Original Research Article

Prognostic Value of Preoperative Carcinoembryonic Antigen and Carbohydrate Antigen 19-9 Levels for Adjuvant Chemotherapy in Stage II Colorectal Cancer: A Nationwide Multicenter Retrospective Study

Suguru Ogata1, Fumihiko Fujita1, Kenji Fujiyoshi1, Tomoya Sudou1, Takefumi Yoshida1, Kenichi Koushi1, Kenta Murotani2, Shinichi Yamauchi3, Kenichi Sugihara3 and Yoshito Akagi1

1) Department of Surgery, Kurume University School of Medicine, Fukuoka, Japan
2) Biostatistics Center, Kurume University, Fukuoka, Japan
3) Department of Surgery, Tokyo Medical and Dental University, Tokyo, Japan

Abstract

Objectives: Adjuvant chemotherapy for stage II colorectal cancer patients with high-risk factors for recurrence can be useful; however, its advantage in prognosis remains to be controversial. Thus, in this study, we aimed to assess whether a combination of preoperative serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels can predict the prognosis and advantage of adjuvant chemotherapy.

Methods: Using a Japanese nationwide database, in total, 3,688 patients with curative resected stage II colorectal cancer were registered retrospectively between 2008 and 2012 in 24 referral institutions. Patients were classified into three groups as follows: Group A (both non-high levels of CEA and CA19-9), Group B (either high levels of CEA or CA19-9), and Group C (both high levels of CEA and CA19-9).

Results: Multivariable Cox regression analysis, adjusting the depth of tumor invasion, number of dissected lymph nodes, tumor differentiation, lymphatic and venous invasion, and other covariates, showed that the 5-year disease-free survival and overall survival were shorter in Group C than in Groups A and B. Furthermore, in Group C, the 5-year disease-free survival rate was improved in the surgery-plus-AC group compared to the surgery-alone group.

Conclusions: As with existing high-risk factors for recurrence, the combination assessment of preoperative serum CEA and CA19-9 can predict the prognosis for colorectal cancer. Adjuvant chemotherapy may provide a prolonged disease-free survival advantage in stage II colorectal cancer patients with high levels of both tumor markers.

Keywords: colorectal cancer, risk assessment, prognostic factor, adjuvant chemotherapy, biomarkers

Introduction

Radical resection has been determined as the standard therapy for stage II colorectal cancer (CRC). However, the postoperative 5-year recurrence rate has been reported to range from 7.9% to 22%[1]. To prevent postoperative recurrence, adjuvant chemotherapy (AC) is generally considered. An integrative analysis of three randomized controlled trials for stage II-III CRC in Western countries showed that the surgery-plus-AC group demonstrated prolonged disease-free survival (DFS) and overall survival (OS) compared to the surgery-alone group. This emphasizes the advantage of AC...
for stage III CRC, which could be established as an international standard therapy[2]. In contrast, it remains controversial whether AC for stage II CRC prolongs DFS and OS[3,4]. Current international consensus does not recommend performing AC for all cases of stage II CRC due to its limited benefits[5]. As stage II CRC includes subgroups with different prognoses, various major international guidelines[6-9] identify high-risk factors for recurrence and recommend considering AC for those cases. Nonetheless, clear evidence on whether AC for stage II CRC with high-risk factors can prolong DFS and OS remains to be limited[10,11]. Moreover, 76% of the patients with stage II CRC have at least one high-risk factor[12], indicating potential overtreatment if AC was administered to all patients with at least one high-risk factor[13]. Therefore, it is important to investigate the potential risk factors for recurrence and survival in stage II CRC to determine whether AC is beneficial.

Tumor marker tests are minimally invasive blood tests commonly performed in laboratories that enable an objective assessment compared to histopathological tests. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are well-known tumor markers used in CRC diagnosis[14]. As per the European Society for Medical Oncology (ESMO) guidelines, high levels of preoperative serum CEA can be a high-risk factor for stage II CRC recurrence and a predictive factor for recurrence after surgery[15,16]. However, the role of CEA as a high-risk factor for recurrence is yet to be clarified in the US[6,8] and Japanese[5] guidelines. Not only CEA but also high levels of preoperative serum CA19-9 have been associated with poor prognosis[17,18]. Therefore, we focused on the potential of the combined utilization of these tumor markers.

This study used a Japanese nationwide database to validate whether a combination assessment of preoperative serum CEA and CA19-9 levels could be a useful guide to predict recurrence and evaluate the effectiveness of AC in stage II CRC.

