Preoperative CRP(−)/CEA(−)/CA19-9(−)/non-T4 in Stage III Colorectal Cancer Is Favorable Risk for Recurrence

Mitsunori Ushigome, Hideaki Shimada, Tomoaki Kaneko, Yasuyuki Miura, Yasuo Nagashima, Takayuki Suzuki, Satoru Kagami, Akiharu Kurihara and Kimihiko Funahashi

Department of Surgery, Toho University School of Medicine, Tokyo, Japan

Abstract

Objectives: We evaluated the prognostic impact of a novel C-reactive protein (CRP) cut-off value (0.6 mg/dl) and carcinoembryonic antigen (CEA)/carbohydrate antigen 19-9 (CA19-9) in stage II/III colorectal cancer.

Methods: Four hundred ninety-eight patients with stage II (n = 275) or stage III (n = 223) colorectal cancer, surgically treated between January 2010 and December 2016, were analyzed. The optimal CRP cut-off value was fixed at 0.6 mg/dl to predict recurrence based on the receiver operating characteristic curve. Prognostic factors, including CRP/CEA/CA19-9 status, for relapse-free survival (RFS) were evaluated by multivariate analysis.

Results: Recurrent rates were 15% and 32% in stages II and III, respectively. In stage II, CRP, CEA, and CA19-9 were not significant prognostic factors for RFS. In stage III, the RFS of the low CRP group was significantly better than that of the high CRP group (p = 0.002). In stage III, the RFS of CRP(−)/CEA(−)/CA19-9(−) was significantly better than the other group, as opposed to the RFS of the CEA(−)/CA19-9(−) group that was not. The CRP(−)/CEA(−)/CA19-9(−) group recurrence rate in stage III was significantly better than the CRP(+)/CEA(−)/CA19-9(−) group (20% vs. 50%, p = 0.006). Multivariate analysis revealed that CRP(−)/CEA(−)/CA19-9(−) (p = 0.04) and non-T4 (p < 0.001) were good independent prognostic factors in stage III. The CRP(−)/CEA(−)/CA19-9(−)/non-T4 group recurrence rate in stage III was 11% (8 out of 73).

Conclusions: In stage III, the CRP(−)/CEA(−)/CA19-9(−)/non-T4 group is favorable risk for recurrence.

Keywords
CRP, CEA, CA19-9, colorectal cancer, relapse-free survival

Introduction

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) have been reported to be useful tumor markers for predicting postoperative prognosis in patients with colorectal cancer[1,2]. Previous reports have showed that CEA(+) and/or CA19-9(+) patients were at a high risk for recurrence[3]. In general, the CEA(−)/CA19-9(−) group has been considered the low-risk group for recurrence[4,5]; however, some of the double negative group in stage II/III cancer developed recurrence. Therefore, this double negative group needs to be evaluated with other biomarkers to predict postoperative prognosis more precisely.

C-reactive protein (CRP) (cut-off value = 1.0 mg/dl) has been used as the Glasgow prognostic score (GPS) to predict postoperative prognosis in colorectal cancer[6]. However,
certain Japanese studies have used a modified GPS value of 0.5 mg/dl as a cut-off value [7,8]. Previous reports have also used >1.0 mg/dl [9,10], >0.8 mg/dl [11], >0.5 mg/dl [12], or >0.3 mg/dl [13] as CRP cut-off values to classify the high CRP groups and evaluate the prognostic impact of high CRP in colorectal cancer. However, these cut-off values were not determined to predict postoperative prognosis by the receiver operating characteristic (ROC) curve. Moreover, previous reports have failed to show the usefulness of CRP when combined with CEA/CA19-9. Tumor markers and inflammatory biomarkers each reflect prognosis individually. However, only three research studies have evaluated prognosis in relation to the CRP/CEA/CA19-9 status [13-15], but without assessing the prognostic impact of CRP(−)/CEA(−)/CA19-9 (−).

Therefore, we determined the optimal CRP cut-off value based on the ROC curve to predict disease recurrence. Consequently, we investigated whether the combination status of CRP/CEA/CA19-9 could accurately predict the risk of recurrence in stage II/III colorectal cancer.

