients (5.4%) and 5patients (4.5%), respectively.

Conclusions: FOLFOX4 (SWIFT1) and mFOLFOX6 (SWIFT2) regimens complying with the international standard dosage and schedule can also be administered safely and effectively in Japan.

INTRODUCTION

Colorectal cancer is one of the most common malignancies in Japan and is one of only a few malignant cancers for which the 5-year survival rate of patients has improved in recent years. Colorectal cancer accounts for 11.7% of all malignant cancers and is the fourth leading cause of cancer-related death in Japan. Recently, curative resections for colorectal cancer have improved the clinical diagnosis. Nevertheless, most patients with advanced or recurrent colorectal cancers die from their diseases.

Patients with unresectable locally advanced or metastatic lesions have been treated with systemic chemotherapy, although palliative chemotherapy may be the only reasonable therapeutic option in some cases. Most chemotherapy regimens for colorectal cancer consist of combination chemotherapy regimens, which combine drugs with different mechanisms of action. Several randomized studies have demonstrated the benefits of chemotherapy compared with best-supportive care (1-3).

Until recently, the treatment of advanced or metastatic colorectal cancer has been restricted to fluorouracil (5-FU) infusion and the biomodulation of leucovorin (LV) (4, 5). Oxaliplatin is a new cytotoxic agent from the diaminocyclohexane platinum family that was first synthesized in Japan (4), although its clinical development has mainly been conducted in Europe. Oxaliplatin (L-OHP) has a mechanism of action similar to that of other platinum derivatives (7-9), and experimental data have shown synergistic activities for oxaliplatin/FU combinations. The recent development of this new agent for the treatment of advanced CRC has markedly enhanced the therapeutic armamentarium for this disease.

Clinical phase III studies have shown that combination chemotherapy regimens, including irinotecan and oxaliplatin, markedly improved the response rates and prolonged the median survival period, compared with 5FU/LV (10-12). These combination chemotherapy regimens have supplanted 5FU/LV as the standard systemic approach for

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treating metastatic CRC. In Japan, phase I and II studies of oxaliplatin as a single agent have been conducted (13, 14), and the recommended dose (RD) was determined to be 130 mg/m² in a tri-weekly regimen. Studies of tri-weekly regimens showed an overall response rate of 8.8% (5/57; 95% CI, 2.9 – 19%) for patients' refractory to fluoropyrimidine-based regimens, with tolerable toxicity.

In addition, oxaliplatin and infusion 5-FU/*l*-LV was approved in Japan in March 2005. To evaluate the value of the FOLFOX regimens for the treatment of advanced colorectal cancer, a retrospective analysis was performed to assess the feasibility and efficacy of combining oxaliplatin with the LV5FU2 schedule in a Japanese population. Therefore, we performed the current phase II study to further evaluate the efficacy, safety and tolerability of the FOLFOX4 regimen (SWIFT-1 study) and the modified FOLFOX6 regimen (SWIFT-2 study) in patients with advanced colorectal cancer.

METHODOLOGY

Eligibility

Patients in this study had histologically proven metastatic colorectal cancer with measurable lesions; additional criteria were 1) an age of 25 to 75 years; 2) a maximum of one prior chemotherapy regimen for metastatic disease and/or one adjuvant chemotherapy regimen completed 4 weeks before the current study; 3) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1; 4) a life expectancy of more than 2 months; 5) adequate bone marrow function (leucopenia > 3,000/mm³, platelet count > 100,000/mm³, and hemoglobin level > 8.0g/dL), adequate renal function (creatinine clearance > 50mL/min), and adequate hepatic function (bilirubin level < 1.5mg/dL and AST, ALT < triple the normal upper limit; 6) no other severe medical conditions; and 7) no active cancer in other organs. All the patients provided a written informed consent, conforming to the institutional guidelines and indicating that they were aware of the investigational nature of the study. This study was approved by the Ethics Committees of the participating institutions.

