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Original Article

Clinical impact of postoperative prognostic nutritional index in colorectal cancer patients undergoing adjuvant chemotherapy

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Abstract: Preoperative Prognostic Nutritional Index (PNI) could be a crucial factor for the prognosis of colorectal cancer (CRC). However, the clinical impact of postoperative PNI is still unclear, and there have been no reports on the significance of postoperative PNI in patients undergoing adjuvant chemotherapy (AC). We retrospectively analysed 227 consecutive patients who underwent AC after radical surgery for high-risk stage II or stage III CRC. PNI value was calculated before radical surgery and before the introduction of AC. In our study, patients with a low PNI value before surgery showed significantly poorer long-term outcomes than those with a high PNI value. Next, we divided the patients into four groups: patients with a high PNI value before surgery and remained after surgery (Group High-High), a high PNI value before surgery but decreased after surgery (Group High-Low), a low PNI value before surgery but recovered after surgery (Group Low-High), and a low PNI value but did not recover after surgery (Group Low-Low). Although the patients in Group Low-Low showed significantly poorer long-term outcomes than those in Group High-High, the prognosis of patients in Group Low-High was the same as that of patients in Group High-High. In addition, in patients with recurrence after AC, those with a high PNI value at the time of recurrence showed a significantly better survival after recurrence than patients with a low PNI value. Postoperative PNI value could be a prognostic biomarker for CRC patients undergoing AC. Even though the PNI value was low before the surgery, recovery of PNI value by the introduction of AC could improve the prognosis of CRC patients.

Keywords: Prognostic nutritional index, colorectal cancer, adjuvant chemotherapy, recurrence

Introduction

Colorectal cancer was the third most frequent malignancy worldwide in 2018. More than 1,800,000 cases occurred worldwide, and nearly 860,000 died from it in 2018 according to GLOBOCAN 2018 [1]. Although the prognosis of colorectal cancer has improved due to the development of multidisciplinary treatment, it is still one of the cancers with a poor prognosis. Surgical treatment is the most curative method for non-metastatic resectable colorectal cancer, but it has been reported that patients with high-risk stage II or stage III colorectal cancer have a high possibility of recurrence after radical surgery [2]. Therefore, postoperative adjuvant chemotherapy is recommended to prevent recurrence in these cases [3, 4].

However, the ability of adjuvant chemotherapy to prevent recurrence is limited [2, 5, 6]. In addition, there are problems with side effects and medical costs [7-9] due to postoperative adjuvant chemotherapy itself. Therefore, a novel method for predicting the effects of adjuvant chemotherapy is warranted in terms of precision medicine.

Prognostic Nutritional Index (PNI) is used as a nutritional and immunological index and has been reported as a prognostic marker for gastrointestinal cancer [10-15]. These previous reports have shown that preoperative PNI

Table 1. The relationships between preoperative PNI and clinicopathological factors in colorectal cancer patients

Variables	Preoperative PNI		Univariate[a]
	low[b] (n=57)	high[b] (n=170)	*P*-value
Gender			
Female	26 (46%)	77 (45%)	1.00
Male	31 (54%)	93 (55%)	
Age			
<75	42 (74%)	150 (88%)	0.01
75≤	15 (26%)	20 (12%)	
BMI			
<18	53 (93%)	160 (94%)	0.75
18≤	4 (7%)	10 (6%)	
Location			
Colon	38 (67%)	102 (60%)	0.43
Rectum	19 (33%)	68 (40%)	
Histopathological type			
differentiated	43 (77%)	157 (92%)	<0.01
undifferentiated	13 (23%)	13 (8%)	
Tumor depth			
T1, T2, T3	38 (67%)	138 (83%)	0.01
T4	19 (33%)	28 (17%)	
Lymph node metastasis			
N0, N1	44 (77%)	124 (73%)	0.60
N2, N3	13 (23%)	46 (27%)	
Lymphatic invasion			
Absent	21 (37%)	54 (32%)	0.51
Present	35 (63%)	115 (68%)	
Venous invasion			
Absent	21 (37%)	73 (43%)	0.53
Present	35 (63%)	96 (57%)	
CEA (ng/mL)			
<5	27 (47%)	113 (67%)	0.01
5≤	30 (53%)	56 (33%)	
CA19-9 (U/mL)			
<37	46 (81%)	156 (92%)	0.02
37≤	11 (19%)	13 (8%)	
Surgical Approach			
Laparoscopic	50 (88%)	156 (92%)	0.42
Open	7 (12%)	14 (8%)	
Complication (≥CD grade 2)			
Absent	46 (81%)	158 (93%)	0.02
Present	11 (19%)	12 (7%)	

A low preoperative PNI value was associated with older age, undifferentiated histological type, deeper tumor depth, higher serum level of CEA and CA19-9, and the occurrence of postoperative complications. a, Univariate analysis was assessed using Chi squared test. b, low: PNI<45.6, high: PNI≥45.6.

value is associated with short and long-term outcomes of patients with gastrointestinal cancer, but few reports have shown a relationship between postoperative PNI value and the outcomes of patients with colorectal cancer.

This study examined the relationship between postoperative PNI value and the outcomes of patients with colorectal cancer, in particular the clinical impact of nutritional status at the time of introduction of adjuvant chemotherapy on the prognosis.

Material and methods

Patients and laboratory data

This study was conducted in accordance with the ethical standards of the Kyoto Prefectural University of Medicine and the Helsinki Declaration. We retrospectively analyzed 227 consecutive patients who underwent adjuvant chemotherapy after radical surgery for high-risk stage II or stage III colorectal cancer at Kyoto Prefectural University of Medicine between 2008 and 2017. In this study, high-risk stage II colorectal cancer was defined as lesions that adhered to or invaded local organs (T4), cases of perforation or obstruction, fewer than 12 analyzed lymph nodes, vascular and perineural invasion, or poorly differentiated histology [2, 16]. All patients were pathologically staged according to the 8th edition of the TNM Classification of Malignant Tumors (Union for International Cancer Control). Patients were staged using colonoscopy, barium enema, computed tomography, and positron emission tomography/computed tomography. Patients were followed up every 3 months during the first 3 years and

