

Table 1. Patient characteristics and correlation with preoperative obstruction

Variables	No. of Patients	%	stage II and III (n=641)				Preoperative obstruction colon cancer (n=384)				rectal cancer (n=257)			
			positive	negative	positive rate (%)	P*	positive	negative	positive rate (%)	P*	positive	negative	positive rate (%)	P*
Gender														
Male	380	59.3	39	341	10.3	0.688	30	193	13.5	0.261	9	148	5.7	0.327
Female	261	40.7	24	237	9.2		15	146	9.3		9	91	9.0	
Age (years)														
<60	274	42.7	29	245	10.6	0.594	18	137	11.6	>0.999	11	108	9.2	0.225
≥60	367	57.3	34	333	9.3		27	202	11.8		7	131	5.1	
Tumor location														
right	169	26.4	24	145	14.2	0.051	24	145	14.2	0.203	-	-	-	-
left	215	33.5	21	194	9.8		21	194	9.8		-	-	-	-
rectum	257	40.1	18	239	7.0		-	-	-		-	-	-	-
Differentiation														
non-poor	583	91.0	51	532	8.7	0.009	38	314	10.8	0.080	13	218	5.6	0.025
poor†	58	9.0	12	46	20.7		7	25	21.9		5	21	19.2	
T factor‡														
T1	14	2.2	0	14	0.0	0.007	0	6	0.0	0.265	0	8	0.0	0.007
T2	40	6.2	0	40	0.0		0	16	0.0		0	24	0.0	
T3	563	87.8	57	506	10.1		42	305	12.1		15	201	6.9	
T4	24	3.7	6	18	25.0		3	12	20		3	6	50.0	
N factor‡														
N0	207	32.3	16	191	7.7	0.454	13	118	9.9	0.517	3	73	3.9	0.089
N1	311	48.5	33	278	10.6		26	165	13.6		7	113	5.8	
N2	123	19.2	14	109	11.4		6	56	9.6		8	53	13.1	
ND (%)														
≥20	138	21.5	16	122	11.6	0.423	8	74	9.8	0.699	8	48	14.3	0.032
<20	503	78.5	47	456	9.3		37	265	12.3		10	191	5.0	
Intramural lymphatic invasion														
negative	21	3.3	1	20	4.8	0.711	1	12	7.7	>0.999	0	9	0.0	>0.999
positive	620	96.7	62	558	10.0		44	327	11.9		18	230	7.3	
Intramural vascular invasion														
negative	62	9.7	7	55	11.3	0.654	7	34	17.1	0.300	0	21	0.0	0.376
positive	579	90.3	56	523	9.7		38	305	11.1		18	218	7.6	
Preoperative CEA														
normal (<2.5ng/ml)	418	65.2	29	389	6.9	0.001	18	239	7.0	<0.001	11	150	6.8	>0.999
elevated (≥2.5ng/ml)	223	34.8	34	189	15.2		27	100	21.3		7	89	7.3	
Preoperative CA19-9														
normal (<37ng/ml)	574	89.5	52	522	9.1	0.079	37	306	10.8	0.120	15	216	6.5	0.406
elevated (≥37ng/ml)	67	10.5	11	56	16.4		8	33	19.5		3	23	11.5	
Laparoscopic operation														
Yes	83	12.9	5	78	6.0	0.321	2	64	3.0	0.041	3	14	17.6	0.105
No	558	87.1	58	500	11.6		36	282	11.3		15	225	6.3	
Number of total dissected lymph nodes														
<6	28	4.4	2	26	7.1	0.175	2	15	11.8	0.205	0	11	0.0	0.337
6-10	84	13.1	4	80	4.8		4	53	7.0		0	27	0.0	
11-15	129	20.1	10	119	7.8		6	77	7.2		4	42	8.7	
>15	400	62.4	47	353	11.8		33	194	14.5		14	159	8.1	
Anastomotic leakage														
present	28	4.4	1	27	3.6	0.510	1	6	14.3	0.585	0	21	0.0	0.376
absent	613	95.6	62	551	10.1		44	333	11.7		18	218	7.6	
Adjuvant chemotherapy														
Yes	527	82.2	50	477	9.5	0.493	7	34	17.1	0.300	13	191	6.4	0.544
No	114	17.8	13	101	11.4		38	305	11.1		5	48	9.4	
Perioperative transfusion														
Yes	122	19.0	16	106	13.1	0.178	10	33	23.3	0.021	6	73	7.6	0.795
No	519	81.0	47	472	9.1		35	206	10.3		12	166	6.7	

Abbreviations: ND, node density (metastatic lymph node ratio).

*compared by Pearson's chi-square test or Fisher's exact test. †poor includes poorly differentiated, mucinous, and undifferentiated types. ‡T and N factors mean pathological T and N factor.

Table 2. Prognostic analysis on 5-year DFS* in patients with stage III colon cancer (n=253)

Variables	univariable analysis		multivariable analysis			
			model 1		model 2	
	HR (95% CI)	P**	HR (95% CI)	P**	HR (95% CI)	P**
Preoperative obstruction (present)	2.18 (1.26-3.77)	0.005	1.98 (1.09-3.58)	0.024	1.83 (1.02-3.25)	0.041
Gender (Female)	0.89 (0.58-1.38)	0.606	0.85 (0.53-1.36)	0.495	n/d	n/d
Age (≥60)	0.73 (0.47-1.13)	0.160	0.76 (0.48-1.20)	0.236	n/d	n/d
Tumor location (left-side)	0.58 (0.37-0.89)	0.014	0.49 (0.29-0.83)	0.008		
Differentiation (poor†)	1.38 (0.67-2.87)	0.386	1.15 (0.53-2.46)	0.726	n/d	n/d
T factor‡						
T1	reference		reference		n/d	n/d
T2	n/d	n/d	n/d	n/d	n/d	n/d
T3	n/d	n/d	n/d	n/d	n/d	n/d
T4	n/d	n/d	n/d	n/d	n/d	n/d
N factor‡ (N2)	2.49 (1.59-3.90)	<0.001	2.76 (1.54-4.93)	0.001	n/d	n/d
ND (≥20)	1.25 (0.79-1.96)	0.343	0.89 (0.46-1.73)	0.729	n/d	n/d
Intramural lymphatic invasion (positive)	20.86 (0.04-11498.43)	0.346	n/d	n/d	n/d	n/d
Intramural vascular invasion (positive)	1.53 (0.71-3.33)	0.281	1.45 (0.63-3.36)	0.385	n/d	n/d
Preoperative CEA (elevated)	1.77 (1.14-2.75)	0.01	1.92 (1.16-3.16)	0.011	n/d	n/d
Preoperative CA19-9 (elevated)	1.32 (0.66-2.64)	0.433	0.78 (0.36-1.68)	0.518	n/d	n/d
Laparoscopic operation (Yes)	0.92 (0.55-1.56)	0.758	1.00 (0.55-1.79)	0.987	n/d	n/d
Number of total dissected lymph nodes						
<6	reference		reference		n/d	n/d
6-10	0.54 (0.18-1.61)	0.266	0.33 (0.10-1.09)	0.069	n/d	n/d
11-15	0.63 (0.23-1.73)	0.372	0.38 (0.12-1.16)	0.088	n/d	n/d
>15	0.90 (0.36-2.26)	0.823	0.35 (0.11-1.14)	0.081	n/d	n/d
Anastomotic leakage (present)	1.79 (0.25-12.88)	0.562	2.34 (0.28-19.32)	0.431	n/d	n/d
Adjuvant chemotherapy (Yes)	2.35 (1.08-5.09)	0.031	2.32 (1.05-5.11)	0.037	n/d	n/d
Perioperative transfusion (Yes)	0.88 (0.43-1.84)	0.741	0.60 (0.27-1.33)	0.206	n/d	n/d
Propensity score	n/d	n/d	n/d	n/d	5.53 (1.07-28.65)	0.042

Abbreviations: DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; ND, node density (metastatic lymph node ratio).