Treatment

To prevent reactions arising from hypersensitivity, pre-medication consisting of dexamethasone (16 mg, iv) and cimetidine (50mg, iv) was given 30 min before each administration. Two combination methods (FOLFOX4 and mFOLFOX6) of oxaliplatin with LV (leucovorin) and the intravenous infusion of 5FU were used. Oxaliplatin was administered on day 1 at a dose of 85 mg/m² as an infusion over 2 hours concurrent with l-LV in both regimens. The FOLFOX4 regimen consisted of l-LV at 100 mg/m² as a 2-hour infusion followed by a bolus of 5FU at 400 mg/m² and a 22-hour infusion of 5FU at 600 mg/m² on days 1 and 2 every two weeks. The mFOLFOX 6 regimen consisted of l-LV at 200 mg/m² as a 2-hour infusion followed by a bolus of 5FU at 400 mg/m² and a 46-hour infusion of 5FU at 2400mg/m² from day 1 to 2 every two weeks. These treatments were repeated at two-week intervals (**Figure 1**). The administration of granulocyte-colony stimulating factor (G-CSF) was permitted if Grade 4 leucopenia or neutropenia occurred. This administration was continued until the leukocyte or neutrophil counts recovered to at least 10,000/μL and 5,000μL, respectively.

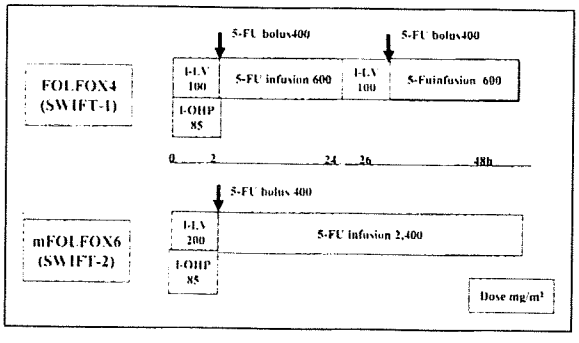
Patient Evaluation and Follow-up

Pretreatment evaluation included a baseline medical history and physical examinations in addition to laboratory studies, a chest X-ray, and an electrocardiogram. Computed tomography (CT) and magnetic resonance imaging studies were performed to clarify and document the location, size, and extent of the disease, when measurable. A complete blood cell count, urinalysis, electrolytes, and renal and liver function tests were evaluated at least once weekly and before subsequent cycles, as well as at the conclusion of the study.

Response to Treatment and Adverse Events

Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) (15). A complete response (CR) was defined as the disappearance of all clinical evidence of the tumor for a period of at least 4 weeks. A partial response (PR) was defined as a 30% decrease in the bi-dimensional tumor measurements for at least 4 weeks, without the appearance of any new lesions or the progression of any existing lesions. Progressive disease (PD) was defined as the development of any lesions or a 20% increase in the sum of the products of all measurable lesions. Stable disease (SD) was defined as a tumor response that did not meet the criteria for CR, PR or PD. Toxicities were evaluated based on the National Cancer Institute (NCI) common toxicities criteria (CTC), version 3. During treatment, weekly complete hematological blood cell counts, the determination of liver and renal function, and the assessment of non-hematological toxicities were preformed. Dose modification and treatment delays were performed as necessary, according to the extent of hematological and organ toxicity.

FIGURE 1 Chemotherapy regimens of FOLFOX4 (SWIFT-1) and mFOLFOX6 (SWIFT-2)



Parameter	ALL SWIFT-1&2 No. of patient	(%)	FOLFOX4 (SWIFT-1) No. of patient	mFOLFOX6 (SWIFT-2) No. of patient
No. of patient	112		54	58
Gender				
Male	70	62.5	35	35
Female	42	37.5	19	23
Age. year				
median	61.5		62	63
range	25-75		25-74	25-75
Performance status (ECOG)				
0	87	77.7	42	45
1	25	22.3	12	13
Primary cancer site				
Colon	55	49.1	27	28
Rectum	57	50.9	27	30
Site of metastases				
Liver	85	75.9	44	41
Lung	23	20.5	12	11
Limph node	30	26.8	15	15
Prior treatment (colorectomy)				
Yes	103	92	48	55
No	9	8	6	3
Previus adjuvant chemoterapy				
Yes	26	23.2	13	13
No	86	76.8	41	45
Median courses				
Range	1-19		1-19	1-16
Average	8		7.5	8