**Methods**

**Patients**

A total of 498 patients with consecutive stage II/III colorectal cancer, who were surgically treated at Toho University Hospital between January 2010 and December 2016, were enrolled in this retrospective study. Patients with neoadjuvant chemotherapy or chemoradiotherapy were excluded. A total of 288 (58%) men and 210 (42%) women with a median age of 69 (range, 34-92) years were included. TNM classification [16] was established by pathological evaluation of resected specimens. Two hundred seventy-five patients had stage II, and 223 patients had stage III. All patients were considered curable by resection of the primary tumor with D2 or more extended lymphadenectomy. Postoperative adjuvant chemotherapy was recommended for stage II patients with pathologic T4 and/or lymphovascular invasion and/or histology of poorly differentiated or mucinous type, and for stage III patients. Postoperative adjuvant chemotherapy was used in 52.8% (263) of all patients, with 37.8% (104) in stage II and 71.3% (159) in stage III. The standard regimens were as follows: oral fluoropyrimidines (capecitabine, tegafur-uracil + leucovorin) or oxaliplatin-based chemotherapy (CapeOX, mFOLFOX6) [17]. Patients were followed up by the end of 2020 or until death.

The procedures in this retrospective study were conducted in compliance with the Helsinki Declaration of 1964 and its later versions. The protocol for this retrospective study for medical record review was approved by the ethics committee of Toho University Omori Medical Center (approval nos. M21039, M20200, 20196, M19056, M18002). In this retrospective study, approval was obtained from the Omori Hospital Ethics Committee on the condition that the potential participants were given the opportunity to decline to be further enrolled in the study (opt-out) if written consent was not obtained from all participating patients. Details about this study were disclosed in our institutional website, and the potential participants were given an opportunity to opt-out of this study.

**Cut-off value of serum markers: CRP, CEA, and CA19-9**

In the current study, the optimal CRP (0.6 mg/dl) cut-off value was fixed by the ROC curve (Figure 1a). The area under the curve was 0.525. The cut-off value of CEA was 5.0 ng/ml, and CA19-9 levels were 37 U/ml in accordance with the manufacturer's instructions.

**Statistical analysis**

Comparisons of paired groups were performed with the Fischer's exact probability test. Survival probabilities after surgery were calculated by the Kaplan-Meier product limit method. Comparisons of clinicopathological factors associated with relapse-free survival (RFS) were evaluated by univariate analysis using log-rank test. Multivariate analyses were performed using Cox proportional hazards model. All statistical analyses were performed using EZR statistical software [18]. The p-values of <0.05 were considered statistically significant.

**Results**

T4 tumors significantly more frequently developed recurrence than T1-T3 tumors (p < 0.001). Furthermore, positive lymph nodes significantly more frequently developed recurrence than negative lymph nodes (p < 0.001). Although CEA(+)/CA19-9(+) was associated with disease recurrence, CRP(+) was not significantly associated. The remaining clinicopathological factors were not associated with recurrence (Table 1).

**Comparisons of RFS according to each CRP cut-off level**

Figure 1a shows the ROC curve for recurrent events using preoperative CRP values. We used the log-rank test to identify the risk of recurrence for each cut-off value of CRP (0.3, 0.6, and 1.0 mg/dl). The definition for each cut-off value was as follows: the 0.3 mg/dl cut-off value was the clinically abnormal value used in the test (Figure 1b); the 0.6 mg/dl cut-off value was the value obtained by the ROC curve in this study (Figure 1c); and the 1.0 mg/dl cut-off value was the value used in the GPS. As shown in Figure 1d, there was a significant difference in RFS between the low and high CRP groups, CRP(−) versus CRP(+) using the 0.6 and 1.0 mg/dl CRP cut-off values (Figure 1c, d).
Figure 1. Comparisons of relapse-free survival according to each cut-off levels of preoperative C-reactive protein in patients with colorectal cancer. (b) Cut-off = 0.3 mg/dl, (c) cut-off = 0.6 mg/dl, (d) cut-off = 1.0 mg/dl.