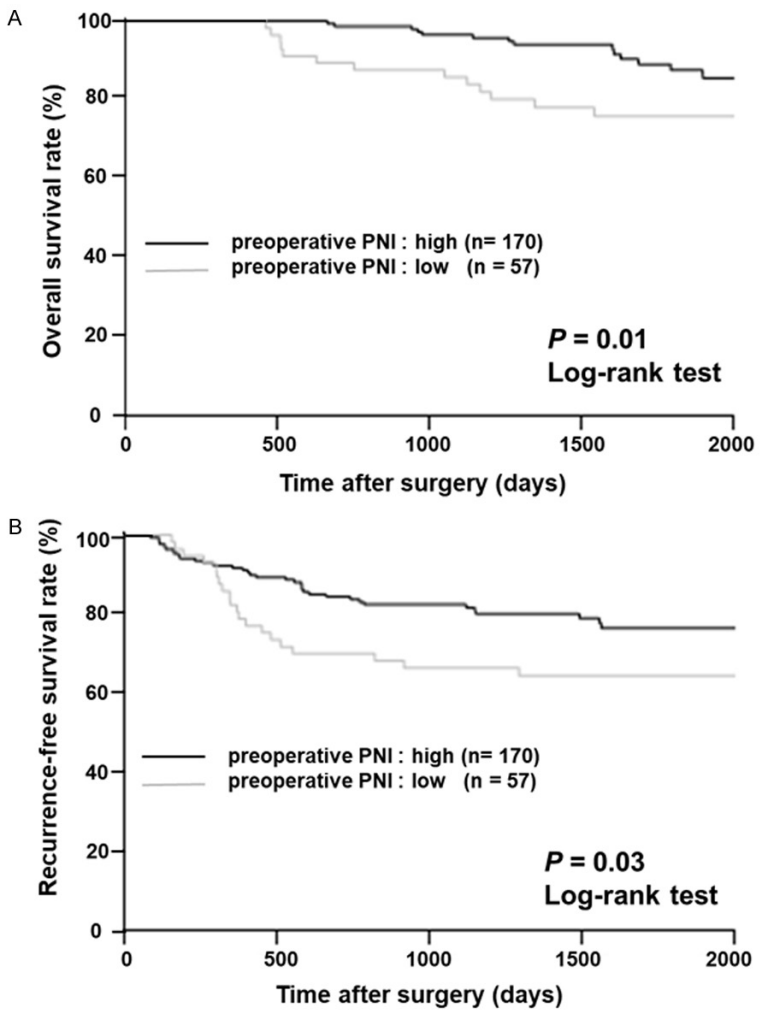

Figure 1. Kaplan-Meier survival analysis comparing patients with preoperative low-PNI value (≤45.6) and patients with preoperative high-PNI value (>45.6). The patients with low-PNI value showed significantly poorer overall survival and recurrence-free survival than those with high-PNI value.

every 6 months thereafter. The treatment plan was decided according to the Japan Colorectal Cancer Guidelines [17]. The regimen of adjuvant chemotherapy was combination therapy consisting of 5-fluorouracil and oxaliplatin or monotherapy of 5-fluorouracil.

Preoperative blood samples were obtained at the first visit to our department almost within one month before the operation. The postoperative blood samples were obtained at the time of introduction of adjuvant chemotherapy and at the point of identifying tumor recurrence. The PNI value was calculated as follows: 10 × serum albumin level (g/dL) +0.005 × TLC (/mm^3).

Statistical analysis

Statistical analyses were performed using JMP version 10 (ASA Institute, Cary, NC). Differences in categorical variables were compared using a Chi-squared test and Fisher's exact probability test. Differences in continuous variables were analyzed with the Student's t-test and the Mann-Whitney U-test to compare the clinicopathological characteristics between the three groups. Survival curves of the overall survival (OS) and recurrence-free survival (RFS) were estimated using the Kaplan-Meier method, and statistical differences were examined using the log-rank test. In multiple comparison analysis, significant difference was evaluated by Bonferroni correction. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox's proportional hazards model. $P<0.05$ derived from a two-tailed test was considered statistically significant.

Results

Patient characteristics

A total of 227 patients consisted of 40 high-risk stage II patients (17.6%) and 187 stage III patients (82.4%) (Supplementary Table 1). Postoperative complications occurred in 23 cases (10.1%), including anastomotic leakage in 3 cases, anastomotic bleeding in 1 case, intra-abdominal abscess in 4 cases, ileus in 2 cases, surgical site infection in 2 cases and others. The median follow-up period was 52 months (range 9-119 months). Tumor recurrence was identified in 7 patients of high-risk stage II (17.5%) and 48 patients of stage III (25.7%) (Supplementary Figure 1). Among all patients, 89 patients (39.2%) received a combination therapy consisting of 5-fluorouracil and oxaliplatin, such as mFOLFOX6 or CapeOX,

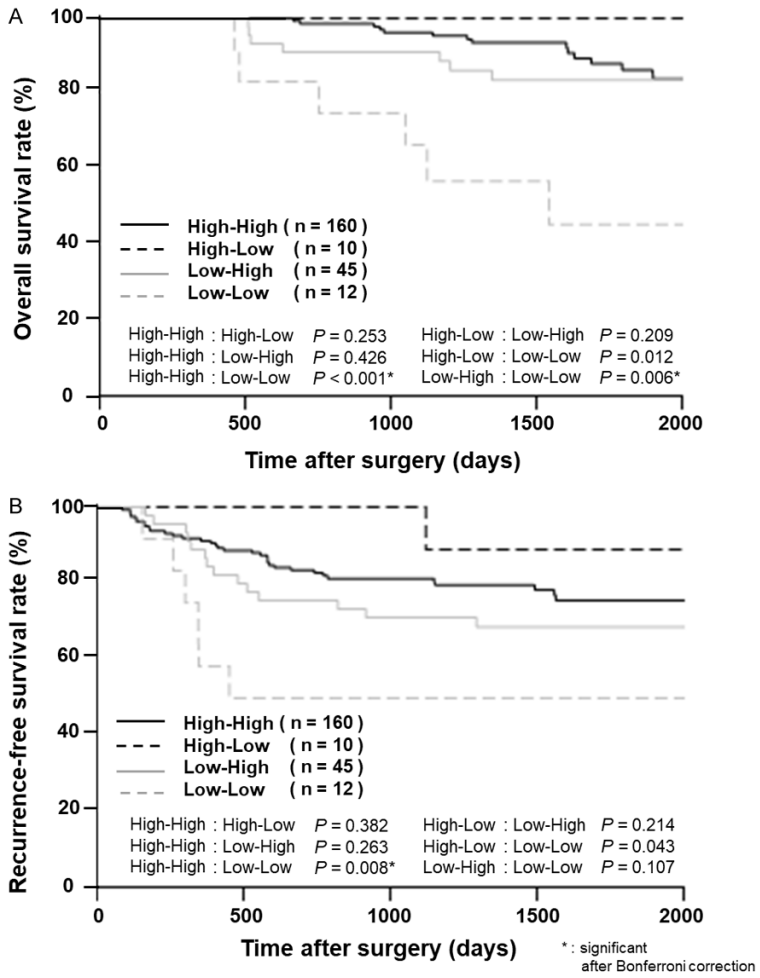

Figure 2. Kaplan-Meier survival analysis comparing patients with high-PNI value (≥45.6) before radical surgery and remained after surgery (Group High-High), those whose PNI value was high and decreased (<45.6) after surgery (Group High-Low), those whose PNI value was low (<45.6) before surgery but recovered after surgery (Group Low-High), and those whose PNI value was low (<45.6) and did not recover after surgery (Group Low-Low). In multiple comparison analysis, significant difference was evaluated by Bonferroni correction. While the patients in Group Low-Low showed significantly poorer OS and RFS than those in Group High-High, the prognosis of patients in Group Low-High was as same as that of patients in Group High-High.

and 138 patients (60.8%) received monotherapy of 5-fluorouracil, such as TS-1, UFT/LV, or capecitabine.