*End-point: date of death or March 31, 2007, if survived. **Cox's proportional hazard model.

†poor includes poorly differentiated, mucinous, and undifferentiated types. ‡T and N factor mean pathological factors.

There was no event in T1, T2, and intramural lymphatic invasion negative cases, so that these variables were excluded from multivariable analysis.

Multivariable Model 2 indicates the adjusted effect of preoperative obstruction by applying propensity score which is a conditional probability of presenting preoperative obstruction given by other clinicopathologic factors.

Table 3. Prognostic analysis on 5-year DFS* in patients with stage III rectal cancer (n=181)

Variables	univariable analysis		multivariable analysis			
	HR (95% CI)	P**	model 1		model 2	
	HR (95% CI)	P**	HR (95% CI)	P**	HR (95% CI)	P**
Preoperative obstruction (present)	2.78 (1.46-5.28)	0.002	2.34 (1.06-5.17)	0.035	2.17 (0.98-4.79)	0.056
Gender (Female)	0.92 (0.58-1.45)	0.716	1.21 (0.72-2.01)	0.471	n/d	n/d
Age (≥60)	1.21 (0.77-1.90)	0.418	1.62 (0.98-2.69)	0.059	n/d	n/d
Differentiation (poor†)	2.00 (1.13-3.51)	0.017	1.85 (0.95-3.57)	0.070	n/d	n/d
T factor‡						
T1	reference		reference		n/d	n/d
T2	2.53 (0.31-20.54)	0.386	2.73 (0.31-24.28)	0.367	n/d	n/d
T3	4.35 (0.60-31.37)	0.145	3.77 (0.44-32.61)	0.229	n/d	n/d
T4	12.36 (1.52-100.75)	0.019	7.35 (0.67-81.01)	0.104	n/d	n/d
N factor‡ (N2)	2.42 (1.54-3.80)	<0.001	1.55 (0.78-3.08)	0.209		
ND (≥20)	1.96 (1.24-3.11)	0.004	1.57 (0.77-3.18)	0.214	n/d	n/d
Intramural lymphatic invasion (positive)	20.32	0.617	n/d	n/d	n/d	n/d
Intramural vascular invasion (positive)	1.61 (0.59-4.41)	0.353	0.74 (0.22-2.48)	0.629	n/d	n/d
Preoperative CEA (elevated)	1.58 (1.01-2.49)	0.046	1.31 (0.78-2.18)	0.309	n/d	n/d
Preoperative CA19-9 (elevated)	2.42 (1.30-4.51)	0.005	2.24 (1.12-4.45)	0.022	n/d	n/d
Laparoscopic operation (Yes)	0.70 (0.28-1.73)	0.434	0.86 (0.29-2.55)	0.781	n/d	n/d
Number of total dissected lymph nodes						
<6	reference		reference		n/d	n/d
6-10	0.93 (0.26-3.29)	0.908	1.40 (0.34-5.73)	0.643	n/d	n/d
11-15	1.23 (0.41-3.75)	0.711	1.15 (0.34-3.92)	0.822	n/d	n/d
>15	1.25 (0.45-3.47)	0.664	1.12 (0.32-3.99)	0.860	n/d	n/d
Anastomotic leakage (present)	0.79 (0.32-1.95)	0.601	1.08 (0.40-2.86)	0.884	n/d	n/d
Adjuvant chemotherapy (Yes)	1.07 (0.61-1.88)	0.815	1.20 (0.62-2.33)	0.594	n/d	n/d
Perioperative transfusion (Yes)	1.20 (0.74-1.96)	0.458	1.03 (0.57-1.85)	0.932	n/d	n/d
Propensity score	n/d	n/d	n/d	n/d	2.38 (0.55-10.23)	0.246

Abbreviations: DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; ND, node density (metastatic lymph node ratio); n/d, not determined.

*End-point: date of death or March 31, 2007, if survived. **Cox's proportional hazard model.

†poor includes poorly differentiated, mucinous, and undifferentiated types. ‡T and N factor mean pathological factors.

There was no event in intramural lymphatic invasion negative cases, so that this variable was excluded from multivariable analysis.

Multivariable Model 2 indicates the adjusted effect of preoperative obstruction by applying propensity score which is a conditional probability of presenting preoperative obstruction given by other clinicopathologic factors.

Supplemental Table 1. Prognostic analysis on 5-year DFS* in stage II and III CRC patients (n=641)

Variables	univariable analysis		multivariable analysis			
	HR (95% CI)	P**	model 1		model 2	
	HR (95% CI)	P**	HR (95% CI)	P**	HR (95% CI)	P**
Preoperative obstruction (present)	2.21 (1.50-3.27)	<0.001	2.05 (1.35-3.11)	0.001	1.92 (1.28-2.89)	0.002
Gender (Female)	0.97 (0.73-1.31)	0.858	1.05 (0.77-1.42)	0.763	n/d	n/d
Age (≥60)	0.98 (0.73-1.31)	0.885	1.16 (0.85-1.58)	0.347	n/d	n/d
Tumor location						
right-side colon	reference		reference		n/d	n/d
left-side colon	0.65 (0.44-0.96)	0.031	0.57 (0.38-0.84)	0.004	n/d	n/d
rectum	1.12 (0.80-1.58)	0.511	0.91 (0.62-1.32)	0.607	n/d	n/d
Differentiation (poor†)	1.77 (1.15-2.72)	0.009	1.23 (0.78-1.95)	0.367	n/d	n/d
T factor‡						
T1	reference		reference		n/d	n/d
T2	2.60 (0.32-21.09)	0.372	1.87 (0.23-15.46)	0.563	n/d	n/d
T3	4.66 (0.65-33.28)	0.125	4.01 (0.54-29.82)	0.175	n/d	n/d
T4	8.98 (1.17-69.04)	0.035	7.11 (0.86-58.65)	0.068	n/d	n/d
N factor‡						
N0	0.16 (0.10-0.25)	<0.001	0.16 (0.09-0.27)	<0.001	n/d	n/d
N1	0.39 (0.29-0.54)	<0.001	0.42 (0.28-0.64)	<0.001	n/d	n/d
N2	reference		reference		n/d	n/d
ND (≥20)	2.18 (1.60-2.97)	<0.001	1.02 (0.66-1.56)	0.946	n/d	n/d
Intramural lymphatic invasion (positive)	21.42 (0.84-546.66)	0.064	n/d	n/d	n/d	n/d
Intramural vascular invasion (positive)	1.83 (1.00-3.37)	0.051	1.49 (0.78-2.83)	0.225	n/d	n/d
Preoperative CEA (elevated)	1.61 (1.20-2.15)	0.001	1.37 (1.00-1.87)	0.051	n/d	n/d
Preoperative CA19-9 (elevated)	1.38 (0.89-2.13)	0.153	1.30 (0.81-2.08)	0.281	n/d	n/d
Laparoscopic operation (Yes)	1.02 (0.66-1.56)	0.932	1.11 (0.69-1.79)	0.672	n/d	n/d
Number of total dissected lymph nodes						
<6	reference		reference		n/d	n/d
6-10	0.61 (0.29-1.32)	0.210	0.49 (0.22-1.01)	0.086	n/d	n/d
11-15	0.78 (0.39-1.57)	0.483	0.55 (0.26-1.19)	0.128	n/d	n/d
>15	0.84 (0.44-1.60)	0.589	0.46 (0.21-1.01)	0.053	n/d	n/d
Anastomotic leakage (present)	1.43 (0.78-2.64)	0.248	1.77 (0.93-3.38)	0.083	n/d	n/d
Adjuvant chemotherapy (Yes)	1.26 (0.83-1.91)	0.280	1.44 (0.93-2.23)	0.100	n/d	n/d
Perioperative transfusion (Yes)	1.13 (0.79-1.62)	0.501	0.89 (0.60-1.32)	0.563	n/d	n/d
Propensity score	n/d	n/d	n/d	n/d	6.60 (1.47-29.77)	0.014