(a) The ROC curve for recurrent events using preoperative CRP values. The optimal point was that the CRP value was 0.6 mg/dl (sensitivity, specificity, and AUC were 0.366, 0.720, and 0.525, respectively.). The CRP cut-off values were set to 0.3, 0.6, and 1.0 mg/dl. The $p$-values at the cut-off values of 0.6 and 1.0 mg/dl were 0.007 and 0.020, respectively, with significant differences (c, d). The $p$-values were based on the log-rank test. ROC: receiver operating characteristic, AUC: area under the curve

**Comparison of RFS according to the CRP/CEA/CA19-9 status**

Figure 2 shows the RFS of four groups according to the status of CRP/CEA and CRP/CA19-9. The CRP(+)/CEA(-) group showed a similar prognosis to the CRP(-)/CEA(+) group (Figure 2a). However, the CRP(-)/CA19-9(-) group showed the best prognosis among the four groups. Similarly, the CRP(+)/CA19-9(+) group showed a similar prognosis to the CRP(-)/CA19-9(+) group (Figure 2b), and the CRP(-)/CA19-9(-) group showed the best prognosis among the four groups.

**Comparisons of RFS between the CRP(+) and CRP(-) groups using a cut-off value of 0.6 mg/dl**

In patients with stage II, CRP(-) revealed a better RFS than CRP(+); however, the difference was not significant (Figure 3a). Furthermore, in patients with stage III, CRP(-) revealed a significantly better RFS than CRP(+) ($p = 0.002$) (Figure 3b).

**Comparisons of RFS according to the status of CRP and tumor markers**

The upper and lower panels of Figure 4 highlight the RFS of patients with stage II (Figure 4a-d) and stage III (Figure 4e-h), respectively. The blue lines demonstrate the prognosis for patients with negative serum biomarker sets, that is, CRP (-)/CEA(-), CRP(-)/CA19-9(-), CEA(-)/CA19-9(-), and CRP(-)/CEA(-)/CA19-9(-). In contrast, the black lines demonstrate the prognosis for patients with positive serum
Table 1. Clinicopathological Features of Patients with or without Recurrence of Colorectal Cancer.

| Variables                        | Total n = 498 | No recurrence n = 386 | Recurrence n = 112 | p-value* |
|----------------------------------|---------------|-----------------------|--------------------|----------|
| Age, median (range)              |               |                       |                    |          |
| ≥75                              | 174           | 134                   | 40                 | 0.91     |
| <75                              | 324           | 252                   | 72                 |          |
| ≥65                              | 357           | 278                   | 79                 | 0.81     |
| <65                              | 141           | 108                   | 33                 |          |
| Gender                           |               |                       |                    |          |
| Male                             | 288           | 228                   | 60                 | 0.33     |
| Female                           | 210           | 158                   | 52                 |          |
| Location                         |               |                       |                    |          |
| Colon                            | 330           | 250                   | 80                 | 0.21     |
| Rectum                           | 168           | 136                   | 32                 |          |
| Histology                        |               |                       |                    |          |
| Tubular 1, 2                     | 461           | 358                   | 103                | 0.84     |
| Mucinous, poorly                 | 37            | 28                    | 9                  |          |
| T factor                         |               |                       |                    |          |
| T1, T2, T3                       | 365           | 304                   | 61                 | <0.001   |
| T4                               | 133           | 82                    | 51                 |          |
| Lymph node metastasis           |               |                       |                    |          |
| Negative                         | 275           | 235                   | 40                 | <0.001   |
| Positive                         | 223           | 151                   | 72                 |          |
| (N1/N2, N3) (180/43) (125/26) (55/17) |   |                       |                    |          |
| Stage                            |               |                       |                    |          |
| II                               | 275           | 235                   | 40                 | <0.001   |
| III                              | 223           | 151                   | 72                 |          |
| Adjuvant chemotherapy            |               |                       |                    |          |
| No                               | 235           | 193                   | 42                 | 0.02     |
| Yes (non-OX/OX) (122/141) (88/105) (34/36) |   |                       |                    |          |
| CEA (cut-off = 5.0 ng/ml)        |               |                       |                    |          |
| Negative                         | 276           | 224                   | 52                 | 0.04     |
| Positive                         | 224           | 164                   | 60                 |          |
| CA19-9 (cut-off = 37.0 U/ml)     |               |                       |                    |          |
| Negative                         | 438           | 346                   | 92                 | 0.05     |
| Positive                         | 60            | 40                    | 20                 |          |
| CRP (mg/dl), mean (range)        | 0.83 (0–15.6) | 1.30 (0–24.7)         | 0.06*              |          |
| CRP (cut-off = 0.3 mg/dl)        | Negative 262  | 204                   | 58                 | 0.91     |
| Positive                         | 236           | 182                   | 54                 |          |
| CRP (cut-off = 0.6 mg/dl)        | Negative 349  | 278                   | 71                 | 0.10     |
| Positive                         | 149           | 108                   | 41                 |          |
| CRP (cut-off = 1.0 mg/dl)        | Negative 401  | 314                   | 87                 | 0.42     |
| Positive                         | 97            | 72                    | 25                 |          |
| Albumin (g/dl), mean (range)     | 3.59 (1.7–4.9)| 3.58 (1.2–4.7)        | 0.91*              |          |
| GPS                              |               |                       |                    |          |
| 0                                | 311           | 239                   | 72                 | 0.46     |
| 1                                | 104           | 85                    | 19                 |          |
| 2                                | 83            | 62                    | 21                 |          |