Statistical Analysis

The primary endpoint of this study was the response rate to combination chemotherapy comprised of either the FOLFOX4 or mFOLFOX6 regimen for the treatment of advanced or metastatic colorectal cancer. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), and peripheral sensory neuropathy was graded using an oxaliplatin-specific scale (DEB-NTC). Overall survival (OS) and progression-free survival (PFS) were the secondary endpoints. OS was calculated from the start of the study registration until death. PFS was calculated from the start of registration until the date of progression. The OS and PFS curves were obtained using the Kaplan-Meier method.

RESULTS

Patient Characteristics

A phase II study on FOLFOX4 (SWIFT-1) and mFOLFOX6 (SWIFT-2) was initiated in patients with unresectable, advanced, and recurrent colorectal cancer in July 2005 as a multi-center cooperative clinical trial (by the SWIFT Study Group). Enrollment was completed in April 2006 with 112 patients from 18 medical institutions with evaluable lesions. The patient characteristics for all 112 patients are summarized in **Table 1**. Fifty-four patients were treated with the FOLFOX4 regimen (SWIFT-1), and 58 patients were treated with the mFOLFOX6 regimen (SWIFT-2). Seventy male patients and 42 female patients were treated. The median age was 61.5 years (range, 25 – 75 years); 87 patients had an ECOG performance status (PS) of 0, and 25 patients had a PS of 1. Twenty-six patients (23.2%) had received adjuvant chemotherapy. The major metastatic sites were the lymph nodes (30 patients: 15 in SWIFT-1 and 15 in SWIFT-2), the liver (85 patients: 44 in SWIFT-1 and 41 in SWIFT-2), and the lung (23 patients: 12 in SWIFT-1 and 11 in SWIFT-2). One hundred and twelve evaluable patients were included in the analysis.

Toxicity

All 112 patients were fully evaluated for adverse reactions. Toxicities associated with treatment are listed in **Table 2**, and the incidence of neurotoxicity is listed in **Table 3**. In the FOLFOX4 regimen, Grade 3 or severer hematological toxicities included leucopenia, neutropenia, anemia and thrombocytopenia in 20.4%, 51.9%, 0% and 3.7% of the patients, respectively. Grade 3 or severer non-hematological toxicities included diarrhea and stomatitis in 1.9% and 1.9% of the patients, respectively. Grade 2 or severer neuropathy, a characteristic adverse reaction of oxaliplatin, occurred in 24.1% (13/54) of the patients according to the NCI-CTCAE criteria and 27.8% (15/54) of the patients according to the DEB-NTC criteria. Both the hemotoxic and the non-hemotoxic changes were well tolerated. In the mFOLFOX6 regimen, Grade 3 or severer hematological toxicities included leucopenia, neutropenia, anemia and thrombocytopenia in 6.9%, 44.8%, 3.5% and 1.7% of the patients, respectively. Grade 3 or severer non-hematological toxicities included anorexia, nausea, vomiting, diarrhea and Hand-foot syndrome in 10.3%, 6.9%, 3.5%, 1.7% and 1.7% of the patients, respectively. Grade 2 or severer neuropathy occurred in 29.3% (17/58) of the patients according to the NCI-CTCAE criteria and 41.4% (24/58) of the patients according to the DEB-NTC criteria.