Abbreviations: DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; ND, node density (metastatic lymph node ratio); n/d, not determined.

*End-point: date of death or March 31, 2007, if survived. **Cox's proportional hazard model.

†poor includes poorly differentiated, mucinous, and undifferentiated types. ‡T and N factor mean pathological factors.

There was no event in intramural lymphatic invasion negative cases, so that this variable was excluded from multivariable analysis.

Multivariable Model 2 indicates the adjusted effect of preoperative obstruction by applying propensity score which is a conditional probability of presenting preoperative obstruction given by other clinicopathologic factors.

Supplemental Table 2. Characteristics and 5-year DFS* of stage II patients (n=207)

Variables	No. of Patients	%	Average Survival (rate, %)	P**
Gender				
Male	127	61	84.3	0.146
Female	80	39	91.3	
Age, years				
<60	94	45	88.3	0.558
≥60	113	55	85.8	
Tumor location				
right-side colon	56	27	87.5	0.993
left-side colon	75	36	86.7	
rectum	76	37	86.8	
Differentiation				
non-poor	194	94	86.6	0.568
poor†	13	6	92.3	
T factor				
T3	199	96	86.9	0.985
T4	8	4	87.5	
Intramural lymphatic invasion				
negative	16	8	100.0	0.119
positive	191	92	85.9	
Intramural vascular invasion				
negative	19	9	100.0	0.086
positive	188	91	85.6	
Preoperative CEA				
normal (≤2.5ng/ml)	138	67	87.7	0.635
elevated (>2.5ng/ml)	69	33	85.5	
Preoperative CA19-9				
normal (≤37ng/ml)	183	88	86.3	0.464
elevated (>37ng/ml)	24	12	91.7	
Preoperative obstruction				
Yes	16	8	81.3	0.478
No	191	92	87.4	
Laparoscopic operation				
Yes	8	4	87.5	0.965
No	199	96	86.9	
Number of total dissected lymph nodes				
<6	5	2	80.0	0.918
6-10	27	13	85.2	
11-15	34	17	85.3	
>15	141	68	87.9	
Anastomotic leakage				
Yes	12	6	58.3	0.001
No	195	94	88.7	
Adjuvant chemotherapy				
Yes	180	87	86.1	0.838
No	27	13	92.6	
Perioperative transfusion				
Yes	45	22	84.4	0.574
No	162	78	87.7	

Abbreviations: DFS, disease-free survival.

*End-point: date of death or April 30, 2007, no patient was lost to follow up.

**Log-rank test.

†poor consists of poorly differentiated, mucinous, and undifferentiated types.

Supplemental Table 3. 5-year DFS* of stage III CRC patients (n=434)

Variables	univariable analysis		multivariable analysis			
	HR (95% CI)	P**	model 1		model 2	
			HR (95% CI)	P**	HR (95% CI)	P**
Preoperative obstruction (present)	2.25 (1.49-3.41)	<0.001	1.98 (1.26-3.09)	0.003	1.88 (1.22-2.89)	0.004
Gender (Female)	0.91 (0.66-1.25)	0.554	1.02 (0.73-1.42)	0.910	n/d	n/d
Age (≥60)	0.90 (0.66-1.23)	0.505	1.13 (0.80-1.58)	0.498	n/d	n/d
Tumor location						
right-side colon	reference				n/d	n/d
left-side colon	0.58 (0.37-0.90)	0.015	0.51 (0.33-0.79)	0.003	n/d	n/d
rectum	1.10 (0.76-1.59)	0.612	0.90 (0.60-1.36)	0.623	n/d	n/d
Differentiation (poor†)	1.80 (1.16-2.81)	0.009	1.34 (0.83-2.16)	0.230	n/d	n/d
T factor‡						
T1	reference		reference		n/d	n/d
T2	2.59 (0.32-21.08)	0.373	1.90 (0.23-15.88)	0.552	n/d	n/d
T3	6.54 (0.92-46.79)	0.061	3.74 (0.50-28.14)	0.201	n/d	n/d
T4	13.98 (1.80-108.32)	0.012	7.30 (0.86-62.06)	0.069	n/d	n/d
N factor‡ (N2)	2.52 (1.84-3.46)	<0.001	2.28 (1.49-3.51)	<0.001	n/d	n/d
ND (≥20)	0.52 (1.10-2.10)	0.010	1.03 (0.66-1.62)	0.896	n/d	n/d
Intramural lymphatic invasion (positive)	20.64 (0.10-4237.61)	0.265	n/d	n/d	n/d	n/d
Intramural vascular invasion (positive)	1.62 (0.88-2.99)	0.123	1.17 (0.61-2.26)	0.635	n/d	n/d
Preoperative CEA (elevated)	1.70 (1.24-2.32)	0.001	1.38 (0.98-1.95)	0.065	n/d	n/d
Preoperative CA19-9 (elevated)	1.77 (1.12-2.80)	0.015	1.50 (0.90-2.48)	0.118	n/d	n/d
Laparoscopic operation (Yes)	0.88 (0.70-1.09)	0.257	1.09 (0.67-1.80)	0.725	n/d	n/d
Number of total dissected lymph nodes						
<6	reference		reference		n/d	n/d
6-10	0.95 (0.48-1.88)	0.880	0.47 (0.19-1.14)	0.096	n/d	n/d
11-15	0.62 (0.36-1.07)	0.083	0.56 (0.25-1.27)	0.164	n/d	n/d
>15	0.79 (0.52-1.18)	0.248	0.46 (0.20-1.07)	0.071	n/d	n/d
Anastomotic leakage (present)	1.04 (0.46-2.35)	0.928	1.21 (0.52-2.84)	0.660	n/d	n/d
Adjuvant chemotherapy (Yes)	1.46 (0.93-2.29)	0.100	1.51 (0.93-2.43)	0.093	n/d	n/d
Perioperative transfusion (Yes)	1.20 (0.80-1.77)	0.373	0.89 (0.57-1.38)	0.597	n/d	n/d
Propensity score	n/d	n/d	n/d	n/d	11.39 (2.61-49.72)	0.001

Abbreviations: DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; ND, node density (metastatic lymph node ratio).