* Fisher’s exact probability test. # Student’s t-test. GPS: Glasgow prognostic score, OX: oxaliplatin-based chemotherapy
Figure 2. Comparison of relapse-free survivals according to the CRP/CEA/CA19-9 status. RFS of four groups according to the status of CRP/CEA and CRP/CA19-9 in stage II/III. The CRP (−)/CEA (−) and CRP (−)/CEA (−) groups showed the best prognosis among the four groups in each analysis. The p-values were based on the log-rank test.

Figure 3. Comparisons of relapse-free survival between the CRP (+) and CRP (−) groups using a cut-off value of 0.6 mg/dl. In stage II, CRP (−) revealed a better RFS than CRP (+); however, the difference was not significant (a). In stage III, CRP (−) revealed significantly better RFS than CRP (+) (p = 0.002) (b). The p-values were based on the log-rank test. CI: confidence interval.

Biomarkers in one or more of the biomarker sets. In patients with stage II, no statistical differences were identified between the two groups (Figure 4a-d). In patients with stage III, the RFS of the double negative or triple negative group showed a better prognosis than that of the non-double negative or non-triple negative group. When CRP was included in the analysis, the RFS indicated by the blue line was significantly improved compared to the RFS indicated by the black line, p = 0.002, p < 0.001, and p = 0.003, respectively (Figure 4e-h). In contrast, when CRP was not included in the analysis, the difference was not statistically significant (p = 0.12, Figure 4g).

Univariate and multivariate analyses to evaluate the prognostic impact of the clinicopathological factors for RFS in stage III patients (Table 2)

In Model A, CEA (−) alone, CA19-9 (−) alone, and CRP (−) alone were not noted as independent factors, as opposed to non-T4 that was the only good independent prognostic factor (p < 0.001). Similarly, in Model B, CA19-9 (−)/CEA...
Figure 4. Comparisons of relapse-free survival according to the status of CRP and tumor markers. The RFS of patients with stage II (a, b, c, d) and stage III (e, f, g, h) in the upper and lower panels, respectively. The blue lines demonstrate the prognosis for the patients with negative serum biomarker sets. The black lines demonstrate the prognosis for the patients with positive serum biomarkers in one or more of the biomarker sets. In patients with stage II, no statistical differences were identified between the two groups (a, b, c, d). In patients with stage III, the RFS of the double-negative or triple-negative group showed a better prognosis than that of the non-double-negative or non-triple-negative group. However, the analysis used only tumor markers not including CRP; the difference was not statistically significant ($p = 0.12$, g). The $p$-values were based on the log-rank test. CI: confidence interval