Relationships between preoperative PNI value and long-term outcomes

The median preoperative PNI was 49.5 (range 28-64.5). The cut-off value of the PNI was set to 45.6 using a receiver operative characteristic (ROC) curve analysis. The association between preoperative PNI status and clinicopathological features is shown in **Table 1**. A low preoperative PNI value (PNI≤ 45.6) was associated with older age (P=0.01), undifferentiated histological type (P< 0.01), deeper tumor depth (P=0.01), higher serum level of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) (P=0.01 and P=0.02, respectively), and the occurrence of postoperative complications (P= 0.02). Patients with a low-PNI value showed significantly poorer overall survival (OS) and recurrence-free survival (RFS) than those with a high-PNI value (PNI>45.6) (P=0.01, P=0.03, respectively) (**Figure 1**).

Relationships between postoperative PNI value and long-term outcomes

Next, we assessed the clinical impact of PNI value on the introduction of adjuvant chemotherapy. The median postoperative PNI value on the introduction of adjuvant chemotherapy was 50.2 (range 37.1-64.3). The cut-off value was set to 45.6. To investigate whether the recovery of nutritional status in patients with preoperative low PNI value improves long-term outcomes, we divided the patients into four groups: patients with a high-PNI value before radical surgery and remained after surgery (Group High-High), a high-PNI value before surgery but decreased after surgery (Group High-Low), a low-PNI value before surgery but recovered after surgery (Group Low-High), and a low-PNI value but did not recover after surgery (Group Low-Low). Group High-High had 160 patients (70.4%), Group High-Low had 10 patients (4.4%), Group Low-High had 45 patients (19.8%), and Group Low-Low had 12 patients (5.2%). Regarding the long-term outcomes, although the patients in Group Low-Low showed significantly poorer OS and RFS than those in Group High-High

Table 2. Univariate and multivariate analyses for overall survival of patients with low PNI at the introduction of adjuvant chemotherapy using the Cox's proportional hazard model

Variable		n	Univariate[a]		Multivariate[b]	
			P-value	HR[c]	95% CI[d]	*P*-value
Gender	male vs female	31 vs 27	0.62			
Age (75 years old)	75≤ vs <75	15 vs 43	0.10	7.20	1.170-140.7	0.03
T stage (TNM classification)	T4 vs T1, 2, 3	19 vs 39	0.05	3.84	1.181-13.43	0.02
N stage (TNM classification)	N2, 3 vs N0, 1	13 vs 45	0.55			
PNI at the introduction of chemotherapy	<45.6 vs 45.6≤	12 vs 46	<0.01	4.55	1.184-19.65	0.02
Charlson Comorbidity Index	4≤ vs 0-3	21 vs 37	0.13			

Low PNI status at the introduction of adjuvant chemotherapy was an independent prognostic factor (hazard ratio: 4.55). a, Kaplan-Meier method; significance was determined by log-rank test. b, Multivariate survival analysis was performed using Cox's proportional hazard model. c, HR: Hazard ratio. d, CI: Confidence interval.

(P<0.001, P=0.009, respectively), the prognosis of patients in Group Low-High was the same as that of patients in Group High-High (P=0.426, P=0.263, respectively) (**Figure 2**). Multivariate analyses using Cox's proportional hazard model identified that low PNI status at the introduction of adjuvant chemotherapy was an independent prognostic factor (hazard ratio: 4.55) (**Table 2**). The characteristics of patients in Group Low-Low and Group Low-High are shown in **Table 3**. There were no significant differences in patients' background between these two groups. These results suggested that recovery of nutritious status after the introduction of adjuvant chemotherapy would improve long-term outcomes even when the PNI status was low before radical surgery.

Relationships between PNI value at tumor recurrence and long-term outcomes

The median PNI at tumor recurrence was 50.5 (range 29.1-64.5). The cut-off value was set to 46.1 using an ROC curve analysis. Patients with a low-PNI value (PNI<46.1) at tumor recurrence showed a significantly poorer 5-year survival after tumor recurrence than those with a high-PNI value (PNI≥46.1) (*P*<0.01) (**Figure 3**). Similar to the association between PNI status before the introduction of adjuvant chemotherapy and clinicopathological factors, there was no significant association between PNI at tumor recurrence and those factors (**Table 4**).

Discussion

Preoperative PNI value is widely used as a nutritional, immunological, and prognostic index for cancer patients. In general, patients with a low preoperative PNI status were reported to show a poor prognosis, so careful treatment is required for those patients. However, the clinical impact of postoperative PNI status is still unclear. In this study, we found that the postoperative PNI value could be a prognostic factor for patients with colorectal cancer who underwent adjuvant chemotherapy after radical surgery. This was true even when the PNI value was low and the nutritional status was poor during radical surgery. Moreover, we showed that PNI value at tumor recurrence also might be a prognostic marker. These results may support the decision-making process for preventing postoperative poor nutritional status in patients with colorectal cancer.

Concerning the association between postoperative nutritional status and long-term outcomes in colorectal cancer, Shibutani et al. reported that a low postoperative PNI value was associated with poor overall survival in stage II/III colorectal cancer patients who had undergone curative surgery [18]. Ihara et al. reported that a low PNI value before adjuvant chemotherapy tended to induce worse disease-free survival [19]. However, no report has evaluated the clinical impact of the change of PNI value between before and after surgery on the prognosis of patients with adjuvant chemotherapy following radical surgery for colorectal cancer. In this study, we focused on the clinical impact of recovery of PNI value, and the recovery by the introduction of adjuvant chemotherapy could improve the prognosis of the patients with adjuvant chemotherapy even if PNI value was low before surgery. In addition, we also found that PNI value at tumor-recurrence

Table 3. The relationships between PNI at the introduction of adjuvant chemotherapy and clinicopathological factors in colorectal cancer patients

Variables	Group		Univariate[a]
	Low-Low (n=12)	Low-High (n=45)	*P*-value
Gender			
Female	5 (42%)	21 (47%)	1.00
Male	7 (58%)	24 (53%)	
Age			
<75	10 (83%)	32 (71%)	0.48
75≤	2 (17%)	13 (29%)	
BMI			
<18	1 (8%)	3 (7%)	1.00
18≤	11 (92%)	42 (93%)	
Location			
Colon	8 (67%)	30 (67%)	1.00
Rectum	4 (33%)	15 (33%)	
Histopathological type			
differentiated	8 (73%)	35 (78%)	0.70
undifferentiated	3 (27%)	10 (22%)	
Tumor depth			
T1, T2, T3	10 (83%)	28 (67%)	0.30
T4	2 (17%)	17 (33%)	
Lymph node metastasis			
N0, N1	8 (67%)	36 (80%)	0.44
N2, N3	4 (33%)	9 (20%)	
Lymphatic invasion			
Absent	4 (33%)	17 (39%)	1.00
Present	8 (67%)	27 (61%)	
Venous invasion			
Absent	4 (33%)	17 (39%)	1.00
Present	8 (67%)	27 (61%)	
CEA (ng/mL)			
<5	6 (50%)	21 (47%)	1.00
5≤	6 (50%)	24 (53%)	
CA19-9 (U/mL)			
<37	9 (75%)	37 (82%)	0.68
37≤	3 (25%)	8 (18%)	
Surgical Approach			
Laparoscopic	10 (83%)	40 (89%)	0.63
Open	2 (17%)	5 (11%)	
Complication (≥CD grade 2)			
Absent	9 (75%)	39 (87%)	0.38
Present	3 (25%)	6 (13%)	

