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Identification of the Risk Factors for Recurrence of Stage III Colorectal Cancer

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Abstract. *Background/Aim: This study aimed to identify risk factors for recurrence of patients with stage III colorectal cancer by assessing clinicopathological features. Patients and Methods: The study included 231 patients with stage III colorectal cancer who underwent curative resection between 2006 and 2012 at the Department of Surgery of the Jikei University Hospital, Tokyo, Japan. Clinicopathological data of the patients were retrospectively evaluated. Results: The recurrence rate was 27.7% (64/231) in the study group. The univariate analysis for recurrence identified five risk factors: site of primary tumor (rectal cancer), surgical procedure (open surgery), preoperative serum CEA level (>5 ng/ml), preoperative serum CA19-9 level (>37 U/ml), and number of metastatic lymph nodes (over three metastases). The multivariate analysis for recurrence identified three risk factors: rectal cancer, preoperative serum CEA level >5.0 ng/ml 95%, and more than three metastatic lymph nodes. Conclusion: The risk factors for stage III colorectal cancer recurrence seem to be rectal cancer, preoperative serum CEA level >5.0 ng/ml, and more than three metastatic lymph nodes.*

For stage III colon cancer, several randomized controlled trials (RCTs) have indicated that addition of oxaliplatin (L-OHP) to 5-fluorouracil (5-FU)+leucovorin (LV) as a postoperative adjuvant chemotherapy was effective for both suppression of recurrence and extension of survival time (1-5). Currently, a regimen with 5-FU+LV+L-OHP is positioned as a standard for postoperative adjuvant chemotherapy for stage III colon cancer. However, L-OHP has severe side-effects such as peripheral neuropathy and leukopenia (3). In addition, L-OHP is expensive, and may not be cost-effective. For these reasons, L-OHP is not unusually recommended to be included in postoperative adjuvant chemotherapy for stage III colorectal cancers in Japan. Furthermore, as postoperative adjuvant chemotherapy for colorectal cancer [except for rectum/below the peritoneal reflection (Rb) rectal cancer], oral 5-FU+LV and capecitabine are not inferior to intravenous 5-FU+LV (6-8). Oral 5-FU+LV and capecitabine are less expensive and associated with fewer side-effects compared to intravenous 5-FU+LV. Therefore, clarifying the postoperative recurrence risk factors for stage III colorectal cancer may be able to select cases who benefit from L-OHP as adjuvant chemotherapy, and might reduce the use of not only L-OHP, but also 5-FU+LV. For such a purpose, here we report the high-risk factors for postoperative recurrence of stage III colorectal cancer in our hospital.

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Key Words: Risk factors, colorectal cancer, stage III.

Patients and Methods

The subjects were 310 patients with stage III colorectal cancer who underwent curative resection between 2006 and 2012 at the Department of Surgery of the Jikei University Hospital, Tokyo, Japan. Of the 310 patients, we excluded four patients with insufficient histopathological factor descriptions and 75 patients for whom preoperative serum CA19-9 levels were not measured. Consequently, the remaining 231 patients were studied, of whom retrospectively retrieved data regarding their clinicopathologic characteristics, treatments, and clinical outcomes from their medical records were analyzed.

The variables studied consisted of the following patient factors: gender (male/female), age at surgery (≥75 years/<75 years), site of primary tumor (colon/rectum), surgical procedure (open/laparoscopic), preoperative serum carcinoembryonic antigen (CEA) levels (≤5 ng/ml/>5 ng/ml), preoperative serum carbohydrate antigen 19-9 (CA19-9) levels (≤37 U/ml/> 37 U/ml), postoperative adjuvant chemotherapy (yes/no), T category (≤ T3/T4), histological differentiation (tubular adenocarcinoma/mucinous adenocarcinoma/others), number of metastatic lymph nodes (over three metastases/equal or less than three metastases), venous invasion (yes/no) and lymphatic invasion (yes/no). Pathologic staging of the primary tumors was performed according to the Union for International Cancer Control TNM Classification of Malignant Tumors, seventh edition. Univariate Cox's proportional hazard (PH) regression analysis was performed to identify the risk factors for recurrence of patients with stage III colorectal cancer. Univariate

analysis was performed using the Student's t-test and the Pearson's Chi-square test. All *p*-values were considered statistically significant when the associated probability was less than 0.05. Variables with $p<0.05$ were included in the multiple Cox's PH regression model to identify independent risk factors associated with the incidence. The study protocol was reviewed and approved by the ethics committee and Institutional Review Board (27-283 8168).

