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The Latest Update of Prognostic Factors of Stage III Colon Cancer Who Underwent Curative Operation and Postoperative Adjuvant Chemotherapy

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This study aimed to explore the predicting factor of the poor prognosis of stage III colon cancer. Adjuvant chemotherapy for stage III colon cancer has become popular. However, the choice of the optimal adjuvant chemotherapy regimen still remains unclear. A total of 135 patients with stage III colon cancer, treated with postoperative adjuvant chemotherapy from January 2007 to December 2012 at the Kitasato University East Hospital, were reviewed retrospectively in terms of clinicopathologic characteristics associated with survival and recurrence (median observation: 61 months). We used a multivariate Cox hazards model to identify independent prognostic factors in stage III colon cancer. Of the 135 patients, 38 had recurrence. Five-year overall survival was 83.9%, while 3-year recurrence-free survival was 72.8%. Oxaliplatin-containing adjuvant chemotherapy was almost exclusively applied to stage IIIB colon cancer. Univariate analysis of the negative prognostic factors were N2 ($P = 0.0004$); operation time ($P = 0.0346$); tumor size ($P = 0.0092$); depth of invasion ($P = 0.005$); histology ($P = 0.0403$); infiltration type ($P < 0.0001$); lymphatic permeation (ly3, $P = 0.0001$); and vascular permeation (v3, $P = 0.0005$). On multivariate analysis, the independent prognostic factors for relapse-free survival were v3 ($P = 0.032$) and N2 ($P = 0.0216$). Combination of the prognostic factors clearly stratified prognosis of stage III colon cancer patients, and those with either factor positive had a poor prognosis despite administration of adjuvant chemotherapy. Both v3 and pN2 may be critical prognostic factors in stage III colon cancer with adjuvant chemotherapy. This

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information would elucidate areas of concern in the present therapeutic strategy in stage III colon cancer.

Key words: Colon cancer – Stage III – Prognostic factors – Adjuvant chemotherapy – Venous invasion

Colorectal cancer (CRC) is third leading cause of death in Japan.[1] Due to the latest reports of the Japanese Society for Cancer of the Colon and Rectum, the recurrence rate of stage III colon cancer is 30.8%.[2] The improvement of the prognosis of these patients is required.

The efficacy of postoperative adjuvant chemotherapy for colon cancer has been reported,[3–7] and several regimens are used in Japan [infusional fluorouracil + leucovorin (LV); uracil and tegafur (UFT) + LV; capecitabine; folinic acid, 5-FU, and oxaliplatin (FOLFOX); and capecitabine and oxaliplatin (CapeOX)]. However, there is no consensus about which regimen is the most appropriate for these patients. Thus, there is a possibility that determining the best the regimen will lead to the improvement of the prognosis of patients with stage III colon cancer.

Prognostic factors that can predict poor outcomes are important to determine the most optimal regimen, and those factors that predict recurrence should be updated based on the latest clinical outcome. We therefore conducted this retrospective study to identify clinicopathologic high-risk factors of stage III colon cancer patients who underwent curative resection and postoperative adjuvant chemotherapy.

Patients and Methods

We retrospectively reviewed the medical records of 628 patients with primary colon cancer who underwent curative resection at Kitasato University East Hospital between January 2007 and December 2012. All patients had undergone colectomy with sufficient lymph-node dissection and 181 were histopathologically diagnosed with stage III colon cancer, as defined in the 7th edition of the "General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus."[8] The histopathologic diagnosis of all patients was adenocarcinoma. The following patients were excluded: (1) patients who underwent additional colectomy after endoscopic mucosal resection; (2) patients who underwent total colectomy for ulcerative colitis; and (3) patients who did not receive postoperative adjuvant chemotherapy. After such exclusions, 135 patients were included in the analysis. This study was conducted in accordance to the tenets of the Declaration of Helsinki, and all patients signed a consent form approved by the Research Ethics Committee of Kitasato University School of Medicine.