The incidence of neurotoxicity along with the number of treatment cycles is listed in **Figure 2**. Grade 1 neuropathy occurred during the first

Toxicity	SWIFT 1: FOLFOX4 (n=54)				SWIFT 2: mFOLFOX6 (n=58)			
	No. of patient (%)				No. of patient (%)			
	G2	G3	G4	G3 and 4	G2	G3	G4	G3 and 4
Leucocytopenia	12(22.2%)	11(20.4%)	0	11(20.4%)	24(41.4%)	3(5.2%)	1(1.7%)	4(6.9%)
Neutropenia	11(20.4%)	18(33.4%)	10(18.5%)	28(51.9%)	16(27.6%)	19(32.8%)	7(1.2%)	26(44.8%)
Anemia	10(18.5%)	0	0	0	18(31.0%)	2(3.5%)	0	2(3.5%)
Thombocytopenia	9(16.7%)	2(3.7%)	0	2(3.7%)	9(15.5%)	1(1.7%)	0	1(1.7%)
AST elevation	9(16.7%)	1(1.9%)	0	1	7(12.1%)	0	0	0
ALT elevation	3(5.6%)	2(3.7%)	0	2	8(13.8%)	2(3.5%)	0	2(3.5%)
Anorexia	8(14.8%)	0	0		11(19.0%)	6(10.3%)	0	6(10.3%)
Nausea	2(3.7%)	0	0		5(8.6%)	4(6.9%)	0	4(6.9%)
Vomiting	2(3.7%)	1(1.9%)	0		2(3.5%)	2(3.5%)	0	2(3.5%)
Diarrhea	0	1(1.9%)	0	1	2(3.5%)	1(1.7%)	0	1(1.7%)
Stomatitis	1(1.9%)	1(1.9%)	0	1	3(5.2%)	0	0	0
Hand-foot syndrome	0	0	0	0	2(3.5%)	1(1.7%)	0	1(1.7%)

course in five patients (11.1%) in the SWIFT-1 series and in 17 patients (36.9%) in the SWIFT-2 series. Grade 2 or 3 neuropathy frequently developed in the fourth or later courses. No difference in the frequency of Grade 2 or 3 neuropathy was observed between the SWIFT1 and SWIFT2 series. The relative dose intensities (RDI) in this trial were 81.9% for oxaliplatin, 83.2% for bolus 5FU, and 81.8% for infusion 5FU in SWIFT1, and 82.1%, 84.1%, and 84.4%, respectively, in SWIFT2 (**Table 4**). Ten patients (18.2%) were withdrawn from the study because of adverse events in SWIFT1 and 14 (24.1%) were withdrawn because of adverse events in SWIFT2.

Efficacy

Overall, out of 112 evaluable patients, the median number of treatment courses was 7.5 (range, 1 – 19 courses) in SWIFT1 and 8 (range, 1 – 16 courses) in SWIFT2. The objective responses are listed in **Table 5**. Three patients had complete responses (CRs), and 53 patients had partial responses (PRs; total responses, 56/112 [50.0%]). Forty-four patients had stable diseases (SDs; 44/112 [39.3%]), and 5 patients had progressive diseases (PDs; 5/112: [4.5%]); 6 patients could not be evaluated (NE; 6/112 [5.4%]). The objective response rate was 50.0% (95% CI, 27.1% to 54.6%) for SWIFT-1&2. In the SWIFT1 series, the antitumor efficacy rating was CR, PR, SD, and PD in 1.9%, 51.9%, 37%, and 3.7% of the patients, respectively, with a response rate (CR + PR: 30/54) of 55.6%. In the SWIFT2 series, the antitumor efficacy rating was CR, PR, SD, and PD in 3.4%, 43.1%, 41.4%, and 5.2% of the patients, respectively, with a response rate (CR + PR: 27/58) of 46.6%. The response rates (CR + PR) according to metastatic site were 54.1% (46/85) for the liver, 17.4% (4/23) for the lung, and 23.3% (7/30) for the lymph nodes in SWIFT-1&2 (**Table 6**). The median progression-free survival time was 9.0 months in SWIFT-1 and months in SWIFT-2 (**Figure 3**). The median survival time was 21.5 months in SWIFT-1 and 21.6 months in SWIFT-2 (**Figure 4**).