There were no significant differences in patients' background between Group Low-Low and Group Low-High. a, Univariate analysis was assessed using Chi squared test and Fisher's exact probability test.

was associated with the long-term prognosis after recurrence in CRC patients. The results of our study suggested that perioperative nutritional intervention could improve the postoperative nutritional status resulting in prognostic benefits for patients after adjuvant chemotherapy. Recently, Marian et al. reported the overall positive effect of nutritional interventions during chemo(radio) therapy in the meta-analysis [20]. Prieto et al. also reported that nutrition interventions might improve the outcomes of patients with various cancers [21]. Our data would strongly support these clinical insights.

In this study, patients with a high PNI value at the introduction of adjuvant chemotherapy had better recurrence-free survival than those with a low PNI value. In addition, patients with a high PNI value at recurrence had better long-term outcomes after recurrence than those with a low PNI value. These results suggested that a high level of nutritional status would improve the chemosensitivity and suppress tumor progression. Yoshida et al. reported that low PNI values were significantly correlated with small intratumoral CD8+ cell counts and reflected low tumor immunity in oral squamous cell carcinoma patients [22]. Some kinds of inflammatory cytokines from cancer cells have been reported to activate neutrophil proliferation and activity, suppress lymphocytes, and increase the degradation of proteins including albumin [23]. Given the insights of these reports, there may be a relation between some kinds of immune-onco-

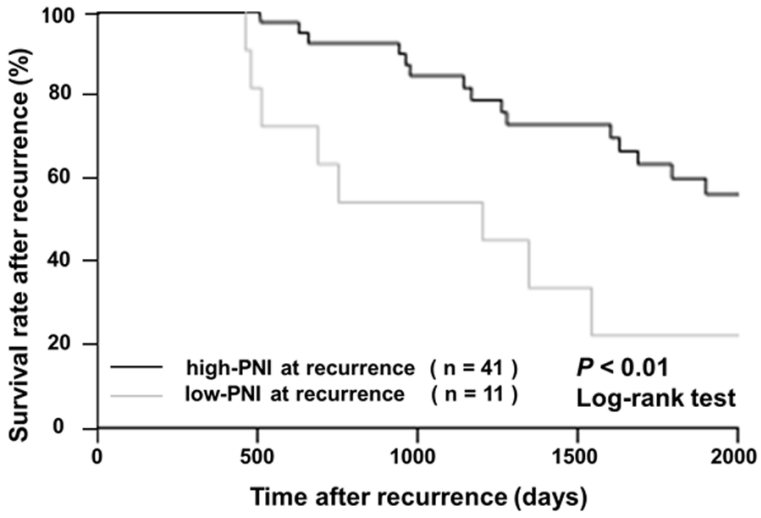

Figure 3. Kaplan-Meier survival analysis comparing patients with low-PNI value (<46.1) at tumor recurrence and patients with high-PNI value (≥46.1) at tumor recurrence. The patients with low-PNI value at tumor recurrence showed significantly poorer overall survival than those with high-PNI value.

Table 4. The relationships between PNI at tumor recurrence and clinicopathological factors in colorectal cancer patients

Variables	PNI at tumor recurrence		Univariate[a]
	low[b] (n=11)	high[b] (n=41)	*P*-value
Gender			
Female	4 (36%)	16 (39%)	1.00
Male	7 (64%)	25 (61%)	
Age			
<75	8 (73%)	34 (83%)	0.42
75≤	3 (27%)	7 (17%)	
BMI			
<25	8 (73%)	27 (66%)	1.00
25≤	3 (27%)	14 (34%)	
Location			
Colon	8 (73%)	20 (49%)	0.19
Rectum	3 (27%)	21 (51%)	
Histopathological type			
differentiated	7 (70%)	37 (90%)	0.12
undifferentiated	3 (30%)	4 (10%)	
Tumor depth			
T1, T2, T3	5 (46%)	25 (61%)	0.49
T4	6 (54%)	16 (39%)	
Lymph node metastasis			
N0, N1	7 (64%)	24 (58%)	1.00
N2, N3	4 (36%)	17 (42%)	
Lymphatic invasion			
Absent	2 (18%)	14 (34%)	0.46
Present	9 (82%)	27 (66%)	
Venous invasion			

logical responses and the nutritional status of colorectal cancer patients after radical surgery. Mismatch repair deficiency (dMMR) and microsatellite instability (MSI) have recently been focused on as clinical biomarkers reflecting immuno-oncological status [24, 25], so it is warranted to clarify the association between these immuno-oncological biomarkers and PNI values.

Our study had some limitations. First, we analysed a limited number of patients from a single institution. Second, we could not evaluate the applied dose of adjuvant chemotherapy because of a lack of data. Moreover, there might have been some biases that influenced PNI status and patients' prognosis because this study was a retrospective analysis. However, this study is the first report that strongly suggests the clinical benefit of a high postoperative PNI status in colorectal cancer patients with adjuvant chemotherapy. Therefore, our study may be a milestone in the field of perioperative management of colorectal cancer patients with high-risk stage II or stage III lesions. A large prospective study is warranted to confirm these results in a clinical setting.

Conclusions

Postoperative PNI value has potential as a prognostic marker of colorectal cancer patients undergoing adjuvant chemotherapy. Although a low PNI value before surgery is a disadvantageous factor for the prognosis, improvement of nutritional status by the

Absent	5 (46%)	10 (24%)	0.26
Present	6 (54%)	31 (76%)	
CEA (ng/mL)			
<5	3 (27%)	21 (51%)	0.19
5≤	8 (73%)	20 (49%)	
CA19-9 (U/mL)			
<37	8 (73%)	32 (78%)	0.70
37≤	3 (27%)	9 (22%)	
Surgical Approach			
Laparoscopic	6 (60%)	29 (85%)	0.17
Open	4 (40%)	5 (15%)	
Complication (≥CD grade 2)			
Absent	9 (82%)	34 (83%)	1.00
Present	2 (18%)	7 (17%)	

There were no significant differences in patients' background between patients with low-PNI at tumor recurrence and with high-PNI. a, Univariate analysis was assessed using Chi squared test. b, low: PNI<46.1, high: PNI≥46.1.

induction of adjuvant chemotherapy would improve the prognosis of the patients. Nutritional intervention may increase the postoperative PNI value resulting in an improvement of prognosis in colorectal cancer patients undergoing adjuvant chemotherapy.