Results

The patients' age ranged from 25 to 95 years, with a median age of 66 years. The overall recurrence rate was 27.7% (64/231). The patients' characteristics are shown in Table I. The results of the univariate analysis of the background factors and recurrence in patients with stage III cancer are shown in Table II, and demonstrated five factors to be significant: surgical procedure (open surgery; $p=0.012$), site of primary tumor (rectal surgery; $p=0.010$), preoperative serum CEA levels (>5 ng/ml; $p=0.010$), preoperative serum CA19-9 levels (>37 U/ml; $p=0.009$) and numbers of metastatic lymph nodes (over three metastases; $p<0.001$) (Table II). In the multivariate analysis, rectal cancer (HR=2.37, 95%CI=1.269-4.433, $p=0.007$), preoperative serum CEA level >5.0 ng/ml (HR=2.020, 95%CI=1.070-3.811, $p=0.030$), and more than three metastatic lymph nodes (HR=2.890, 95%CI=1.479-5.646, $p=0.002$) were independent risk factors for recurrence (Table III).

Discussion

Currently, combination therapy of 5-FU/LV/L-OHP (FLOX, FOLFOX) is the standard regimen for adjuvant chemotherapy for stage III colorectal cancer. FOLFOX therapy has also been approved for insurance coverage in Japan as postoperative adjuvant chemotherapy for colorectal cancer. However, the inclusion of L-OHP remains controversial, because FOLFOX has serious side effects such as peripheral neuropathy, vasculitis and pancytopenia (3). In addition, FOLFOX is expensive. Nowadays, the surge in medical expenses is a national concern in Japan, and therefore reduction of medical expenses is very important for the Japanese medical economy.

According to the results of the Japanese Phase III study in the American Society of Clinical Oncology (ASCO) in 2012, for adjuvant chemotherapy for stage III colon cancer, the use of oral 5-FU was not inferior to FOLFOX (8). Based on this study, FOLFOX may be used as adjuvant chemotherapy for the high-risk group of stage III colorectal cancer. In the current study, we reviewed retrospectively the risk factors of recurrence of stage III colorectal cancer cases in our hospital.

In the current study, the overall recurrence rate was 28.1% (65/231), which was slightly better than the aggregations (30.8%) by the Japanese Society for Cancer of the Colon and Rectum (9).

Table I. *Clinical characteristics of patients.*

Factor	Number	Rate (%)
Age		
<75	190	82.3
≥75	41	17.7
Gender		
Male	146	63.2
Female	85	36.8
Site of primary tumor		
Colon	134	58
Rectum	97	42
Surgical procedure		
Open	141	61
Laparoscopic	90	39
CEA (ng/ml)		
≤5	120	51.9
>5	111	48.1
CA19-9 (U/ml)		
≤37	194	84
>37	37	16
Adjuvant chemotherapy		
Yes	175	75.8
No	56	24.2
T category		
≤T3	189	81.8
>T3	42	18.2
Histological differentiation		
Tub	207	89.6
Muc	8	3.5
Others	16	6.9
Number of metastatic lymph nodes		
≤3	172	74.5
>3	59	25.5
Venous invasion		
Yes	176	76.2
No	55	23.8
Lymphatic invasion		
Yes	158	68.4
No	73	31.6

CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; Tub: tubular adenocarcinoma; Muc: mucinous adenocarcinoma.