DISCUSSION

In Western countries, the standard chemother-

TABLE 3. Neurologic Toxicity

	SWIFT 1: FOLFOX4 (n=54)				SWIFT 2: mFOLFOX6 (n=58)			
	No. of patient (%)				No. of patient (%)			
Neurologic toxicity	G1	G2	G3	G4	G1	G2	G3	G4
NCI-CTCA	26 (48.1%)	10 (18.5%)	3 (5.6%)	0	29 (50%)	14 (24.1%)	3 (5.2%)	0
DEB-NTC	23 (42.6%)	12 (22.2%)	3 (5.6%)	0	24 (41.4%)	22 (37.9%)	2 (3.5%)	0

NCI-CTCA: V3.0
DEB-NTC: oxaliplatin-specific scale

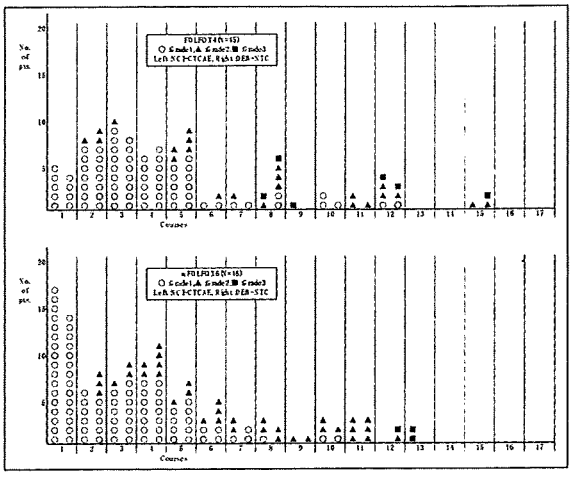


FIGURE 2
Appearance of neuropathy

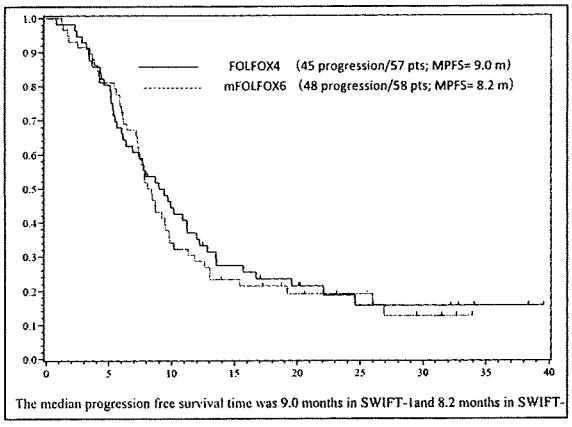


FIGURE 3
Progression-free survival rate of all enrolled patients. The median progression-free survival time was 9.0 months in SWIFT-1 and 8.2 months in SWIFT-2

apy regimens for the treatment of advanced colorectal cancer are L-OHP + 5FU/LV (FOLFOX4 and mFOLFOX6 regimens)(11,16,17), CPT-11 + 5FU/LV (FOLFIRI and AIO regimens), and additional molecular-targeting therapies. The median survival time (MST) after these therapies currently exceeds 20 months. In Japan, 5FU/LV has been recognized as a treatment for advanced colorectal cancer since l-LV was approved in 1999. When CPT-11 and L-OHP were developed (18, 19), their clinical trials were conducted in combination with 5FU/LV. Later, a controlled trial of LV/5FU2 versus L-OHP versus FOLFOX4 was conducted in patients who were resistant to IFL therapy, which was the standard treatment for advanced colorectal cancer in the U.S. The study reported that the FOLFOX regimen was significantly superior (16). Subsequently, a phase III randomized controlled clinical trial showed that

TABLE 4 Relative Dose Intensity

	SWIFT-1	SWIFT-2
	FOLFOX4	mFOLFOX6
oxaliplatin	81.9%	82.1%
5FU (bolus)	83.2%	84.1%
Infusional 5FU	81.8%	84.4%

combination therapies including CPT-11 or L-OHP had a much better response rate and progression-free survival period than 5FU/LV (12, 14, 17, 20). Thus, these combinations replaced 5FU/LV as the standard systemic treatments for metastatic advanced colorectal cancer.