Disclosure of conflict of interest

None.

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Supplementary Table 1. The characteristics of all colorectal cancer patients

age	sex	location	histological type[a]	pathological stage	adjuvant chemotherapy	tumor recurrence	recurrence free survival (days)	outcome	overall survival (days)	PNI		
										preoperative	at introduction of adjuvant chemotherapy	at tumor recurrence
79	M	rectum	differentiated	III	Capecitabine	present	107	alive	1076	53.5	47.0	46.8
66	F	colon	differentiated	III	CapeOX	absent	1206	alive	1206	48.8	51.6	-
35	M	colon	differentiated	III	UFT/LV	absent	1129	alive	1129	57.8	59.2	-
80	F	colon	differentiated	III	UFT/LV	absent	1187	alive	1187	43.5	51.0	-
67	F	rectum	differentiated	III	CapeOX	absent	1361	alive	1361	51	45.8	-
64	F	colon	differentiated	III	CapeOX	absent	1327	alive	1327	48.2	50.2	-
66	M	rectum	differentiated	III	CapeOX	absent	1287	alive	1287	48.6	47.4	-
66	F	rectum	differentiated	III	CapeOX	present	127	death	1136	53.6	50.6	53.3
71	F	colon	differentiated	III	UFT/LV	present	473	alive	1028	30.5	46.9	52.5
71	F	colon	differentiated	III	CapeOX	absent	1070	alive	1070	52.5	49.5	-
73	F	colon	differentiated	III	Capecitabine	absent	836	death	1043	44.9	44.1	-
73	F	colon	differentiated	III	UFT/LV	absent	1083	alive	1083	63.4	64.4	-
68	M	colon	differentiated	III	CapeOX	absent	1112	alive	1112	52.3	52.6	-
79	M	colon	differentiated	III	CapeOX	absent	1088	alive	1088	40.6	51.9	-
69	M	rectum	differentiated	III	CapeOX	absent	1109	alive	1109	56.3	55.5	-
49	M	colon	differentiated	III	CapeOX	present	550	alive	1091	50.9	53.3	51.0
56	M	colon	differentiated	III	UFT/LV	absent	1142	alive	1142	54.5	48.3	-
58	F	rectum	differentiated	III	CapeOX	present	225	alive	1075	49	48.7	53.4
71	M	colon	differentiated	III	CapeOX	absent	1186	alive	1186	50.1	48.3	-
73	M	rectum	others	III	CapeOX	present	148	death	455	40.6	44.9	40.0
63	M	rectum	differentiated	III	CapeOX	absent	1233	alive	1233	55.5	47.5	-
68	M	colon	differentiated	III	UFT/LV	absent	1333	alive	1333	44.5	53.2	-
53	F	colon	differentiated	III	CapeOX	absent	1357	alive	1357	49.8	47.3	-
71	F	rectum	differentiated	III	CapeOX	absent	1352	alive	1352	47.7	45.2	-
63	F	rectum	differentiated	III	CapeOX	absent	1373	alive	1373	52.8	57.4	-
63	F	colon	differentiated	III	CapeOX	absent	1459	alive	1459	54.8	49.8	-
74	M	rectum	differentiated	III	CapeOX	absent	1385	alive	1385	46.8	58.3	-
56	F	rectum	differentiated	II	CapeOX	absent	1105	alive	1105	43.7	37.1	-
72	M	colon	differentiated	II	UFT/LV	absent	1111	alive	1111	61.8	56.4	-
72	F	colon	undifferentiated	II	UFT/LV	absent	1235	alive	1235	44.5	47.5	-
65	M	colon	differentiated	II	UFT/LV	present	251	death	969	46.9	56.4	56.9

67	F	rectum	differentiated	II	UFT/LV	absent	1451	alive	1451	50.9	49.0	-
72	M	rectum	differentiated	II	UFT/LV	present	362	alive	1489	40.7	47.5	49.8
69	F	colon	differentiated	III	CapeOX	absent	1529	alive	1529	55.5	53.1	-
60	M	colon	differentiated	III	UFT/LV	absent	1378	alive	1378	54.9	53.0	-
46	F	rectum	undifferentiated	III	CapeOX	present	505	death	505	37.8	47.2	46.0
66	F	colon	differentiated	III	CapeOX	absent	1509	alive	1509	51.5	48.8	-
74	M	colon	differentiated	III	UFT/LV	absent	1502	alive	1502	53.2	56.3	-
65	F	colon	differentiated	II	UFT/LV	absent	1464	alive	1478	46.1	51.7	-
65	M	colon	differentiated	III	CapeOX	absent	1394	alive	1572	44.5	60.5	-
72	M	rectum	differentiated	III	CapeOX	absent	1511	alive	1511	49.5	45.7	-
68	F	colon	undifferentiated	III	CapeOX	absent	1618	alive	1654	39.8	43.9	-
59	M	rectum	differentiated	III	UFT/LV	absent	1503	alive	1575	42.8	39.8	-
78	F	colon	undifferentiated	III	CapeOX	absent	1616	alive	1616	44.2	45.8	-
63	F	rectum	differentiated	III	CapeOX	absent	558	alive	558	51.3	51.2	-
73	M	rectum	differentiated	II	UFT/LV	absent	573	alive	573	45.7	47.8	-
36	M	colon	undifferentiated	III	CapeOX	absent	544	alive	544	45.8	54.2	-
59	M	rectum	differentiated	II	UFT/LV	present	367	alive	1709	43.9	48.0	47.7
73	M	rectum	differentiated	II	UFT/LV	absent	1550	alive	1550	52	45.3	-
65	M	rectum	differentiated	II	CapeOX	present	545	alive	1674	33.5	51.5	41.7
68	F	colon	differentiated	III	CapeOX	absent	601	alive	601	48.2	47.8	-
68	M	rectum	differentiated	III	CapeOX	absent	612	alive	612	50.4	55.9	-
54	F	colon	differentiated	III	UFT/LV	absent	626	alive	626	46.3	53.4	-
76	M	rectum	differentiated	III	UFT/LV	absent	1639	alive	1799	43.8	51.9	-
67	F	colon	differentiated	III	CapeOX	absent	1556	alive	1556	44.7	50.2	-
42	M	rectum	differentiated	III	CapeOX	absent	745	alive	745	48.8	50.3	-
67	F	rectum	differentiated	III	CapeOX	absent	290	alive	290	50	52.3	-
70	M	colon	undifferentiated	III	CapeOX	absent	694	alive	694	48.8	45.6	-
78	M	colon	differentiated	III	UFT/LV	absent	629	alive	629	56.8	51.6	-
55	M	colon	differentiated	III	CapeOX	absent	654	alive	654	50.5	48.7	-
77	F	colon	differentiated	III	UFT/LV	absent	400	alive	400	45.8	47.7	-
76	F	colon	differentiated	III	CapeOX	absent	683	alive	683	46.3	49.5	-
71	F	rectum	differentiated	III	UFT/LV	absent	740	alive	740	48	49.4	-
73	F	colon	differentiated	III	UFT/LV	absent	752	alive	752	46.2	46.4	-
70	M	rectum	differentiated	III	UFT/LV	absent	1683	alive	1683	40.4	52.2	-
68	F	rectum	undifferentiated	III	CapeOX	present	398	alive	797	53	48.4	54.6