*End-point: date of death or March 31, 2007, if survived. **Cox's proportional hazard model.

†poor includes poorly differentiated, mucinous, and undifferentiated types. ‡T and N factor mean pathological factors.

There was no event in intramural lymphatic invasion negative cases, so that this variable was excluded from multivariable analysis.

Multivariable Model 2 indicates the adjusted effect of preoperative obstruction by applying propensity score which is a conditional probability of presenting preoperative obstruction given by other clinicopathologic factors.

Supplemental Table 4. Preoperative obstruction and first recurrence site in stage III

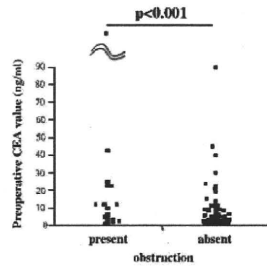
		Preoperative obstruction			P*
		present	absent	%	
local, P, LN	present	10	58	14.7	0.287
	absent	37	329	10.1	
local	present	7	28	20.0	0.085
	absent	40	359	10.0	
P	present	2	16	11.1	>0.999
	absent	45	247	15.4	
LN	present	1	17	5.6	0.328
	absent	46	246	15.8	
hematogenous	present	20	84	19.2	0.003
	absent	27	303	8.2	
H	present	13	54	19.4	0.019
	absent	34	333	9.3	
LM	present	7	36	16.3	0.296
	absent	40	351	10.2	
bone	present	2	5	28.6	0.170
	absent	45	382	10.5	
brain	present	1	4	20.0	0.438
	absent	46	383	10.7	
other (penis)	present	1	0	100.0	0.108
	absent	46	387	10.6	

Abbreviations: P, peritoneal; LN, lymph node.

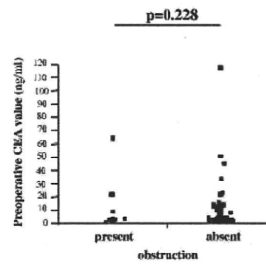
*Fisher's exact test.

Fig. 1

A. stage III colon cancer



B. stage III rectal cancer



C. stage II colorectal cancer

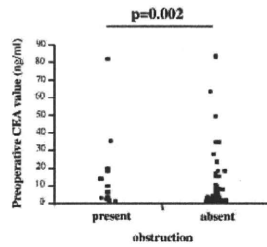
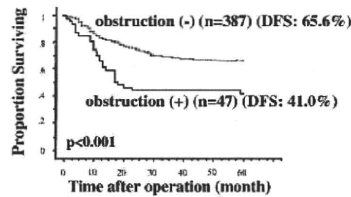


Figure 1. Preoperative CEA values were compared between obstructed cases and non-obstructed cases, respectively in (A) colon cancer (n=253), (B) rectal cancer (n=181) and stage II CRC (n=207).

190x254mm (600 x 600 DPI)

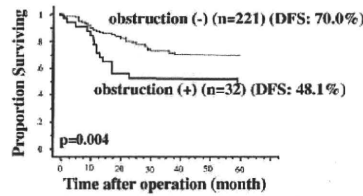
Fig. 2

A. All (n=434)



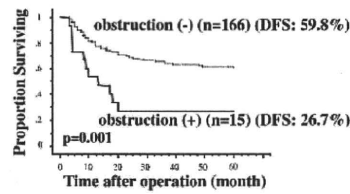
No. at risk	
obstruction (+)	47 37 21 19 19 18
obstruction (-)	387 336 297 262 250 243 242

B. Colon (n=253)



No. at risk	
obstruction (+)	32 27 16 15 15 14
obstruction (-)	221 199 181 157 149 146 146

C. Rectum (n=181)



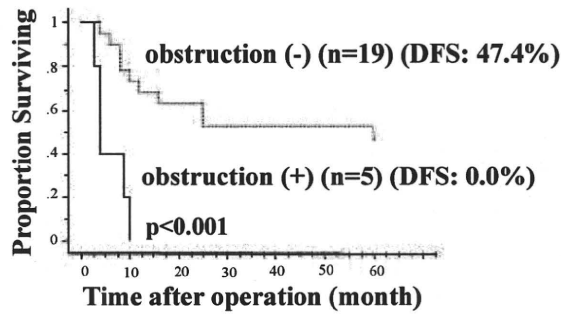
No. at risk	
obstruction (+)	15 9 5 4 4 4 4
obstruction (-)	166 138 116 105 101 97 96

Figure 2. Kaplan-Meier analysis of 5-year disease-free survival (DFS) according to preoperative obstruction in patients with stage III CRC. (A) All stage III colorectal cancer (n=434). (B) Stage III colon cancer (n=253). (C) Stage III rectal cancer (n=181).
190x264mm (600 x 600 DPI)

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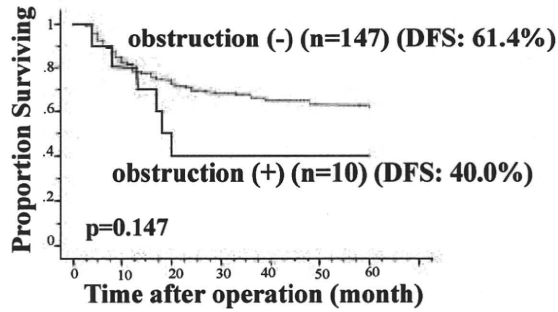
Supplemental Fig. 1

A. poorly differentiated stage III rectal cancer



No. at risk							
obstruction (+)	5	1	0	0	0	0	0
obstruction (-)	19	15	12	10	10	10	10

B. non-poorly differentiated stage III rectal cancer



No. at risk							
obstruction (+)	10	8	5	5	5	5	5
obstruction (-)	147	123	104	95	91	87	86

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Supplemental Table 1. Prognostic analysis on 5-year DFS* in stage II and III CRC patients (n=641)