Figure 5a shows the number of stage III patients and recurrence rates in each subgroup classified by the CRP status and tumor markers

Figure 5b shows the number of recurrence patients and the recurrence rates of each subgroup in stage III. In stage III, the recurrence rates of the CRP(−), CEA(−), and CA19-9(−) groups were 46%, 39%, and 47%, respectively, which were higher than that of the CRP(−)/CEA(−)/CA19-9(−) group (Figure 5a). Furthermore, the recurrence rate of the CRP(−)/CEA(−)/CA19-9(−) group was the lowest among the subgroup (Group H in Figure 5b), and the recurrence rate of the CRP(−)/CEA(−)/CA19-9(−) group was significantly lower than that of the non-CRP(−)/CEA(−)/CA19-9(−) group (20% vs. 40%, $p = 0.001$). Finally, the recurrence rate of the CRP(−)/CEA(−)/CA19-9(−) group was also significantly lower than that of the CRP(+)/CEA(+)/CA19-9(−) group (20% vs. 50%, $p = 0.006$).

Recurrence rates and RFS of groups according to risk factors in stage III

Recurrence rates of each subgroup in stage III are compared in Figure 6a. Among the non-T4 group, the recurrence rate of CRP(−)/CEA(−)/CA19-9(−) was only 11% (8 out of 73), and the recurrence rate of non-CRP(−)/CEA(−)/CA19-9(−) was 35% ($p < 0.001$). The recurrence rate in the group
Table 2. Univariate and Multivariate Analyses to Evaluate the Prognostic Impact of the Clinicopathological Factors for Relapse-Free Survival in Stage III.

| Model A | Variables | Univariate | Multivariate |
|---------|-----------|------------|--------------|
|         |           | p-value | Hazard ratio | 95% CI | p-value** |
| Age (years): 75/>=75 | 0.16 | 0.77 | 0.46–1.30 | 0.33 |
| Location: colon/rectum | 0.17 | 1.06 | 0.64–1.76 | 0.83 |
| T factor: T1, T2, T3/T4 | <0.001 | 0.38 | 0.23–0.62 | <0.001 |
| N factor: N1/N2, N3 | 0.17 | 0.70 | 0.39–1.25 | 0.23 |
| Histology: Tub1, Tub2/poorly, mucinous | 0.09 | 0.50 | 0.22–1.11 | 0.09 |
| Adjuvant chemotherapy: (+)/(−) | 0.46 | 0.89 | 0.51–1.54 | 0.68 |
| CEA (cut-off = 5 ng/ml): negative/positive | 0.13 | 0.98 | 0.60–1.61 | 0.95 |
| CA19-9 (cut-off = 37 U/ml): negative/positive | 0.03 | 0.66 | 0.36–1.22 | 0.19 |
| CRP (cut-off = 0.6 mg/dl): negative/positive | 0.002 | 0.64 | 0.39–1.07 | 0.09 |

| Model B | Variables | p-value* | Hazard ratio | 95% CI | p-value** |
|---------|-----------|------------|--------------|-------|----------|
| Age (years): 75/>=75 | 0.16 | 0.78 | 0.47–1.31 | 0.35 |
| Location: colon/rectum | 0.17 | 1.17 | 0.71–1.91 | 0.54 |
| T factor: T1, T2, T3/T4 | <0.001 | 0.33 | 0.21–0.53 | <0.001 |
| N factor: N1/N2, N3 | 0.17 | 0.70 | 0.40–1.23 | 0.22 |
| Histology: Tub1, Tub2/poorly, mucinous | 0.09 | 0.52 | 0.24–1.15 | 0.11 |
| Adjuvant chemotherapy: (+)/(−) | 0.46 | 0.89 | 0.52–1.51 | 0.65 |
| CEA (−) and CA19-9 (−): Yes/No | 0.12 | 0.85 | 0.53–1.37 | 0.51 |