**Methods**

**Study design and setting**

This study used the Japanese Study Group for Postoperative Follow-Up of Colorectal Cancer (JFUP-CRC) database, which contains retrospectively collected data from all consecutive patients with stage I to III CRC who underwent curative surgical resection between 2008 and 2012 at 24 affiliated referral institutions (see Acknowledgments). This study was approved by the Institutional Review Board or Ethics Committee at each hospital (approval number: M2017-268) and was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research. All patients provided written informed consent.

**Participants**

In total, 11,703 patients with CRC and 3,688 with pathological stage II CRC and available medical information regarding clinicopathological findings, AC treatment, and prognosis and for whom curative resection was performed were included in this study (Figure 1).

**Tumor markers**

The cut-off values for CEA and CA19-9 were 5.0 ng/mL and 37.0 U/mL, respectively. The patients were classified into three groups as follows: Group A (both preoperative serum CEA levels ≤5.0 ng/mL and serum CA19-9 levels ≤37.0 U/mL), Group B (either preoperative serum CEA levels >5.0 ng/mL or serum CA19-9 levels >37.0 U/mL), and Group C (both preoperative serum CEA levels >5.0 ng/mL and serum CA19-9 levels >37.0 U/mL).

**High-risk factors for recurrence**

The high-risk factors for recurrence have been reported in the American Society of Clinical Oncology (ASCO), ESMO, Japanese Society for Cancer of the Colon and Rectum (JSCCR), and National Comprehensive Cancer Network (NCCN) guidelines. In this study, T4 depth of tumor invasion, poorly differentiated histology, positive venous invasion, positive lymphatic invasion, and a number of dissected lymph nodes <12 were considered as high-risk factors.

**Outcomes**

The primary endpoint was DFS, which is defined as the time from the date of CRC resection to recurrence, second cancers, or death, whichever occurred first. Second cancers included metachronous cancers that developed in both the colorectum and other organs. The secondary endpoint was OS, which is defined as the time between CRC resection and death from any cause.

**Statistical analyses**

Categorical variables are presented as frequencies and percentages. Patients with unknown or missing data were excluded from the statistical comparisons. Univariate and multivariable Cox regression models were used for survival analyses. For the comparison of multivariable Cox regression models, the concordance index (C-index) for DFS was calculated. The DFS and OS rates were calculated using Kaplan-Meier methods, whereas the log-rank test was used to detect any differences in the survival rates. Covariates used for multivariable models included depth of tumor invasion (T3 vs. T4), tumor differentiation (well to moderate vs. poor), venous and lymphatic invasion (negative vs. positive), number of dissected lymph nodes (<12 vs. ≥12), age (<75 vs. ≥75 years), sex (male vs. female), tumor location (colon...
vs. rectum), performance status (0-1 vs. 2-4), lymph node dissection level (paraintestinal lymph node dissection [D1] and intermediate lymph node dissection [D2] vs. main lymph node dissection [D3]), AC/no AC (surgery-alone vs. surgery-plus-AC), and preoperative CEA and CA19-9 levels. P < 0.05 was considered statistically significant. All the statistical analyses were performed using JMP statistical software (version 16.0; SAS Institute Inc., Cary, NC, USA) and R 4.0.3 with the rms and Hmisc packages (R Project for Statistical Computing, Vienna, Austria, www.r-project.org).

Results

Patient characteristics

Among the 3,688 patients with stage II CRC, 2,587 (70%) patients were aged <75 years, and 2,201 (60%) patients were males. T4 depth of tumor invasion was seen in 952 (26%) patients, while 326 (9%) had poorly differentiated histology. Venous and lymphatic invasions were observed in 2,464 (67%) and 1,470 (40%) patients, respectively. The number of patients with <12 dissected lymph nodes was 614 (17%). AC was performed in 580 (16%) patients. Uracil-tegafur/leucovorin (UFT/LV) was the most frequent regimen in this study (69%), followed by capecitabine (10%), tegafur-gimeracil-oteracil (S-1: 6%), 5-fluorouracil and oxaliplatin (FOLFOX; 5%), capecitabine and oxaliplatin (CAPOX; 2%), and 5-fluorouracil (5FU)/LV (1%).

There were 2,187 (59%) patients in Group A, 1,226 (33%) in Group B, and 275 (8%) in Group C. Among these three groups, patients aged ≥75 years (P = 0.0001), exhibiting T4 depth of tumor invasion (P < 0.0001), poorly differentiated histology (P = 0.03), and venous invasion (P < 0.0001) were significantly frequent in Group C. Regarding AC regimens, no significant difference was observed among the three groups (Table 1).