Variables	univariable analysis		multivariable analysis			
			model 1		model 2	
	HR (95% CI)	p**	HR (95% CI)	p**	HR (95% CI)	p**
Preoperative obstruction (present)	2.21 (1.50-3.27)	<0.001	2.05 (1.35-3.11)	0.001	1.92 (1.28-2.89)	0.002
Gender (Female)	0.97 (0.73-1.31)	0.858	1.05 (0.77-1.42)	0.763	n/d	n/d
Age (≥60)	0.98 (0.73-1.31)	0.885	1.16 (0.85-1.58)	0.347	n/d	n/d
Tumor location						
right-side colon	reference		reference		n/d	n/d
left-side colon	0.65 (0.44-0.96)	0.031	0.57 (0.38-0.84)	0.004	n/d	n/d
rectum	1.12 (0.80-1.58)	0.511	0.91 (0.62-1.32)	0.607	n/d	n/d
Differentiation (poor†)	1.77 (1.15-2.72)	0.009	1.23 (0.78-1.95)	0.367	n/d	n/d
T factor‡						
T1	reference		reference		n/d	n/d
T2	2.60 (0.32-21.09)	0.372	1.87 (0.23-15.46)	0.563	n/d	n/d
T3	4.66 (0.65-33.28)	0.125	4.01 (0.54-29.82)	0.175	n/d	n/d
T4	8.98 (1.17-69.04)	0.035	7.11 (0.86-58.65)	0.068	n/d	n/d
N factor‡						
N0	0.16 (0.10-0.25)	<0.001	0.16 (0.09-0.27)	<0.001	n/d	n/d
N1	0.39 (0.29-0.54)	<0.001	0.42 (0.28-0.64)	<0.001	n/d	n/d
N2	reference		reference		n/d	n/d
ND (≥20)	2.18 (1.60-2.97)	<0.001	1.02 (0.66-1.56)	0.946	n/d	n/d
Intramural lymphatic invasion (positive)	21.42 (0.84-546.66)	0.064	n/d	n/d	n/d	n/d
Intramural vascular invasion (positive)	1.83 (1.00-3.37)	0.051	1.49 (0.78-2.83)	0.225	n/d	n/d
Preoperative CEA (elevated)	1.61 (1.20-2.15)	0.001	1.37 (1.00-1.87)	0.051	n/d	n/d
Preoperative CA19-9 (elevated)	1.38 (0.89-2.13)	0.153	1.30 (0.81-2.08)	0.281	n/d	n/d
Laparoscopic operation (Yes)	1.02 (0.66-1.56)	0.932	1.11 (0.69-1.79)	0.672	n/d	n/d
Number of total dissected lymph nodes						
<6	reference		reference		n/d	n/d
6-10	0.61 (0.29-1.32)	0.210	0.49 (0.22-1.01)	0.086	n/d	n/d
11-15	0.78 (0.39-1.57)	0.483	0.55 (0.26-1.19)	0.128	n/d	n/d
>15	0.84 (0.44-1.60)	0.589	0.46 (0.21-1.01)	0.053	n/d	n/d
Anastomotic leakage (present)	1.43 (0.78-2.64)	0.248	1.77 (0.93-3.38)	0.083	n/d	n/d
Adjuvant chemotherapy (Yes)	1.26 (0.83-1.91)	0.280	1.44 (0.93-2.23)	0.100	n/d	n/d
Perioperative transfusion (Yes)	1.13 (0.79-1.62)	0.501	0.89 (0.60-1.32)	0.563	n/d	n/d
Propensity score	n/d	n/d	n/d	n/d	6.60 (1.47-29.77)	0.014

Abbreviations: DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; ND, node density (metastatic lymph node ratio); n/d, not determined.

*End-point: date of death or March 31, 2007, if survived. **Cox's proportional hazard model.

†poor includes poorly differentiated, mucinous, and undifferentiated types. ‡T and N factor mean pathological factors.

There was no event in intramural lymphatic invasion negative cases, so that this variable was excluded from multivariable analysis.

Multivariable Model 2 indicates the adjusted effect of preoperative obstruction by applying propensity score which is a conditional probability of presenting preoperative obstruction given by other clinicopathologic factors.

Supplemental Table 2. Characteristics and 5-year DFS* of stage II patients (n=207)

Variables	No. of Patients	%	Average Survival (rate, %)	<i>P</i> **
Gender				
Male	127	61	84.3	0.146
Female	80	39	91.3	
Age, years				
<60	94	45	88.3	0.558
≥60	113	55	85.8	
Tumor location				
right-side colon	56	27	87.5	0.993
left-side colon	75	36	86.7	
rectum	76	37	86.8	
Differentiation				
non-poor	194	94	86.6	0.568
poor†	13	6	92.3	
T factor				
T3	199	96	86.9	0.985
T4	8	4	87.5	
Intramural lymphatic invasion				
negative	16	8	100.0	0.119
positive	191	92	85.9	
Intramural vascular invasion				
negative	19	9	100.0	0.086
positive	188	91	85.6	
Preoperative CEA				
normal (≤2.5ng/ml)	138	67	87.7	0.635
elevated (>2.5ng/ml)	69	33	85.5	
Preoperative CA19-9				
normal (≤37ng/ml)	183	88	86.3	0.464
elevated (>37ng/ml)	24	12	91.7	
Preoperative obstruction				
Yes	16	8	81.3	0.478
No	191	92	87.4	
Laparoscopic operation				
Yes	8	4	87.5	0.965
No	199	96	86.9	
Number of total dissected lymph nodes				
<6	5	2	80.0	0.918
6-10	27	13	85.2	
11-15	34	17	85.3	
>15	141	68	87.9	
Anastomotic leakage				
Yes	12	6	58.3	0.001
No	195	94	88.7	
Adjuvant chemotherapy				
Yes	180	87	86.1	0.838
No	27	13	92.6	
Perioperative transfusion				
Yes	45	22	84.4	0.574
No	162	78	87.7	

Abbreviations: DFS, disease-free survival.

*End-point: date of death or April 30, 2007, no patient was lost to follow up.

**Log-rank test.

†poor consists of poorly differentiated, mucinous, and undifferentiated types.

Supplemental Table 3. 5-year DFS* of stage III CRC patients (n=434)

Variables	univariable analysis		multivariable analysis			
	HR (95% CI)	P**	model 1		model 2	
			HR (95% CI)	P**	HR (95% CI)	P**
Preoperative obstruction (present)	2.25 (1.49-3.41)	<0.001	1.98 (1.26-3.09)	0.003	1.88 (1.22-2.89)	0.004
Gender (Female)	0.91 (0.66-1.25)	0.554	1.02 (0.73-1.42)	0.910	n/d	n/d
Age (≥60)	0.90 (0.66-1.23)	0.505	1.13 (0.80-1.58)	0.498	n/d	n/d
Tumor location	reference					
right-side colon	0.58 (0.37-0.90)	0.015	0.51 (0.33-0.79)	0.003	n/d	n/d
left-side colon	1.10 (0.76-1.59)	0.612	0.90 (0.60-1.36)	0.623	n/d	n/d
rectum	1.80 (1.16-2.81)	0.009	1.34 (0.83-2.16)	0.230	n/d	n/d
Differentiation (poor†)						
T factor‡	reference		reference			
T1	2.59 (0.32-21.08)	0.373	1.90 (0.23-15.88)	0.552	n/d	n/d
T2	6.54 (0.92-46.79)	0.061	3.74 (0.50-28.14)	0.201	n/d	n/d
T3	13.98 (1.80-108.32)	0.012	7.30 (0.86-62.06)	0.069	n/d	n/d
T4	2.52 (1.84-3.46)	<0.001	2.28 (1.49-3.51)	<0.001	n/d	n/d
N factor‡ (N2)	0.52 (1.10-2.10)	0.010	1.03 (0.66-1.62)	0.896	n/d	n/d
ND (≥20)	20.64 (0.10-4237.61)	0.265	n/d	n/d	n/d	n/d
Intramural lymphatic invasion (positive)	1.62 (0.88-2.99)	0.123	1.17 (0.61-2.26)	0.635	n/d	n/d
Intramural vascular invasion (positive)	1.70 (1.24-2.32)	0.001	1.38 (0.98-1.95)	0.065	n/d	n/d
Preoperative CEA (elevated)	1.77 (1.12-2.80)	0.015	1.50 (0.90-2.48)	0.118	n/d	n/d
Preoperative CA19-9 (elevated)						
Laparoscopic operation (Yes)	0.88 (0.70-1.09)	0.257	1.09 (0.67-1.80)	0.725	n/d	n/d
Number of total dissected lymph nodes	reference		reference			
<6	0.95 (0.48-1.88)	0.880	0.47 (0.19-1.14)	0.096	n/d	n/d
6-10	0.62 (0.36-1.07)	0.083	0.56 (0.25-1.27)	0.164	n/d	n/d
11-15	0.79 (0.52-1.18)	0.248	0.46 (0.20-1.07)	0.071	n/d	n/d
>15	1.04 (0.46-2.35)	0.928	1.21 (0.52-2.84)	0.660	n/d	n/d
Anastomotic leakage (present)	1.46 (0.93-2.29)	0.100	1.51 (0.93-2.43)	0.093	n/d	n/d
Adjuvant chemotherapy (Yes)	1.20 (0.80-1.77)	0.373	0.89 (0.57-1.38)	0.597	n/d	n/d
Perioperative transfusion (Yes)						
Propensity score	n/d	n/d	n/d	n/d	11.39 (2.61-49.72)	0.001