In Japan, infusion 5FU/LV was approved in February 2005, and the FOLFOX therapy became available at that time. However, no phase II trial had been conducted in Japanese patients with advanced colorectal cancer examining combination therapies using FOLFOX4 or mFOLFOX6 at that time. Thus, a multicenter phase II clinical trial was conducted to examine the feasibility of these regimens in actual clinical practice. This trial included a total of 112 cases with evaluable lesions treated using either the FOLFOX4 regimen (SWIFT-1, n=54) or the mFOLFOX6 regimen (SWIFT-2, n=58). As for the treatment results, the overall response rate was 50.0% (53.7% in SWIFT-1 and 46.6% in SWIFT-2), the overall MST was 21.5 months (21.5 months in SWIFT-1 and 21.6 months in SWIFT-2), and the overall progression-free survival (PFS) period was 8.7 months (9.0 months in SWIFT-1 and 8.2 months in SWIFT-2). These results were comparable to those reported in Western studies (**Table 7**) (10, 11, 21-23) and in the study by Shimizu *et al.* (24), and no significant differences were observed between SWIFT-1 and SWIFT-2. In this trial, many patients had liver metastasis, and the response rate in the patients with liver metastasis was 54.1%, which was the highest value among the patient groups according to metatastic site. This finding strongly suggests that the L-OHP + 5FU/LV regimen is effective and useful as an initial therapy in patients with liver metastasis.

As for adverse reactions, the incidences of grade 3 or higher adverse events were 13.4% for leukopenia, 48.2% for neutropenia, and 1.8% for anemia. These results were also comparable to those reported in Western studies. The mean number of courses

TABLE 5 Response

	CR	PR	SD	PD	NE	Response rate
	No. of patient (%)					
SWIFT-1: FOLFOX4	1(1.9%)	28(51.9%)	20(37%)	2(3.7%)	2(3.7%)	29/54 (53.7%)
SWIFT-2: mFOLFOX6	2(3.4%)	25(43.1%)	24(41.4%)	3(5.2%)	4(6.9%)	27/58 (46.6%)
SWIFT-1&2	3(2.7%)	53(47.3%)	44(39.3%)	5(4.5%)	6(5.4%)	56/112 (50.0%)

administered to the subjects was 7.5 (range, 1 – 19 courses) in SWIFT-1 and 8 (range, 1 – 16 courses) in SWIFT-2. In the SWIFT-1 series, the incidence of grade 2 and grade 3 peripheral sensory neuropathy, a characteristic adverse reaction of L-OHP, was 18.5%/5.6% according to the NCI-CTCAE criteria and 22.2%/5.6% according to the DEB-NTC criteria; in the SWIFT-2 series, the respective incidences were similar: 24.1%/5.2% and 37.9%/3.5%, respectively. In Western countries, the incidence of grade 2 and 3 peripheral neurotoxicity was reported as 29.2%/18.2% after FOLFOX4 therapy used as an initial therapy. Although a direct comparison is not appropriate, these results are almost comparable to those for the SWIFT-1 and SWIFT-2 series.