| Model C | Variables | p-value* | Hazard ratio | 95% CI | p-value** |
|---------|-----------|------------|--------------|-------|----------|
| Age (years): 75/>=75 | 0.16 | 0.77 | 0.46–1.29 | 0.33 |
| Location: colon/rectum | 0.17 | 1.09 | 0.66–1.78 | 0.75 |
| T factor: T1, T2, T3/T4 | <0.001 | 0.36 | 0.23–0.58 | <0.001 |
| N factor: N1/N2, N3 | 0.17 | 0.68 | 0.40–1.17 | 0.17 |
| Histology: Tub1, Tub2/poorly, mucinous | 0.09 | 0.49 | 0.22–1.09 | 0.08 |
| Adjuvant chemotherapy: (+)/(−) | 0.46 | 0.90 | 0.53–1.54 | 0.70 |
| CRP (0.6 mg/dl >), CEA (−), and CA19-9 (−): Yes/No | 0.003 | 0.60 | 0.34–0.98 | 0.04 |

*p-Log-rank test. **Cox proportional hazard model. CI: confidence interval

with the T4 factor was 55%. RFS of the three subgroups is shown in Figure 6b. Among the non-T4 group, the RFS of the CRP(−)/CEA(−)/CA19-9(−) group was significantly better than that of the non-CRP(−)/CEA(−)/CA19-9(−) group (p < 0.001).

**Discussion**

In the present study, we determined that 0.6 mg/dl was the new appropriate cut-off value of CRP based on the ROC curve. Consequently, we found that the CRP(−)/CEA(−)/CA 19-9(−) status could accurately predict the favorable risk of recurrence in stage III colorectal cancer.

The cut-off value of 0.6 mg/dl used in this study was fixed by using the ROC curve. Compared to previous reports, the 0.6 mg/dl value may be an appropriate cut-off value in colorectal cancer. The majority of previous reports, associated with GPS and CRP values, have used a cut-off value of 1.0 mg/dl, and which probably used the same values for GPS scoring. GPS was first reported in a study of non-small cell lung carcinoma[19]. The cut-off value of 1.0 mg/dl for CRP used in that study is useful, but it is not a value calculated using the ROC curves or any other similar methods. In contrast, our present study reveals that a CRP cut-off value of 0.6 mg/dl was firstly determined by the ROC curve. Thus, 0.6 mg/dl clearly reflects recurrence risk in colorectal cancer.

Although previous reports have evaluated the prognostic impact of GPS/CEA, information about the prognostic impact of CRP/CEA/CA19-9 in colorectal cancer is limited. There may be differences in the prognostic mechanisms between tumor markers secreted by the tumor and inflammatory responses based on hypercytokinemia resulting from host-tumor interactions[14]. However, when tumor markers and CRP are combined, CRP may predict prognosis, especially in the CEA(−)/CA19-9(−) group, which represents approximately 40% of all patients with colorectal cancer. Actually, based on our present study, the RFS in the CRP(−)/CEA(−) group or the CRP(−)/CA19-9(−) group was better than any other groups. On a different note, the fact that the RFS of CRP(+)/CEA(+) was not the same as that of CRP (+)/CA19-9(+) may indicate a difference in the prognostic impact of these tumor markers. This may be due to the fact that prognosis in the CA19-9(+) group is generally consid-
Figure 5. Number of patients and recurrence rates in each group classified by the status of CRP and tumor markers.

(a) The number of stage III patients and recurrence rates in the following subgroups: CEA (+), CA19-9 (+), CRP (+), CRP (−)/CEA (−)/CA19-9 (−), and non-CRP (−)/CEA (−)/CA19-9 (−). Patients with CEA (−)/CA199 (−) were divided into two subgroups: Group G, in which CRP is positive, and Group H, in which CRP is also negative. (b) The number of recurrence patients and the recurrence rates of each subgroup in stage III. The gray bars show the positive rates of the subgroups included in the CRP (+) group. The blue bar shows the recurrence rate (20%) of Group H that is the lowest among the subgroup. The recurrence rate of Group H was significantly lower than that of Group I \((p = 0.001)\). Furthermore, the recurrence rate of Group H was significantly lower than that of Group G \((p = 0.006)\). The \(p\)-values were based on Fisher’s exact test. Rec: recurrent, Group A: CRP (−)/CEA (+)/CA19-9 (−) group, Group B: CRP (+)/CEA (+)/CA19-9 (−) group, Group C: CRP (+)/CEA (+)/CA19-9 (−) group, Group D: CRP (−)/CEA (+)/CA19-9 (−) group, Group E: CRP (−)/CEA (−)/CA19-9 (−) group, Group F: CRP (+)/CEA (−)/CA19-9 (−) group, Group G: CRP (+)/CEA (+)/CA19-9 (−) group, Group H: CRP (−)/CEA (−)/CA19-9 (−) group, Group I: non-CRP (−)/CEA (−)/CA19-9 (−) group.