Association between tumor markers and prognosis

Among the 3,688 patients, 558 (15%) had a recurrence, whereas 545 (15%) reportedly died of all causes. Table 2 shows DFS and OS in different tumor marker combination groups. Regarding DFS and OS, Groups B and C were associated with shorter prognosis than Group A (DFS: Group C, hazard ratio [HR]: 2.16, 95% confidence interval [CI]: 1.67-2.79; Group B, HR: 1.47, 95% CI: 1.24-1.74, P<0.0001; OS: Group C, HR: 2.71, 95% CI: 2.01-3.67; Group B, HR: 1.59, 95% CI: 1.28-1.97, P<0.0001) (Table 2). The C-index of Group C was 0.62 (95% CI: 0.59-0.64), and those of other variables such as T4 depth of invasion, poorly differentiated histology, positive venous and lymphatic invasion, and the number of dissected lymph nodes <12, are shown in Supplementary Table S1.

Furthermore, the Kaplan-Meier curves showed shorter 5-year DFS and OS in Group C than in Groups A and B (P <
Table 1. Stage II Colorectal Cancer Patient Characteristics According to Tumor Marker Combination.

| Characteristics                        | Total No. (N = 3,688) | Tumor marker combination | P-value<sup>a</sup> |
|----------------------------------------|------------------------|---------------------------|---------------------|
|                                        |                        | Group A<sup>b</sup> (N = 2,187) | Group B<sup>b</sup> (N = 1,226) | Group C<sup>b</sup> (N = 275) |
| Age (years)                            |                        | 2,587 (70%) | 1,580 (72%) | 841 (69%) | 166 (60%) | 0.0001 |
| <75                                    |                        | 2,036 (73%) | 1,321 (72%) | 480 (62%) | 115 (55%) |         |
| ≥75                                    |                        | 1,101 (30%) | 637 (32%)  | 361 (47%) | 51 (25%)  |         |
| Sex                                    |                        | 2,201 (70%) | 1,293 (72%) | 765 (62%) | 143 (55%) | 0.005  |
| Male                                   |                        | 1,146 (89%) | 630 (80%)  | 410 (54%) | 76 (46%)  |         |
| Female                                 |                        | 955 (21%)  | 663 (20%)  | 355 (26%) | 67 (14%)  |         |
| Performance status                     |                        | 2,805 (76%) | 1,682 (77%) | 938 (77%) | 185 (67%) | 0.84   |
| 0–1                                    |                        | 2,598 (76%) | 1,661 (77%) | 911 (77%) | 186 (67%) |         |
| 2–4                                    |                        | 1,210 (32%) | 521 (22%)  | 357 (28%) | 42 (14%)  |         |
| Tumor location                         |                        | 2,336 (64%) | 1,413 (65%) | 742 (61%) | 181 (66%) | 0.04   |
| Colon                                  |                        | 2,336 (64%) | 1,413 (65%) | 742 (61%) | 181 (66%) |         |
| Rectum                                 |                        | 1,000 (27%) | 620 (27%)  | 360 (25%) | 80 (29%)  |         |
| Lymph node dissection level            |                        | 1,311 (36%) | 753 (34%)  | 468 (38%) | 90 (33%)  | 0.69   |
| D1, D2                                 |                        | 847 (23%)  | 510 (23%)  | 271 (22%) | 66 (24%)  |         |
| D3                                     |                        | 2,819 (77%) | 1,662 (76%) | 948 (77%) | 209 (76%) |         |
| T-stage (depth of tumor invasion)      |                        | 2,726 (74%) | 1,717 (79%) | 847 (69%) | 162 (59%) | <0.0001|
| T3 (subserosa)                         |                        | 2,726 (74%) | 1,717 (79%) | 847 (69%) | 162 (59%) |         |
| T4 (serosa or other organs)            |                        | 952 (26%)  | 463 (21%)  | 376 (31%) | 113 (41%) |         |
| Tumor differentiation                  |                        | 3,334 (90%) | 1,989 (91%) | 1,107 (90%) | 238 (87%) | 0.03   |
| Well to moderate                       |                        | 3,334 (90%) | 1,989 (91%) | 1,107 (90%) | 238 (87%) |         |
| Poor                                   |                        | 326 (9%)   | 178 (8%)   | 112 (9%)  | 36 (13%)  |         |
| Venous invasion                        |                        | 1,090 (30%) | 697 (32%)  | 338 (28%) | 55 (20%)  | <0.0001|
| Negative                               |                        | 1,090 (30%) | 697 (32%)  | 338 (28%) | 55 (20%)  |         |
| Positive                               |                        | 2,464 (67%) | 1,410 (65%) | 846 (69%) | 208 (76%) |         |
| Lymphatic invasion                     |                        | 2,086 (57%) | 1,246 (57%) | 704 (57%) | 136 (50%) | 0.05   |
| Negative                               |                        | 2,086 (57%) | 1,246 (57%) | 704 (57%) | 136 (50%) |         |
| Positive                               |                        | 1,470 (40%) | 862 (39%)  | 481 (39%) | 127 (46%) |         |
| Number of dissected lymph nodes        |                        | 3,108 (84%) | 1,863 (85%) | 1,020 (83%) | 225 (82%) | 0.32   |
| <12                                    |                        | 3,108 (84%) | 1,863 (85%) | 1,020 (83%) | 225 (82%) |         |
| ≥12                                    |                        | 3,069 (83%) | 1,828 (84%) | 1,019 (83%) | 222 (80%) |         |
| Postoperative adjuvant chemotherapy    |                        | 580 (16%)  | 324 (15%)  | 206 (17%) | 50 (18%)  | 0.16   |
| Surgery-alone                          |                        | 580 (16%)  | 324 (15%)  | 206 (17%) | 50 (18%)  |         |
| Surgery+AC                             |                        | 310 (5%)   | 20 (6%)    | 14 (7%)   | 5 (2%)    |         |
| Chemotherapy regimen                   |                        | 580 (16%)  | 324 (15%)  | 206 (17%) | 50 (18%)  | 0.54   |
| UFT/LV                                 |                        | 403 (69%)  | 229 (71%)  | 142 (69%) | 32 (64%)  |         |
| Capecitabine                           |                        | 59 (10%)   | 33 (10%)   | 21 (10%)  | 5 (10%)   |         |
| S-1                                    |                        | 37 (6%)    | 20 (6%)    | 14 (7%)   | 5 (2%)    |         |
| FOLFOX                                 |                        | 31 (5%)    | 15 (5%)    | 12 (6%)   | 4 (8%)    |         |
| CAPOX                                  |                        | 11 (2%)    | 5 (2%)     | 3 (2%)    | 3 (6%)    |         |
| 5FU/LV                                 |                        | 9 (1%)     | 6 (2%)     | 2 (1%)    | 1 (2%)    |         |
| Other                                  |                        | 29 (5%)    | 15 (5%)    | 12 (6%)   | 2 (4%)    |         |