Surgical Treatment

All patients had curative resection according to the 7th edition of the "General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus."[8] At the time of preoperative and/or intraoperative diagnosis, the 2nd tier of lymph node dissection was performed if tumor depth was diagnosed as submucosal level, and the 3rd tier of lymph node dissection was performed when tumor depth was diagnosed as muscularis propria or beyond.

Pathologic Diagnosis

Depth of invasion and lymph node status were classified according to the primary tumor, regional lymph nodes, and distant metastasis (TNM) classification.[9] The degrees of lymphatic invasion (ly0–ly3) and venous invasion (v0–v3) were defined according to the 7th edition of the "General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus."[8] Venous invasion was evaluated on histopathologic evaluation of specimens stained with hematoxylin and eosin and with elastic van Gieson stain as previously described.[10] Lymphatic invasion was evaluated on histopathologic evaluation of specimens stained with hematoxylin and eosin. In our hospital, v0, v1, v2, and v3 are defined as follows: v0, no venous invasion found on any slide examined; v1, 1 or 2 sites of venous invasion found throughout all slides examined (8 slides); v2, intermediate level between v1 and v3; v3, 1 or more sites of venous invasions found on every slide examined. Ly0, ly1, ly2, and ly3 are defined in the same way.

Adjuvant Chemotherapy

The adjuvant chemotherapy begins 4 to 8 weeks after first discharge of the operation for the primary tumors. The following patients were excluded from adjuvant chemotherapy: (1) patients who had severe

Table 1 Clinicopathologic parameters of all patients

Clinicopathologic parameters	n = 135
Age	
Mean ± SD	62.8 ± 11.2
Median (range)	65 (26–80)
Sex	
Male/female	82/53
Location	
Right/transverse/left/sigmoid	35/12/7/81
Lymph node metastasis (7th UICC)	
N1/N2	98/37
Operation time, min	234
Surgical procedure	
Open/laparoscopic	41/94
Lymph node dissection	
D2/D3	20/115
Tumor size, cm	
Mean ± SD	4.65 ± 2.77
Median (range)	4.0 (1–24)
Primary tumor	
T1/T2/T3/T4	8/18/49/60
Histology	
Tub/pap/muc/por	109/10/8/8
INF	
INFa/INFb/INFc	5/123/7
Lymphatic invasion	
Ly0/ly1/ly2/ly3	12/63/47/13
Venous invasion	
V0/v1/v2/v3	18/51/46/20
Patient with recurrence	38
3-year RFS, %	72.80
5-year OS, %	83.90

UICC, Union for International Cancer Control.

systemic diseases; (2) patients who rejected chemotherapy; and (3) patients whose drug compliance was not guaranteed due to psychologic disease including dementia. The duration of chemotherapy was 6 months, and the chemotherapy was stopped or changed to another regimen when the patient couldn't continue due to moderate to severe adverse effects or rejection. The regimen was also changed when the patient had recurrence.

UFT + LV chemotherapy was performed in 75 cases, capecitabine in 16, CapeOX in 9, mFOLFOX6 in 21, and 14 cases received other regimens.

Patient Follow-Up

After colectomy, the patients were generally assessed at 3-month intervals for the first 3 years and 6-month intervals thereafter. The baseline assessment included physical examination, hematologic examination, serum chemical analysis, measurement of serum values of carcinoembryonic antigen (CEA) and cancer antigen 19-9. Computed tomography was performed at 6-month intervals. Colonoscopy was performed 1 and 3 years after colectomy. Recurrence was diagnosed on the basis of imaging studies and histologic confirmation. The median observation period was 61 months, ranging from 7 to 113 months. The clinicopathologic factors of the patients we analyzed are shown in Table 1.

Statistical Analysis

Survival was calculated by the Kaplan-Meier method. Significant univariate negative prognostic factors were identified with regard to relapse-free survival (RFS) using a log-rank test. Significant univariate negative prognostic factors on RFS were then applied to a multivariate Cox proportional hazards model to identify independent prognostic factors. All calculations were performed with the use of commercial software (JMP 10; SAS Institute, Inc, Cary, North Carolina). P values < 0.05 were considered statistically significant.