Abbreviations: DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; ND, node density (metastatic lymph node ratio).

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*End-point: date of death or March 31, 2007, if survived. **Cox's proportional hazard model.

†poor includes poorly differentiated, mucinous, and undifferentiated types. ‡T and N factor mean pathological factors.

There was no event in intramural lymphatic invasion negative cases, so that this variable was excluded from multivariable analysis.

Multivariable Model 2 indicates the adjusted effect of preoperative obstruction by applying propensity score which is a conditional probability of presenting preoperative obstruction given by other clinicopathologic factors.

For Peer Review

Supplemental Table 4. Preoperative obstruction and first recurrence site in stage III

		Preoperative obstruction		%	P*
		present	absent		
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	absent	37	329	10.1	
local	present	7	28	20.0	0.085
	absent	40	359	10.0	
P	present	2	16	11.1	>0.999
	absent	45	247	15.4	
LN	present	1	17	5.6	0.328
	absent	46	246	15.8	
hematogenous	present	20	84	19.2	0.003
	absent	27	303	8.2	
H	present	13	54	19.4	0.019
	absent	34	333	9.3	
LM	present	7	36	16.3	0.296
	absent	40	351	10.2	
bone	present	2	5	28.6	0.170
	absent	45	382	10.5	
brain	present	1	4	20.0	0.438
	absent	46	383	10.7	
other (penis)	present	1	0	100.0	0.108
	absent	46	387	10.6	

Abbreviations: P, peritoneal; LN, lymph node.

*Fisher's exact test.

Anastomotic Leakage Contributes to the Risk for Systemic Recurrence in Stage II Colorectal Cancer

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Abstract

Purpose In stage II colorectal cancer (CRC), high-risk patient selection is required, but no candidate markers have been elucidated. Our concern was whether anastomotic leakage (Lk) is a potential available clinicopathological factor for selecting high-risk stage II.

Methods Two hundred seven patients with stage II CRC who underwent curative resection were analyzed. Clinical variables were tested for their relationship to survival.

Results The 5-year disease-free survival rate (DFS) was 87.0%. The univariable prognostic analyses indicated that Lk ($P=0.003$) was the only significant factor. The multivariable prognostic analysis revealed that Lk remained to be potently independent [hazard ratio (HR), 4.21, $P=0.021$], and the DFS was 58.3% in cases with Lk, while 88.7% in the counterpart. The multivariable logistic regression analysis revealed perioperative blood transfusion ($P=0.001$) was independently associated with Lk. Intriguingly, Lk was closely associated with hematogenic recurrence ($P=0.003$) rather than peritoneal or local recurrence. Although sustained increase of the serum C-reactive protein at 2 weeks after operation predicted poor prognosis, the multivariable analysis including the C-reactive protein level revealed that Lk still indicated the prognostic potential (HR, 3.70, $P=0.075$).

Conclusions The findings concluded that Lk may be a high risk for systemic recurrence in stage II CRC.

Keywords Colorectal cancer · Stage II · Prognosis · Anastomotic leakage

Introduction

Colorectal cancer (CRC) is the second most prevalent cancer,¹ and chemotherapy has dramatically improved prognostic outcome of CRC patients over the past decades.^{2,3} Nevertheless, CRC remains the fourth leading cause of cancer death worldwide with about 530,000 deaths every year.¹ Recently, as the prognostic outcome of stage III patients has been dramatically improved due to prevalent use of adjuvant chemotherapy and improvement of chemotherapy regimens,^{2,4} adjuvant chemotherapy is consented as standard therapy in stage III CRC. Similarly, application of adjuvant chemotherapy is under discussion for patients with high-risk stage II disease⁵ although no selecting marker has been clinically identified at present. In stage II patients, approximately 20% of the patients have yet suffered from recurrence in spite of potentially curative resection.⁶ Therefore, pre- or postoperative prognostic markers have been anticipated for selecting high-risk patients who may benefit from adjuvant

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chemotherapy after curative operation of stage II CRC. Several prognostic markers or predictors of chemosensitivity for stage II patients have been reported such as allelic imbalance,⁷ gene expression profiling by cDNA microarray,⁸ or microsatellite instability,⁹ respectively. However, such molecular markers have been unsuitable for routine application at present because they have not been finally validated yet and are still costly and time-consuming.

Anastomotic leakage (Lk) is thought to occur at a rate ranged from 3% to 18% and has been reported to be a risk factor for local recurrences in curatively operated CRC patients.^{10–12} In this meaning, at least patients with Lk may be potential candidate for adjuvant chemotherapy. However, these results were based upon curatively operated patients with CRC of several stages, and the impact of Lk on long-term survival remains controversial,^{10–14} especially in stage II CRC. Accordingly, clinicopathological factors including Lk were prognostically analyzed within stage II patients to evaluate whether Lk could be a clinically available parameter for predicting long-term prognosis.

Patients and Methods

Characteristics of Patients with Stage II CRC

A total of 1,101 patients having electively undergone surgical resection of primary CRC at the Kitasato University Hospital from January 1, 1990 to March 31, 2000, were reviewed. Patients with colorectal multiple cancer, malignant disease of other organ, familial adenomatous polyposis, or inflammatory bowel diseases, patients who underwent resections without anastomosis, and patients undergone emergency resection for perforation or one-stage resection for obstruction were excluded. Among the remaining 946 patients of sporadic CRC, 207 patients were diagnosed (21.9%) as stage II CRC disease and were operated on with curative intent. Preoperative chemotherapy or radiation therapy had not been performed in this cohort. Patients without obstruction received mechanical bowel preparation with polyethylene glycol electrolyte solution the day before surgery, and patients with obstruction and patients with rectal cancer received bedside orthograde colorectal lavage with lukewarm water. Prophylactic intravenous antibiotics were administered at the induction of anesthesia and 3 h after the beginning of operation. Patients were followed up until the recurrence of cancer or end point (April 30 2007). All patients were followed up at least every 3 months for the first year and every 6 months thereafter. Follow-up assessment involved a medical history-taking, physical examination, biologic tests, measurement of the serum CEA and CA19-9 levels, colonoscopy, chest radiography, abdominal ultrasonography (US), and chest/abdominal computed tomography

(CT). Serum CEA and CA19-9 were usually evaluated every visit, and abdominal US and CT were performed every 6 months. Chest CT and colonoscopy were examined every year. Recurrence was diagnosed on the basis of imaging and, if necessary, either cytologic analysis or biopsy was performed. Patient demographics, tumor characteristics, and postoperative course were recorded and analyzed. Perioperative transfusion was defined as allogeneic blood transfusion during surgery or in the first two postoperative days, as in previous press,¹⁵ and was performed at the discretion of the treating surgeons and anesthesiologists. The number of total dissected lymph nodes was also classified according to previous press.¹⁶ Pathological TNM classification was made according to the UICC (*Unio Internationalis Contra Cancrum*) staging system.