67	M	rectum	differentiated	III	CapeOX	present	574	alive	395	52.8	48.2	50.9
73	M	rectum	differentiated	III	CapeOX	absent	1912	alive	1912	34.8	48.4	-
78	M	colon	differentiated	III	CapeOX	absent	1898	alive	1898	43.3	47.9	-
70	F	colon	undifferentiated	II	UFT/LV	absent	1743	alive	1787	38.8	53.8	-
45	M	colon	differentiated	III	CapeOX	absent	804	alive	804	52.4	51.2	-
74	M	rectum	differentiated	III	UFT/LV	absent	2036	alive	2036	44.6	45.6	-
56	M	rectum	differentiated	III	CapeOX	absent	563	alive	563	56.7	59.1	-
63	F	colon	differentiated	III	CapeOX	absent	881	alive	881	48.7	56.0	-
61	F	rectum	differentiated	III	CapeOX	absent	1991	alive	1991	37.4	47.4	-
60	M	rectum	differentiated	III	CapeOX	present	109	death	658	56.1	49.3	51.7
62	M	colon	differentiated	III	CapeOX	absent	930	alive	930	52.2	55.0	-
79	F	colon	undifferentiated	II	UFT/LV	absent	1963	alive	1963	44.7	46.8	-
49	M	colon	differentiated	III	CapeOX	absent	2036	alive	2036	45	51.9	-
59	M	rectum	differentiated	III	CapeOX	absent	999	alive	999	55.9	52.8	-
73	M	rectum	differentiated	III	UFT/LV	absent	991	alive	991	55	57.3	-
58	F	colon	differentiated	III	CapeOX	absent	951	alive	951	53.9	53.7	-
56	F	rectum	differentiated	III	CapeOX	absent	960	alive	960	50.8	51.1	-
75	F	colon	differentiated	III	UFT/LV	absent	1109	alive	1109	50.9	54.8	-
64	M	rectum	differentiated	III	UFT/LV	absent	1133	alive	1133	46.6	47.7	-
73	F	rectum	differentiated	III	CapeOX	absent	988	alive	988	50.6	47.3	-
80	F	colon	undifferentiated	II	UFT/LV	absent	2032	alive	2032	42.5	47.5	-
57	M	colon	differentiated	III	CapeOX	absent	1102	alive	1102	54.4	56.9	-
77	F	colon	differentiated	III	CapeOX	present	186	alive	1212	44.3	47.9	46.0
73	M	colon	differentiated	III	CapeOX	absent	1121	alive	1121	49.5	50.8	-
65	M	colon	differentiated	III	CapeOX	absent	1177	alive	1177	48.3	57.8	-
62	M	colon	differentiated	III	CapeOX	absent	1844	alive	2249	45.4	49.9	-
58	M	colon	differentiated	II	UFT/LV	absent	616	alive	616	48.5	50.0	-
51	F	rectum	differentiated	II	UFT/LV	absent	1275	alive	1275	52.7	60.9	-
64	F	colon	differentiated	II	UFT/LV	absent	1298	alive	1298	45.6	47.9	-
70	F	colon	differentiated	III	CapeOX	present	734	alive	1338	47.4	48.4	50.4
79	M	rectum	differentiated	III	UFT/LV	absent	1236	alive	1236	46.4	51.1	-
71	M	rectum	differentiated	III	CapeOX	present	175	alive	499	49.6	46.2	48.8
79	M	colon	differentiated	III	UFT/LV	present	522	alive	935	51.7	51.2	53.6
42	M	rectum	differentiated	II	CapeOX	absent	1273	alive	1273	59.5	55.4	-
61	M	colon	differentiated	III	CapeOX	absent	1361	alive	1361	52.2	52.2	-