Results

We identified univariate negative prognostic factors for RFS in stage III colon cancer patients who underwent curative resection and postoperative adjuvant chemotherapy.

Kaplan-Meier curve for overall survival (OS) and RFS are shown in Fig. 1. The median follow-up term was 61 months, so prognostic analysis was considered to be reliable, especially for RFS, but not sufficient for OS.

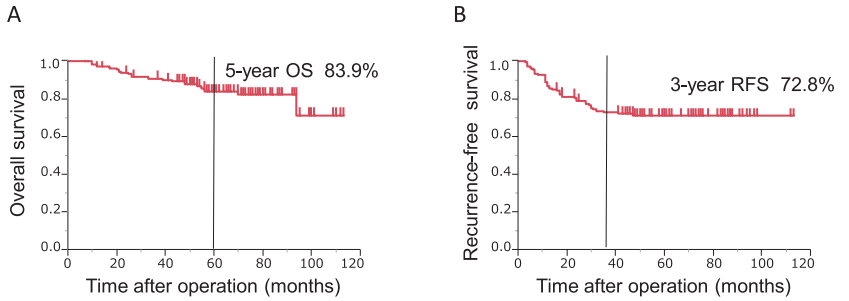

Fig. 1 (A) Overall survival and (B) recurrence-free survival in stage III colon cancer patients who underwent curative colon resection and postoperative adjuvant chemotherapy.

Table 2 Results of univariate and multivariate analysis of the negative prognostic factors

Clinicopathologic parameters	n = 135	3-year RFS	*P* value	HR	95% CI	P-value
Age (y), >55/≤55	110/25	80.0/71.2	0.2783			
Sex, male/female	82/53	67.2/81.1	0.1185			
Location, right/transverse/left/sigmoid	36/12/6/81	71.2/72.7/100/71.6	0.5399			
Lymph node metastasis (UICC), N1/N2	98/37	80.2/54.1	0.0004	1.00/2.39	1.14-5.08	0.0216
Operation time (min), >215/≤215	71/64	63.6/82.7	0.0346			
Surgical procedure, open/laparoscopic	41/94	65.1/76.2	0.348			
Lymph node dissection, D2/D3	20/115	79.0/71.8	0.3853			
Tumor size (cm), >3/≤3	105/30	68.3/89.7	0.0243			
Primary tumor, T1,T2/T3/T4	26/49/60	92.3/76.7/61.2	0.005			
Histology, tub/pap/muc/por	109/10/8/8	76.6/60.0/75.0/37.5	0.0403			
INF, INFa/INFb/INFc	5/123/7	100/75.1/14.3	<0.0001			
Lymphatic invasion, ly0–2/ly3	122/13	77.4/30.8	0.0001			
Venous invasion, v0–2/v3	115/20	77.8/44.4	0.0005	1.00/2.51	1.08–5.59	0.032

With regard to RFS, the univariate negative prognostic factors were lymph node metastasis ($P = 0.0004$); operation time ($P = 0.0346$); tumor size ($P = 0.0092$); depth of invasion ($P = 0.005$); histology ($P = 0.0403$); infiltration type ($P < 0.0001$); lymphatic permeation ($P = 0.0001$); and vascular permeation ($P = 0.0005$). On the other hand, there is no significant relevance of patient age, sex, tumor location, surgical procedure, or lymph node dissection level with regard to RFS. The results of the univariate prognostic analysis for RFS are summarized in Table 2.

Independent Prognostic Factors in Patients Who Underwent Curative Resection and Adjuvant Chemotherapy by Multivariate Cox Proportional Hazards Model

To determine the independent factors associated with the RFS of the patients with stage III colon cancer who underwent postoperative adjuvant chemotherapy, the significant prognostic factors identified on univariate analysis were applied to a Cox proportional hazards model. As a result, N2 [$P = 0.0216$ hazard ratio (HR) 2.39, 95% confidence interval (CI) 1.14–5.08] and v3 factor ($P = 0.032$, HR 2.51, 95% CI 1.08–5.59) was the remnant independent prognostic factor. Kaplan-Meier curve according to vascular invasion and lymph node metastasis for RFS are shown in Fig 2. With regard to vascular permeation, 3-year RFS was 77.8% and 44.4% in v0 through 2 and v3, respectively. With regard to lymph node metastasis, 3-year RFS was 80.2% and 54.1%, in N1 and N2, respectively.