Patients who received adjuvant chemotherapy for more than 3 months were defined as adjuvant chemotherapy “Yes” group. Adjuvant chemotherapy was consisted of oral administration of 5-fluorouracil (5FU)-based regimens: 5FU, Tegafur/uracil (UFT), or Furtulon (5'-deoxy-5-fluorouridine) alone, or one of them plus PSK (protein-bound polysaccharide K). Although curative operation alone is a standard therapy in stage II CRC at present, oral adjuvant chemotherapy had been recommended to patients with stage II CRC during the term of this patient cohort if they fulfilled the following eligibility criteria: age of 20 to 75 years; the absence of prior chemo-immunotherapy or radiotherapy, and the absence of severe liver dysfunction, heart failure, renal dysfunction, or other severe systemic complications. Therefore, patients who received oral adjuvant chemotherapy reached 180 cases, and the remaining 27 patients declined or did not fulfill the above criteria.

Lk was defined as any clinical or radiological evidence of dehiscence of the anastomosis: the presence of peritonitis caused by anastomosis dehiscence, the presence of feculent discharge from the drainage tube, or the presence of abscess with demonstration of Lk. These were also confirmed by radiography from drainage tube, hydrosoluble enema, or CT-guided abscess drainage except the cases with obvious feculent discharge from the drainage tube (Supplemental Table 1). Anastomotic dehiscence, which was basically diagnosed by, later, routine imagings prior to closure of diverting ileostomy, was not included. We performed routine imagings only for patients with diverting ileostomy prior to ileostomy closure more than 3 months after primary operation. Four patients underwent diverting ileostomy, but no anastomotic dehiscence was detected in such routine diagnosis.

Statistical Analysis

The relationship between Lk and clinicopathological parameters were assessed by Pearson's chi-square test or

Fisher's exact test, as appropriate, and multivariate logistic regression analysis were performed to obtain an adjusted effect of each factor. The time of follow-up was calculated from the operation date for the primary lesion to the date of recurrence. Cumulative disease-free survival (DFS) of patients was estimated using the Kaplan–Meier method, and statistical significance of the difference of the survival rate between groups was tested using the log-rank test. For the Kaplan–Meier estimate of the survival curves, we truncated the data at a follow-up period of 5 years to avoid the number at risk to be too small. Those with a survival time of more than 5 years were reported to be 5 years, and events occurring after the end of the 5-year follow-up period were computed as censored data. Five-year cumulative DFS probability was estimated using the life table method with the interval length set at 1 month. Multivariable analysis was performed by employing the Cox proportional hazards model to examine the interaction between Lk and other clinicopathological variables and estimate the independent prognostic effect of Lk on survival by adjusting for confounding factors. For ordinal variable, when zero event was detected in the lowest exposure group, analyses was designed to be performed by grouping categories together, treating it as ordinal data to get an average effect, or by confounding sensitivity analyses excluding it from analysis. Within the present study population, there were 27 recurrences of stage II CRC which allows up to three variables to be included in a multivariable regression model. To avoid over-fitting, all potential confounding factors of Lk were reduced to one single composite characteristic by applying a propensity score.¹⁷ The conventional *P* value of 0.05 or less was used to determine the level of statistical significance. All reported *P* values are two-sided. Analyses were performed independently at our clinical research center using SPSS version 17.0 software (SPSS Inc., Chicago, IL).

Results

Patients' Characteristics and Their Association with Lk

The clinicopathological characteristics were shown in Table 1. One hundred twenty-seven males and 80 females were analyzed with age being 61.0 ± 11.1 years. Lk occurred in 12 (5.8%) cases, and, among them, only one patient had a particularly preoperative complication (diabetes mellitus). The diabetes of this patient was well-controlled by insulin from preoperation through postoperation. And, there was no patient with other factors for poor nourishment such as medication of steroids. Lk occurred in 22.2% of patients with perioperative blood transfusion and in 1.2% of those without perioperative blood transfusion. Lk was signifi-

cantly related to perioperative blood transfusion ($P < 0.001$, Fisher's exact test), followed by T4 factor (direct invasion into other organ; $P = 0.071$), the elevation of preoperative CEA ($P = 0.110$), and tumor position ($P = 0.129$). Preoperative obstruction was observed in only one patient with Lk (Table 1). There was also no significance in relationship between Lk and obstruction in the present study population. Lk occurred in five cases (3.8%) in colon cancer and seven in rectal cancer (9.2%). Among them, two patients required ileostomy (reoperation) for Lk in colon cancer and five in rectal cancer, and one patient (colon cancer) underwent ileostomy before curative resection (two-stage operation) for obstruction, one patient (rectal cancer) underwent diverting ileostomy, and the remaining three patients were conservatively observed with percutaneous drainage and finally cured. The multivariable logistic regression analysis of these factors indicated that Lk was independently associated with perioperative blood transfusion ($P < 0.001$).

Kaplan–Meier Estimate of 5-Year DFS

All the patients were included in the survival analysis. The overall follow-up period ranged from 2 to 207 months (median, 116 months), and the mean DFS was 55.4 months corresponding to a 5-year follow-up. Because a cumulative DFS probability of 50% was not yet reached by the end of 5-year follow-up, the overall median DFS time was not determined. The overall DFS rate was 87.0% (27 cases with recurrence and 180 cases without recurrence). Five-year cumulative DFS of patients with Lk was remarkably worse (58.3%), which corresponded to stage III CRC (63.2%), compared with those without Lk (88.7%; $P < 0.001$, Fig. 1a). Lymphatic involvement (ly; $P = 0.119$) and vascular involvement (v; $P = 0.086$) tended to indicate poor prognosis (Supplemental Fig. 1a, b), and patients with both ly and v involvement ($n = 28$) showed significantly poor prognosis (DFS, 84.9%) compared with the counterpart ($n = 179$; 100.0%; $P = 0.033$; Supplemental Fig. 1c).

When separately analyzed on tumor position, Lk still significantly affected adversely on long-term prognosis in both colon and rectum (Fig. 1b, c), and there was no significant difference between DFS of patients with Lk in colon cancer (60.0%) and that in rectal cancer (57.1%). In addition, Lk was the only significant prognostic factor, and there was no factor which had prognostic potential ($P < 0.1$) both in colon and rectum when separately analyzed (data not shown).