For stage II colorectal cancer, several high recurrence risk factors have been defined. ASCO and the European Society for Medical Oncology have defined high-risk factors for recurrence of stage II colon cancer, which consist of T4, poorly differentiated or undifferentiated carcinoma, lymphatic invasion, neural invasion, intestinal obstruction and/or perforation by the cancer, dissection of <13 lymph nodes, and high preoperative serum CEA levels (10-12). Although we identified three risk factors for recurrence of stage III colorectal cancer by multivariate analysis, some factors were not risk factors for recurrence (T category; $p=0.068$, histological differentiation; $p=0.119$, lymphatic invasion; $p=0.870$, venous invasion; $p=0.153$). T factor

Table II. *Univariate analysis of background factors and recurrence.*

Factor	Recurrence		Rate of recurrence (%)	*p*-Value
	Yes (n=65)	No (n=166)		
Age				
>75	52	138	27.4	0.575
≤75	13	28	31.7	
Gender				
Male	41	105	28.1	0.98
Female	24	61	28.2	
Site of primary tumor				
Colon	29	105	21.6	0.01
Rectum	36	61	37.1	
Surgical procedure				
Open	48	93	34	0.012
Laparoscopic	17	73	18.9	
CEA (ng/ml)				
≤5	25	95	20.8	0.01
>5	40	71	36	
CA19-9 (U/ml)				
≤37	48	146	24.7	0.009
>37	17	20	45.9	
Adjuvant chemotherapy				
Yes	50	125	28.6	0.47
No	15	41	26.8	
T category				
≤T3	58	131	30.7	0.068
>T3	7	35	16.7	
Histological differentiation				
Tub	54	153	26.1	
Muc	4	4	50	0.119
Other	7	9	43.8	
Number of metastatic lymph nodes				
≤3	38	134	22.1	0.001
>3	27	32	45.8	
Venous invasion				
Yes	49	109	31	0.153
No	16	57	21.9	
Lymphatic invasion				
Yes	50	126	28.4	0.87
No	15	40	27.3	

CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; Tub: tubular adenocarcinoma; Muc: mucinous adenocarcinoma.

Table III. *Multivariate analysis for Stage III colorectal cancer*

	Odds ratio	95%CI	*p*-Value
Rectal cancer	2.372	1.269-4.433	0.007
CEA (ng/ml) >5	2.02	1.070-3.811	0.03
More than 3 metastatic lymph nodes	2.89	1.479-5.646	0.002

CEA: Carcinoembryonic antigen.

which is listed as one of the high recurrence risk factors of stage II by ASCO and the European Society for Medical Oncology did not show a significant difference, but a tendency may be observed because of the p-value of 0.068. Serum CEA levels are also reported to correlate with both T category and positive lymph node numbers in colon cancer (13). Although T category in the current study did not show a significant difference as a risk factor for recurrence, serum CEA levels and the number of metastatic lymph nodes were identified as risk factors. This result does not seem to contradict previous reports. In the case of rectal cancer, high preoperative serum CEA levels have been reported as a poor prognostic factor and a risk factor for recurrence (14). As to the risk factor of lymph node metastasis for stage III colorectal cancer in the current study, TNM classification of UICC classifies three or fewer regional lymph node metastases as N1 and more than three metastatic lymph nodes as N2 (15). As our results indicate, the classification based on the number of lymph node metastases is very meaningful in considering the risk of recurrence.

In the current study, the recurrence rate of cases that had no risk factors was only 10.0% (5/50), which was better than the recurrence rate of 13.3% of the Japanese Society for Cancer of the Colon and Rectum for patients with stage II colorectal cancer (9). Therefore, even among stage III colorectal cancer, some cases may not require the use of L-OHP as adjuvant chemotherapy or may not even need any adjuvant chemotherapy. These risk factors seem to be important to establish a postoperative treatment strategy.

The limitation of this study includes its retrospective nature and it being a study at a single center. In the future, prospective clinical trials on adjuvant chemotherapy based on the risk factors for recurrence in patients with stage III cancer are required.

Conclusion

For stage III colorectal cancer, risk factors for recurrence after curative resection consisted of rectal cancer, high preoperative serum CEA levels, and more than three metastatic lymph nodes, which may help cost-effective reduction of patients who benefit from adjuvant chemotherapy.

Conflicts of Interest

The Authors have no conflict of interest to declare regarding this study.

Authors' Contributions

Kai Neki designed the study, wrote the initial draft of the manuscript and analysis and interpretation of data. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All Authors approved the final version of

the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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