Identification of High-Risk Patients With Stage III Colon Cancer Recurrence Who Underwent Postoperative Adjuvant Chemotherapy

Using candidate factors of v3 and N2 to predict RFS, we categorized the patients in a 2 × 2 combination and categorized them as group A (v0-2/N1); group B (v3/N1); group C (v0-2/N2); and group D (v3/N2). The Kaplan-Meier curve of each group on RFS is shown in Fig 3. Three-year RFS of each group was 84.1%, 56.3%, 61.3%, and 16.7%, respectively. Group D is considered definitely as a high-risk group for recurrence, even though adjuvant chemotherapy was administered to such patients, while group B and C exhibited intermediate risk for recurrence. Group A showed excellent prognosis in stage III colon cancer patients who underwent curative resection and postoperative adjuvant chemotherapy.

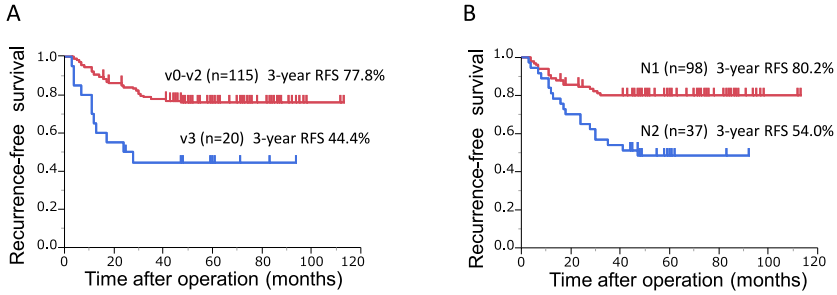

Fig. 2 Recurrence-free survival in stage III colon cancer patients who underwent curative colon resection and postoperative adjuvant chemotherapy according to (A) vascular invasion and (B) lymph node metastasis.

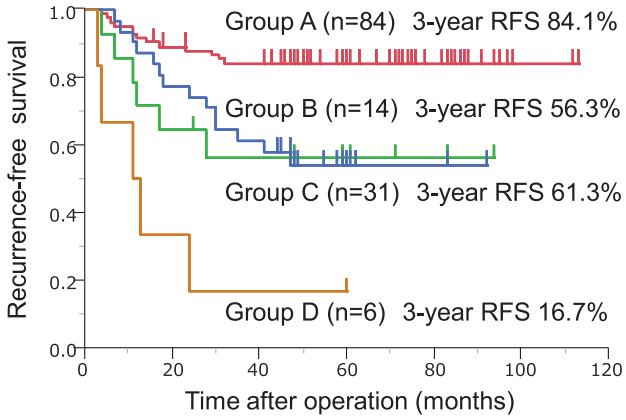

Fig. 3 Recurrence-free survival in stage III colon cancer patients who underwent curative colon resection and postoperative adjuvant chemotherapy by combining independent prognostic factors. Groups were defined as group A (v0-2/N1); group B (v3/N1); group C (v0-2/N2); and group D (v3/N2).

The details of the chemotherapeutic regimens of adjuvant therapy according prognostic group were shown in Fig 4A.

Initial Recurrence Sites and Timing in Stage III Colon Cancer Patients Who Underwent Curative Resection and Postoperative Adjuvant Therapy

Of the 135 patients in our study, 38 (28.1%) had recurrence and 23 died. Of the 38 patients, the initial recurrence sites were 10 in liver, 8 in lung, 6 in extra-regional lymph node, 4 in peritoneum, 4 in locoregion, and 1 in bone. Concurrent recurrence was alternatively found in 5 patients: in the liver and lung (n = 2); liver and peritoneum (n = 1); locoregion and extraregional lymph nodes (n = 1); and liver and extraregional lymph nodes (n = 1). There is no unique characteristic of recurrence sites according to each prognostic group.