Contribution of Lk to the Risk of Recurrence with Multivariable Analysis

Cox proportional hazards model was applied to estimate the effect of Lk on DFS. Lk was the only significant prognostic

Table 1 Characteristics and those in correlation with anastomotic leakage (Lk)

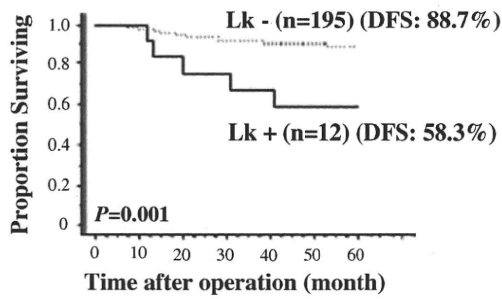
Variables	No. of patients	Percentage	Lk			<i>P</i> ^a values
			Present	Absent	Present rate (%)	
Gender						
Male	127	61	10	117	7.9	0.13
Female	80	39	2	78	2.5	
Age (years)						
<60	94	45	4	90	4.3	0.55
>60	113	55	8	105	7.1	
Tumor position						
Ccolon	131	63	5	126	3.8	0.13
Rectum	76	37	7	69	9.2	
Differentiation						
Non-poor	194	94	12	182	6.2	0.36
Poor ^b	13	6	0	13	0.0	
T factor						
T3	199	96	10	189	5.0	0.07
T4	8	4	2	6	25.0	
Lymphatic involvement (ly)						
Negative	16	8	0	16	0.0	0.61
Positive	191	92	12	179	6.3	
Vascular involvement (v)						
Negative	19	9	1	18	5.3	0.92
Positive	188	91	11	177	5.9	
Preoperative CEA						
Normal (<2.5 ng/ml)	138	67	5	133	3.6	0.110
Elevated (>2.5 ng/ml)	69	33	7	62	10.1	
Preoperative CA19-9						
Normal (<37 ng/ml)	183	88	10	173	5.5	0.64
Elevated (>37 ng/ml)	24	12	2	22	8.3	
Obstruction						
Yes	16	8	1	15	6.3	0.94
No	191	92	11	180	5.8	
Lk						
Yes	12	6	n/a	n/a	n/a	n/a
No	195	94	n/a	n/a	n/a	
Number of total dissected lymph node						
<6	5	2	0	5	0.0	0.78
6–10	27	13	1	26	3.7	
11–15	34	17	3	31	8.8	
>15	141	68	8	133	5.7	
Laparoscopy-assisted operation						
Yes	8	4	0	8	0.0	0.47
No	199	96	12	187	6.0	
Adjuvant chemotherapy						
Yes	180	87	9	171	5.0	0.2
No	27	13	3	24	11.1	
Perioperative transfusion						
Yes	45	22	10	35	22.2	<0.001
No	162	78	2	160	1.2	

OR odds ratio, LNDE lymph node dissection extent, n/a not applicable

^a Compared by Fisher's exact test or chi-square test

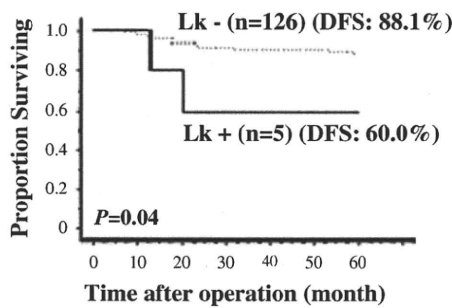
^b Poor consists of poorly differentiated, mucinous, and undifferentiated types

A. total stage II CRC (n=207)



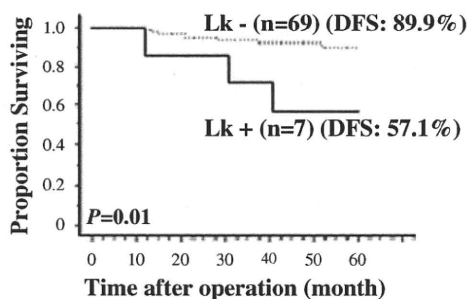
No. at risk	
Lk +	12 12 10 9 8 7 7
Lk -	195 194 185 179 177 177 173

B. colon cancer (n=131)



No. at risk	
Lk +	5 5 4 3 3 3 3
Lk -	126 125 119 115 114 114 111

C. rectal cancer (n=76)



No. at risk	
Lk +	7 7 6 6 5 4 4
Lk -	69 69 66 64 63 63 62

Fig. 1 Kaplan–Meier curve of 5-year DFS according to anastomotic leakage (Lk): **a** Total stage II CRC (n=207). **b** Colon cancer (n=131). **c** Rectal cancer (n=76)

factor, and there was no other factor which had prognostic potential ($P < 0.1$). The crude hazard ratio (HR) of Lk-positive compared to Lk-negative was 4.38 (95% confidence interval (CI), 1.66–11.58; $P = 0.003$), which indicated Lk increased the risk of recurrence of CRC and cancer-related death by more than four times that of without Lk. The effect of Lk on recurrence in colon and rectal cancer

group gave similar results: crude HR (95%CI) was 4.1 (0.9–17.9) for the colon group and 4.9 (1.3–19.0) for the rectal group.

Before multivariable analyses were adopted to estimate adjusted effect of Lk on DFS, we further confirmed that there was no interaction effect between cancer position (colon or rectum) and Lk ($P = 0.874$); taking into account that evaluation in each group would result in a small sample size and thus decrease the power of the study, we finally combined them together. Potential confounders of variables were included in the multivariable analysis (Table 2). The adjusted HR of Lk became 5.27 (95%CI, 1.54–18.10; $P = 0.008$) in comparison to Lk-negative. We also performed an analysis by using propensity score to adjust the effect of Lk by transforming all other confounding variables into a single estimator and revealed that, after the adjustment, the HR of Lk became 4.21 (95%CI, 1.24–14.33; $P = 0.021$). These findings suggested that Lk seems to be an independent and significant risk factor of poorer DFS (Table 2).

Lk was Associated with Hematogenic Recurrence Rather than Local or Peritoneal Recurrence in Stage II CRC

Next, first recurrence site in patients with stage II CRC was analyzed according to Lk. Interestingly, Lk was correlated with hematogenic recurrence ($P = 0.003$ by Fisher’s exact test) rather than local recurrence or peritoneal dissemination ($P = 0.605$; Table 3). Therefore, Lk may cause systemic micrometastasis, leading to systemic recurrence.

Effect of Lk on DFS When Taking Systemic Inflammatory Response into Account

Recently, a systemic inflammatory response, as evidenced by raised circulating levels of C-reactive protein (CRP), has been reported to be associated with poor survival in patients who underwent potentially curative resection for CRC.¹⁸ These reports may explain the above implication of Lk in systemic recurrences, hence circulating level of CRP was analyzed, which was measured as a part of routine blood examination either before or after potentially curative resection for stage II CRC. CRP level was classified as raised (≥ 1.0 mg/dl) or normal (< 1.0 mg/dl) from a clinical practice view. Lk was significantly correlated with CRP level at 1 or 2 weeks after curative operation ($P = 0.018, 0.003$, respectively, by Fisher’s exact test; Supplemental Table 2). Moreover, the sustained elevation of CRP level at 2 weeks after operation predicted significantly worse prognosis (DFS, 75.0%) than its counterpart (89.3%; $P = 0.022$, compared by log-rank test, Supplemental Fig. 2), while preoperative CRP and CRP at 1 week after operation did not show prognostic significance (data not shown). The multivariable prognostic analysis including CRP at 2 weeks