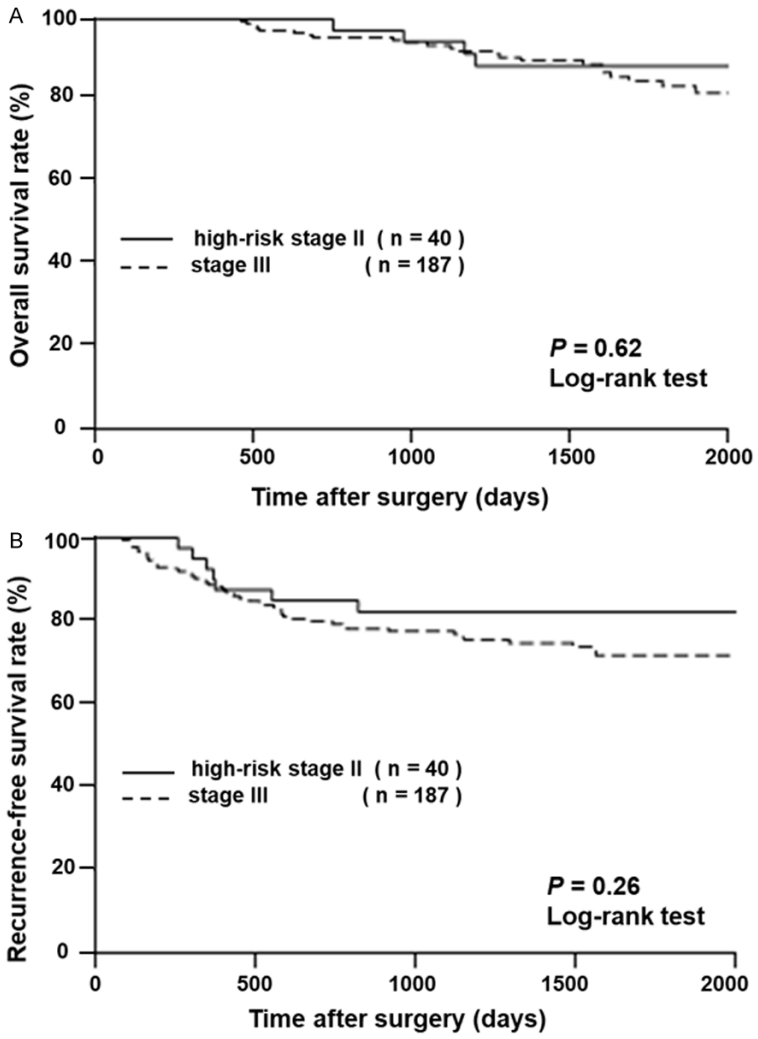
70	M	colon	differentiated	II	UFT/LV	absent	1286	alive	1286	48.1	48.2	-
68	M	rectum	differentiated	III	UFT/LV	absent	1380	alive	1380	51.3	52.9	-
61	M	colon	differentiated	III	UFT/LV	absent	1030	alive	1030	50.3	54.5	-
61	F	rectum	differentiated	III	UFT/LV	absent	2515	alive	2515	51.7	44.2	-
79	M	colon	differentiated	III	UFT/LV	absent	1399	alive	1399	49.9	49.0	-
81	F	colon	undifferentiated	III	UFT/LV	absent	2511	alive	2518	64.5	41.0	-
78	F	colon	differentiated	III	UFT/LV	absent	1797	alive	1797	40.6	47.7	-
59	F	rectum	differentiated	III	mFOLFOX6	absent	1454	alive	1454	51.5	57.7	-
62	M	rectum	differentiated	III	CapeOX	present	404	alive	1128	55.1	56.0	52.3
46	M	colon	differentiated	II	UFT/LV	absent	1410	alive	1410	48	46.3	-
53	M	rectum	differentiated	III	CapeOX	absent	2204	alive	2204	49.6	43.8	-
73	M	rectum	differentiated	III	CapeOX	absent	1473	alive	1473	56.8	53.7	-
66	M	colon	differentiated	III	CapeOX	absent	2509	alive	2509	44.4	46.4	-
77	M	colon	differentiated	III	UFT/LV	absent	1464	alive	1464	47.2	51.0	-
80	M	colon	differentiated	III	UFT/LV	present	444	alive	2208	36	40.3	46.2
82	M	colon	differentiated	III	TS-1	absent	1586	alive	2688	36.6	49.2	-
37	M	rectum	differentiated	III	CapeOX	absent	1554	alive	1554	49.2	51.8	-
78	F	rectum	differentiated	III	UFT/LV	absent	1863	alive	2068	45.3	49.7	-
56	M	rectum	differentiated	III	UFT/LV	absent	1859	alive	1859	44.3	48.8	-
80	M	colon	differentiated	II	UFT/LV	absent	2050	alive	2606	35.7	40.7	-
59	M	rectum	undifferentiated	II	UFT/LV	absent	1858	alive	1858	42.6	53.6	-
67	M	colon	differentiated	III	CapeOX	present	314	death	511	38.1	46.2	
49	F	rectum	undifferentiated	III	CapeOX	absent	1527	alive	1527	56.1	51.8	-
71	M	rectum	differentiated	III	TS-1	absent	1497	alive	1497	45.6	47.8	-
50	F	colon	differentiated	III	CapeOX	absent	1701	alive	1701	50.3	49.1	-
58	F	colon	differentiated	II	UFT/LV	absent	2177	alive	2685	43.3	51.4	-
68	M	rectum	differentiated	III	CapeOX	present	1114	alive	2803	48.7	45.4	53.9
68	F	colon	differentiated	III	CapeOX	absent	1980	alive	1980	35.6	49.6	-
33	F	colon	differentiated	III	UFT/LV	absent	1645	alive	1645	50.1	51.0	-
69	F	colon	differentiated	III	CapeOX	absent	1327	alive	1327	48.5	48.8	-
80	M	colon	differentiated	III	Capecitabine	absent	1645	alive	1645	60.5	57.4	-
39	M	colon	differentiated	III	mFOLFOX6	absent	1648	alive	1648	56.2	55.8	-
57	F	rectum	differentiated	III	mFOLFOX6	present	910	alive	1864	44.6	46.3	51.4
64	F	colon	differentiated	III	UFT/LV	absent	1765	alive	1765	47.7	56.0	-
76	M	colon	differentiated	III	UFT/LV	absent	1681	alive	1681	58.6	59.7	-

63	M	colon	differentiated	II	UFT/LV	absent	2782	alive	2782	39.4	51.6	-
81	F	colon	differentiated	III	UFT/LV	present	1146	alive	1760	47	50.1	49.0
66	M	colon	differentiated	III	mFOLFOX6	absent	2810	alive	2810	28	45.7	-
72	F	rectum	differentiated	III	TS-1	absent	1611	alive	1611	51.3	49.0	-
60	M	rectum	differentiated	III	CapeOX	absent	1733	alive	1733	53.1	54.2	-
70	F	colon	differentiated	II	TS-1	absent	1863	alive	1863	50.1	47.6	-
63	M	colon	differentiated	III	UFT/LV	absent	1869	alive	1869	46	54.7	-
63	F	rectum	differentiated	III	mFOLFOX6	absent	2253	alive	2253	49.5	44.2	-
24	F	rectum	differentiated	II	UFT/LV	absent	1952	alive	1952	48.3	51.0	-
65	F	colon	differentiated	III	UFT/LV	absent	1880	alive	1880	45.8	48.6	-
73	M	colon	undifferentiated	III	UFT/LV	present	294	death	1536	37.8	43.4	34.9
55	F	rectum	differentiated	III	mFOLFOX6	present	779	alive	1489	46.7	48.0	
75	M	colon	undifferentiated	II	UFT/LV	absent	1919	alive	1919	46.9	51.4	-
76	M	colon	differentiated	III	UFT/LV	present	302	alive	3055	42.7	54.7	49.0
66	M	colon	differentiated	III	UFT/LV	absent	1600	death	1600	48.4	48.5	-
71	M	colon	undifferentiated	III	mFOLFOX6	absent	1963	alive	1963	57.2	54.8	-
74	M	colon	differentiated	III	mFOLFOX6	absent	3119	alive	3119	47.1	45.6	-
55	M	rectum	undifferentiated	II	UFT/LV	absent	1557	alive	1557	55.1	53.8	-
53	F	rectum	differentiated	III	UFT/LV	absent	1868	alive	1868	44.9	52.4	-
55	F	colon	undifferentiated	III	Capecitabine	absent	1763	alive	1763	43.8	48.2	-
70	F	rectum	differentiated	III	UFT/LV	absent	2029	alive	2029	56.3	51.7	-
71	M	rectum	differentiated	III	mFOLFOX6	present	1557	alive	2096	52.4	47.9	63.6
37	F	colon	undifferentiated	II	mFOLFOX6	absent	1838	alive	1838	52.3	53.4	-
64	M	colon	undifferentiated	II	UFT/LV	present	297	death	1161	45.4	53.3	58.5
56	F	rectum	differentiated	III	UFT/LV	absent	1838	alive	1838	49.6	47.6	-
83	F	rectum	differentiated	III	UFT/LV	present	580	death	1271	45.6	47.0	46.1
55	M	colon	differentiated	III	mFOLFOX6	absent	2194	alive	2194	55.6	52.5	-
60	F	rectum	differentiated	III	UFT/LV	absent	1773	alive	1773	49.6	50.3	-
54	M	colon	differentiated	II	UFT/LV	absent	2202	alive	2202	50.2	59.1	-
62	M	colon	undifferentiated	III	UFT/LV	absent	1800	alive	1800	51.4	47.5	-
55	M	colon	undifferentiated	III	mFOLFOX6	present	159	death	503	44.3	55.4	50.7
62	F	colon	undifferentiated	II	mFOLFOX6	present	340	death	746	38.7	44.0	45.7
66	M	colon	differentiated	III	UFT/LV	present	655	death	682	51.5	53.4	32.6
57	F	colon	differentiated	III	UFT/LV	absent	1912	alive	1912	49.5	50.9	-
46	M	rectum	differentiated	III	mFOLFOX6	absent	1856	alive	1856	62.7	51.8	-