The recurrence was found within 0 to 12 months after operation in 18 patients, 13 to 24 months in 10 patients, and 25 months or beyond in 10 patients. The patients with v3 factor tended to have earlier recurrence than in the other group [v3 factor group: 7 recurrences (64%) within 1 year after operation among the 11 patients; other group: 11 recurrences (41%) within 1 year after operation among the 27 patients].

Analysis of the Effectiveness of an Oxaliplatin-Containing Regimen According to the Risk Factor Candidate of the Recurrence

We analyzed the regimens for each group as we described. Among the patients in group A, 6 were administered an oxaliplatin-containing regimen and 78 were not; the 3-year RFS in this group was 100% and 83.1%, respectively. In group B, 1 patient was administered an oxaliplatin-containing regimen, and 13 patients were not; the 3-year RFS in this group was 100% and 52.8%, respectively. In group

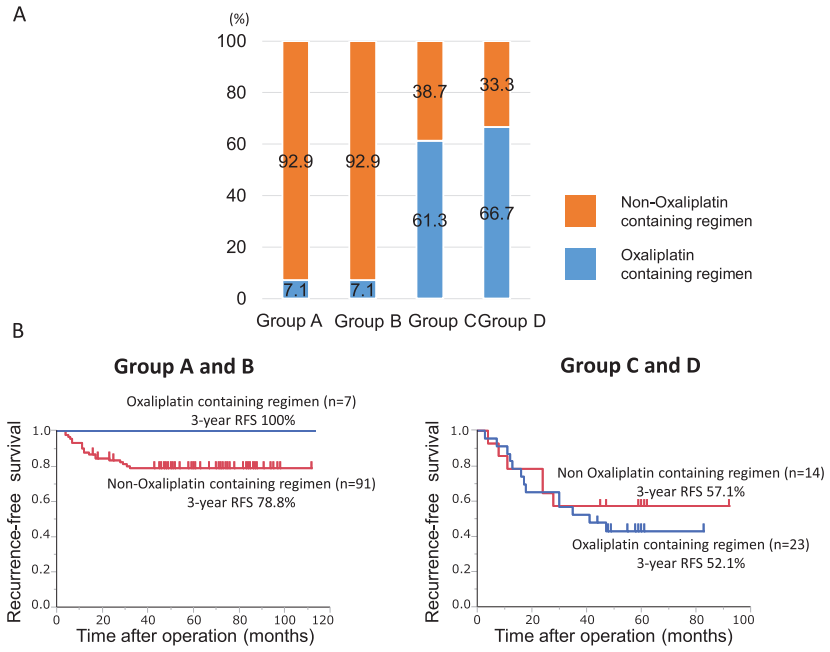

Fig. 4 Postoperative adjuvant therapy and survival outcomes. (A) The proportion of oxaliplatin- and non–oxaliplatin-containing regimens in each group. (B) Recurrence-free survival of N1 (groups A and B) and N2 (groups C and D) disease according to the chemotherapy regimen.

C, 19 patients were administered an oxaliplatin-containing regimen, and 12 were not; the 3-year RFS in this group was 57.9% and 66.7%, respectively. In group D, 4 patients were administered an oxaliplatin-containing regimen, and 2 were not; the 3-year RFS was 25.0% and 0%, respectively. Taking into account for lymph node metastasis, we also separately analyzed the effectiveness of the oxaliplatin between groups A and B and groups C and D (between N1 and N2). The Kaplan-Meier curve for RFS according to the regimen of the chemotherapy was shown in Fig 4B. An oxaliplatin-containing regimen seemed to be effective for the patients with N1, but not for N2 disease.