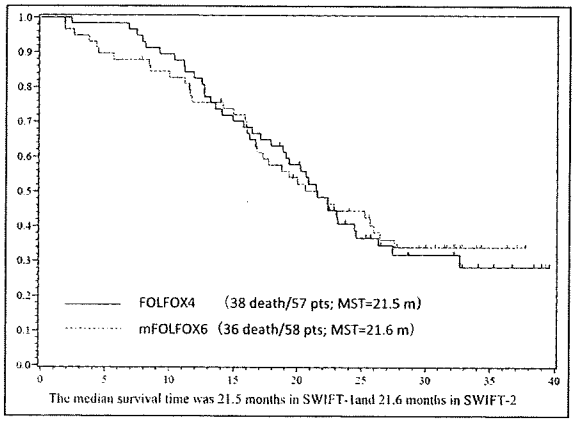


FIGURE 4 Overall survival rate of all enrolled patients. The median survival time was 21.5 months in SWIFT-1 and 21.6 months in SWIFT-2

TABLE 6 Response by metastatic sites

	Total: SWIFT-1&2		FOLFOX4: SWIFT-1		mFOLFOX6: SWIFT-2	
Site of metastases	No. of patient (%)		No. of patient (%)		No. of patient (%)	
	CR+PR/n	Response rate(%)	CR+PR/n	Response rate(%)	CR+PR/n	Response rate(%)
Liver	46/85	54,1	24/43	67,4	22/35	80
Lung	4/23	17,4	5/6	83,3	3/7	42,9
Lymph node	7/30	23,3	3/9	33,3	3/13	23,1

TABLE 7 Comparison of other studies

	FOLFOX4 in First-Line				mFOLFOX6 in First-Line		
	SWIFT1 present study	C95-1 de Gramont[1]	N9741 Goldberg[2]	OPTIMOX1 Tournigand[3]	SWIFT2 present study	OxMdG Cheeseman[4]	FOCUS Seymour[5]
No. of patients	54	210	267	311	58	25	299
Age, years							
Median	62	63	61	65	63	62	64
Range	25-74	20-76	27-88	29-80	25-75	14-77	56-69
PS, %							
0	77.8	43.3	] 93	52	77.6	40	41
1	20.4	46.2		] 48	22.4	44	50
2			5			16	8
Metastatic site, %							
Liver	81.5	86.7	unknown	71	70.7	unknown	unknown
Lung	22.2	23.4	unknown	26	19	unknown	unknown
Other	27.8	12.4	unknown	10	29.3	unknown	unknown
Adjuvant Chemotherapy, %	24.1	20	16	22	20.7	24	unknown
RR, %	55.6	50.7	45	58.5	46.6	72	56.2
PFS, months	9.4	9	8.7	9	8.5	10.6	9.1
OS, months	20.2	16.2	19.5	19.3	21.6	16.7	15.2

Grade 1 peripheral sensory neuropathy developed during the first treatment course, and the frequency of this complication was similar in the SWIFT-1 and SWIFT-2 series. However, grade 2 and 3 peripheral nerve disorders frequently developed during the fourth or later courses. The grade of the disorder was higher for later treatment courses, as reported by de Gramont *et al.* (11). The relative dose intensities (RDI) in this trial were 81.9% for L-OHP, 83.2% for bolus 5FU, and 81.8% for infusion 5FU in SWIFT-1, and 82.1%, 84.1%, and 84.4%, respectively, in SWIFT-2. Factors responsible for RDI reductions included hemotoxicity (leukopenia, neutropenia, and thrombocytopenia) and peripheral nerve disorders in the both studies (25). The response rate, PFS, MST and safety of the FOLFOX4 and mFOLFOX6 combination therapies were equivalent in our multicenter phase II clinical trial and were somewhat better than those reported in foreign trials.

This clinical trial demonstrated that FOLFOX therapy is as effective and safe in Japanese patients with unresectable advanced colorectal cancer as it is in patients in foreign countries and may be remarkably effective if used in general practice in Japan. However, since the manifestations of peripheral sensory neuropathy increase with increases in the number of doses, future treatment strategies require preventive measures to ensure that the QOL of these patients is not reduced.

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A Feasibility Study of UFT/LV and Irinotecan (TEGAFIRI) in Advanced or Metastatic Colorectal Cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) PROG 0304

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