66	M	rectum	differentiated	III	UFT/LV	present	575	death	1623	56.5	54.9	63.2
80	M	colon	differentiated	III	UFT/LV	present	1485	alive	1891	48.7	49.3	45.2
67	M	colon	differentiated	III	UFT/LV	absent	1954	alive	1954	54.5	54.9	-
37	M	colon	differentiated	II	Capecitabine	absent	1880	alive	1880	55.1	58.7	-
65	M	colon	differentiated	III	Capecitabine	absent	1849	alive	1849	53.4	51.2	-
50	M	colon	differentiated	III	UFT/LV	absent	1834	alive	1834	52.8	52.0	-
72	M	colon	differentiated	III	Capecitabine	absent	1826	alive	1826	47	43.7	-
50	F	colon	differentiated	III	UFT/LV	absent	2927	alive	3590	43.6	47.4	-
58	F	colon	differentiated	II	UFT	absent	1112	alive	1112	52.3	50.2	-
68	F	rectum	differentiated	III	UFT/LV	present	598	alive	1841	50.5	47.2	49.2
80	M	colon	differentiated	II	UFT	present	814	death	1196	36.3	56.3	43.6
58	M	colon	differentiated	III	UFT/LV	absent	1837	alive	1837	55	55.7	-
57	M	colon	differentiated	III	Capecitabine	absent	1831	alive	1831	50.8	46.1	-
62	M	rectum	differentiated	III	UFT/LV	absent	2136	alive	2136	53.3	51.1	-
66	M	rectum	differentiated	III	mFOLFOX6	present	381	death	1893	51.4	48.9	50.1
75	M	colon	differentiated	III	mFOLFOX6	present	285	death	935	52	49.3	49.1
72	M	colon	differentiated	III	UFT/LV	absent	1852	alive	1852	50.1	47.3	-
62	F	rectum	differentiated	III	UFT/LV	absent	2113	alive	2113	50.6	54.7	-
57	F	rectum	differentiated	III	UFT/LV	absent	2138	alive	2138	56.6	54.1	-
50	M	rectum	differentiated	III	UFT/LV	absent	1902	alive	1902	58.5	56.4	-
70	M	colon	differentiated	III	UFT/LV	present	253	death	1117	45.2	39.5	
60	M	colon	differentiated	III	UFT/LV	present	1551	alive	2388	46.2	46.7	47.4
70	F	colon	differentiated	III	UFT/LV	absent	1841	alive	1841	56.4	50.0	-
39	F	colon	differentiated	III	UFT/LV	present	425	death	1596	47.5	51.9	50.7
74	M	colon	differentiated	III	Capecitabine	present	1287	death	1340	43	49.0	29.2
65	F	colon	differentiated	II	UFT	absent	2006	alive	2006	49.5	49.4	-
59	F	colon	differentiated	III	UFT/LV	absent	2312	alive	2312	49.6	52.0	-
59	M	colon	differentiated	III	UFT/LV	present	106	alive	2486	50.9	55.2	57.9
21	M	colon	differentiated	III	Capecitabine	absent	1895	alive	1895	52	52.0	-
72	M	colon	undifferentiated	III	Capecitabine	absent	2101	alive	2101	50.2	48.8	-
58	F	rectum	differentiated	III	UFT/LV	absent	1879	alive	1879	54.4		-
73	M	colon	differentiated	III	Capecitabine	absent	2059	alive	2059	50.1	48.2	-
68	F	colon	differentiated	III	UFT/LV	absent	1953	alive	1953	48	51.4	-
44	F	rectum	differentiated	III	UFT/LV	present	172	death	1787	57.5	52.7	55.2
42	F	rectum	differentiated	III	UFT/LV	absent	2040	alive	2040	49.4	52.0	-

62	M	rectum	differentiated	III	TS-1	absent	2488	alive	2488	52.4	50.6	-
52	M	colon	differentiated	III	Capecitabine	absent	1856	alive	1856	63.3	63.3	-
68	F	rectum	differentiated	II	UFT	absent	2097	alive	2533	43.5	52.6	-
74	F	colon	undifferentiated	II	UFT	absent	2550	alive	2550	45.8	51.1	-
56	M	colon	differentiated	III	UFT/LV	present	1142	alive	2521	52.9	53.0	56.9
62	M	colon	differentiated	III	UFT/LV	present	764	death	1681	53.8	54.0	59.9
78	F	colon	differentiated	III	UFT/LV	absent	2034	alive	2034	49.6	60.6	-
67	F	colon	differentiated	III	UFT/LV	absent	2611	alive	2611	55.6	54.1	-
74	F	rectum	differentiated	III	UFT/LV	present	391	death	622	33.4	47.6	47.3
61	F	rectum	differentiated	III	UFT/LV	present	155	death	955	47.1	50.2	54.0
36	M	colon	undifferentiated	III	UFT/LV	present	126	alive	25144	58.8	47.3	64.6
74	F	colon	differentiated	III	UFT/LV	present	338	death	472	41.1	37.2	36.9
39	M	colon	differentiated	III	UFT/LV	present	347	alive	2720	56.3	54.0	55.2
53	F	colon	differentiated	III	UFT/LV	present	78	death	1255	52.1	61.6	59.4
79	F	colon	differentiated	II	UFT	absent	2631	alive	2631	49.4	47.0	-
65	F	colon	differentiated	III	UFT/LV	absent	2700	alive	2700	49.9	47.6	-
75	F	colon	differentiated	III	UFT/LV	absent	2781	alive	2781	58.9	51.0	-
53	F	rectum	differentiated	III	UFT/LV	present	575	death	2160	51.3	55.9	63.6
32	F	colon	differentiated	III	UFT/LV	present	155	alive	2834	54.8	48.5	49.3
73	F	rectum	differentiated	III	UFT/LV	absent	2549	alive	2549	50.9	49.5	-
67	F	colon	differentiated	II	UFT/LV	absent	2259	alive	2259	48	49.0	-

[a]Differentiated: well-differentiated type, moderate-differentiated type and papillary adenocarcinoma; undifferentiated: poorly-differentiated type, mucinous adenocarcinoma and signet-ring cell carcinoma.



Supplementary Figure 1. Kaplan-Meier survival analysis comparing patients with high-risk stage II and patients with stage III colorectal cancer. The patients with high-risk stage II showed equivalent prognosis to those with stage III.