Discussion

Our aim of the current study was to identify a beneficial prognostic predictor that could enrich the patients who exhibited poor prognosis of the stage III colon cancer with curative resection and postoperative adjuvant chemotherapy. Today, the most potent regimen for the adjuvant chemotherapy of the stage III colon cancer is considered to be one containing oxaliplatin; however, every patient who requires adjuvant chemotherapy should not be administered this regimen, given its adverse effect of neurotic toxicity. Nevertheless, there has been no report that indicated the optimal regimen for these patients. Only the age of the patient is taken into account because the effectiveness of the oxaliplatin for elderly patients remains unclear,[11,12] while the opposite is true for nonelderly patients.[13,14] The prognostic predictors will thus play a key role in determining the optimal regimens for postoperative adjuvant chemotherapy.

There have been several reports actually predicting the recurrence of colon cancer. However, there is no study focusing only on patients with stage III colon cancer with adjuvant chemotherapy as far as we could search. This is the first report that shows the predictor of the recurrence for such patients with the latest clinical settings.

In our study, independent prognostic factors were identified as venous invasion (v3) and N2 in stage III colon cancer with curative resection and adjuvant therapy. Moreover, a combination of v3 and N2 could stratify prognosis definitely, supporting their prognostic independency. There have been several reports that showed the venous invasion as the predictor of poor prognosis of the colorectal cancer.[15,16] Tsai *et al*[15] reported the presence of vascular invasion ($P = 0.03$); perineural invasion ($P = 0.005$); and high postoperative CEA levels ($P = 0.001$) were demonstrated to be independent predictors of postoperative early relapse of stages I through III colon cancer patients. Shiono *et al*[16] reported venous invasion ($P = 0.02$) and aerogenous spread with floating cancer cell clusters ($P = 0.02$) were independent prognostic factors of the patient who underwent the complete resection of pulmonary metastasis of primary colorectal carcinoma.[16] In our group, 3-year RFS of stage III colon cancer patients with v3 positive was 44.4%, which itself seems to potentiate significantly high risk of recurrence, as v3-positive patients showed earlier recurrences than other patients. Although it is thought to be a useful prognostic predictor, we can identify only 20 patients (14.8%) who are exposed to the risk of recurrence by only using v3. On the other hand, the combination of the prognostic factors of v3 and N2 revealed 2 median-risk groups (B and C) and 1 high-risk group (D) for the recurrence. Using this classification, we could identify 51 (37%) patients facing the risk of the recurrence, which would be critical prognostic information to select the postoperative adjuvant chemotherapy.

Our analysis that compared patients who received oxaliplatin-containing adjuvant chemotherapeutic regimens in groups A and B with patients who didn't receive oxaliplatin, showed that there was no statistical significance as we described in Fig. 4B. However, the recurrence rate in the oxaliplatin-containing regimen was 0% in groups A and B. The oxaliplatin-containing regimen may have an advantage for inhibiting the recurrence in groups A and B (N1 group). Further analysis of cases outside the present study will be required to confirm this result; however, this finding is noteworthy. On the other hand, in groups C and D (N2 group), there was no difference between the oxaliplatin-containing group and the group that didn't contain oxaliplatin for recurrence. For the N2 group, the oxaliplatin-containing regimen might have no advantage for suppressing the recurrence.

The limitation of our research is the presence of selection bias. The selection of the adjuvant chemotherapy regimen for each patient was determined by each attending physician according to their preferred technique. Thus, our current result that v3 and N2 are independent factors associated with recurrence-free survival may not be presented as the sole prognostic factors representing poor prognosis. A prospective trial would be required to confirm the results. Nevertheless, it would be worth updating the prognostic outcome to identify the optimal

regimen and the predictor of poor prognosis among such patients. In fact, our current research indicated that the patient in group B was classified to a worse-prognosis group among N1 disease, and more potent adjuvant chemotherapy including oxaliplatin-containing regimens may be appropriate for such patients.

In conclusion, for further improvement of the prognosis of stage III colon cancer, the optimal choice of adjuvant chemotherapy and updating the prognostic factor would be important. Both v3 and pN2 may be critical prognostic factors in stage III colon cancer with the latest adjuvant chemotherapy. This information could elucidate areas of concern in the present therapeutic strategy and provide novel insights into stage III colon cancer patients with a poor prognosis.

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