CRP was remarkable. It is possible that even a slight elevated level of IL-6 may affect the respective prognosis. Conversely, if CRP is <0.6 mg/dl, the recurrence rate is significantly low even in stage III. Consequently, CRP (−) is a very important indicator of better RFS in stage III with CEA(−)/CA19-9(−).

In conclusion, we showed that the recurrence rate of CRP (−)CEA(−)CA19-9(−)non-T4 was low even in stage III colorectal cancer. Therefore, predicting recurrence with preoperative CRP, CEA, CA19-9, and pathological T-factors may be useful for postoperative surveillance in patients with stage III colorectal cancer.
Recurrence rates and relapse-free survival of groups according to risk factors in stage III.

Recurrence rates of each subgroup in stage III were compared in (a). Among the non-T4 group, the recurrence rate of CRP (−)/CEA (−)/CA19-9 (−) was only 11% (8 out of 73), and the recurrence rate of non-CRP (−)/CEA (−)/CA19-9 (−) was 35% (*p* < 0.001). The recurrence rate in the group with the T4 factor was 55%. (b) The RFS compared among the three subgroups. Among the non-T4 group, the RFS of the CRP (−)/CEA (−)/CA19-9 (−) group was significantly better than that of the non-CRP (−)/CEA (−)/CA19-9 (−) group (*p* < 0.001). The *p*-values in (a) were based on the Fisher’s exact test. The *p*-values in (b) were based on the log-rank test.

Figure 6. Recurrence rates and relapse-free survival of groups according to risk factors in stage III.

Acknowledgements
The authors would like to thank MARUZEN-YUSHODO Co., Ltd. (https://kw.maruzen.co.jp/kousei-honya ku/) for the English language editing.

Conflicts of Interest
There are no conflicts of interest.

Author Contributions
MU, HS, and KF conceived and designed the current study. MU, TK, YM, YN, and AK contributed to the acquisition of the patient’s clinicopathological data. MU, TS, and HS analyzed the patient data. MU and HS drafted the manuscript. All authors read and approved the final manuscript.

Approval by Institutional Review Board (IRB)
Approval code issued by the institutional review board: M21039, M20200, 20196, M19056, M18002
The name of the institution that granted the approval: the ethics committee of Toho University Omori Medical Center

Disclaimer
Kimihiko Funahashi is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal’s Editorial Board. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

272
References

1. Yang XQ, Chen C, Wang FB, et al. Preoperative serum carcinoembryonic antigen, carbohydrate antigen19-9 and carbohydrate antigen 125 as prognostic factors for recurrence-free survival in colorectal cancer. Asian Pac J Cancer Prev. 2011 Jun; 12(5): 1251-6.

2. Baqar AR, Wilkins S, Staples M, et al. The role of preoperative CEA in the management of colorectal cancer: a cohort study from two cancer centres. Int J Surg. 2019 Apr; 64: 10-5.

3. Ushigome M, Shimada H, Miura Y, et al. Changing pattern of tumor markers in recurrent colorectal cancer patients before surgery to recurrence: serum p53 antibodies, CA19-9 and CEA. Int J Clin Oncol. 2020 Apr; 25(4): 622-32.

4. Basbug M, Arikanoglu Z, Bulbulner N, et al. Prognostic value of preoperative CEA and CA 19-9 levels in patients with colorectal cancer. Hepatogastroenterology. 2011 Mar-Apr; 58(106): 400-5.

5. Shibutani M, Maeda K, Nagahara H, et al. Significance of CEA and CA19-9 combination as a prognostic indicator and for recurrence monitoring in patients with stage II colorectal cancer. Anticancer Res. 2014 Jul; 34(7): 3753-8.

6. He L, Li H, Cai J, et al. Prognostic value of the Glasgow prognostic score or modified Glasgow prognostic score for patients with colorectal cancer receiving various treatments: a systematic review and meta-analysis. Cell Physiol Biochem. 2018; 51(3): 1237-49.

7. Toiyama Y, Miki C, Inoue Y, et al. Evaluation of an inflammation-based prognostic score for the identification of patients requiring postoperative adjuvant chemotherapy for stage II colorectal cancer. Exp Ther Med. 2011 Jan; 2(1): 95-101.

8. Inoue Y, Iwata T, Okugawa Y, et al. Prognostic significance of a systemic inflammatory response in patients undergoing multimodality therapy for advanced colorectal cancer. Oncology. 2013; 84 (2): 100-7.

9. McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg. 2003 Feb; 90(2): 215-9.

10. Ishizuka M, Nagata H, Takagi K, et al. C-reactive protein is associated with distant metastasis of T3 colorectal cancer. Anticancer Res. 2012 Apr; 32(4): 1409-15.

11. Nozoe T, Matsumata T, Kitamura M, et al. Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. Am J Surg. 1998 Oct; 176(4): 335-8.

12. Koike Y, Miki C, Okugawa Y, et al. Preoperative C-reactive protein as a prognostic and therapeutic marker for colorectal cancer. J Surg Oncol. 2008 Dec; 98(7): 540-4.

13. Guo G, Chen X, He W, et al. Establishment of inflammation biomarkers-based nomograms to predict prognosis of advanced colorectal cancer patients based on real world data. PLoS One. 2018 Dec; 13(12): e0208547.

14. Ishizuka M, Nagata H, Takagi K, et al. Inflammation-based prognostic system predicts postoperative survival of colorectal cancer patients with a normal preoperative serum level of carcinoembryonic antigen. Ann Surg Oncol. 2012 Oct; 19(11): 3422-31.

15. Peltonen R, Gramkow MH, Dehlendorff C, et al. Elevated serum YKL-40, IL-6, CRP, CEA, and CA19-9 combined as a prognostic biomarker panel after resection of colorectal liver metastases. PLoS One. 2020 Aug; 15(8): e0236569.

16. Japanese Society for Cancer of the Colon and Rectum. Japanese classification of colorectal, appendiceal, and anal carcinoma: the 3rd English edition [secondary publication]. J Anus Rectum Colon. 2019 Oct; 3(4): 175-95.

17. Koike J, Funahashi K, Yoshimatsu K, et al. Efficacy and safety of neoadjuvant chemotherapy with oxaliplatin, 5-fluorouracil, and levofolinate for T3 or T4 stage II/III rectal cancer: the FACT trial. Cancer Chemother Pharmacol. 2017 Mar; 79(3): 519-25.

18. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant. 2013 Mar; 48(3): 452-8.

19. Forrest LM, McMillan DC, McArdle CS, et al. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2003 Sep; 89(6): 1028-30.

20. Matsuda C, Ishiguro M, Teramukai S, et al. A randomised-controlled trial of 1-year adjuvant chemotherapy with oral tegafur-uracil versus surgery alone in stage II colon cancer: SACURA trial. SACURA Study Group. Eur J Cancer. 2018 Jun; 96: 54-63.

21. André T, Meyerhardt J, Iveson T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol. 2020 Dec; 21(12): 1620-9.

22. Kinoshita T, Ito H, Miki C. Serum interleukin-6 level reflects the tumor proliferative activity in patients with colorectal carcinoma. Cancer. 1999 Jun; 85(12): 2526-31.

23. Kinoshita A, Onoda H, Imai N, et al. C-reactive protein as a prognostic marker in patients with hepatocellular carcinoma. Hepatogastroenterology. 2015 Jun; 62(140): 966-70.