<sup>a</sup>Group A: both serum CEA levels ≤ 5.0 ng/mL and serum CA19-9 levels ≤ 37.0 U/mL.
<sup>b</sup>Group B: either serum CEA levels > 5.0 ng/mL or serum CA19-9 levels > 37.0 U/mL.
<sup>c</sup>Group C: both serum CEA levels > 5.0 ng/mL and serum CA19-9 levels > 37.0 U/mL.
<sup>d</sup>To compare categorical data among three groups, the chi-squared test was performed.

Abbreviations: 5FU/LV, 5-fluorouracil/leucovorin; AC, adjuvant chemotherapy; CA19-9, carbohydrate antigen 19-9; CAPOX, capecitabine and oxaliplatin; CEA, carcinoembryonic antigen; D1, paraintestinal lymph node dissection; D2, intermediate lymph node dissection; D3, main lymph node dissection; FOLFOX, fluorouracil/leucovorin/oxaliplatin; S-1, tegafur-gimeracil-oteracil; T-stage, pathological depth of tumor invasion stage; UFT/LV, tegafur-uracil/leucovorin
Figure 2. Patient survival in the combinations of CEA and CA19-9 levels.

**Characteristics of all patients and Group C in surgery-alone and surgery-plus-AC groups**

Among the 3,688 patients, 3,108 (84%) were included in the surgery-alone group, and 580 (16%) were included in the surgery-plus-AC group. Moreover, there were more patients aged <75 years (P < 0.0001), with rectal cancer (P = 0.0001), T4 depth of tumor invasion (P < 0.0001), venous invasion (P = 0.04), and lymphatic invasion (P < 0.0001) in the surgery-plus-AC group.

Among the 275 patients in Group C, 225 (82%) were included in the surgery-alone group, whereas 50 (18%) were included in the surgery-plus-AC group. There were more patients aged <75 years (P = 0.004) and exhibiting poorly differentiated histology (P = 0.02) in the surgery-plus-AC group (Table 3).

**Survival analysis of tumor marker combination groups with/without adjuvant therapy**

As shown in Table 4, no significant difference was observed in the DFS between the surgery-plus-AC and the surgery-alone groups in all patients with stage II CRC. However, regarding OS, multivariable Cox regression analysis showed greater improvement in the surgery-plus-AC group compared to the surgery-alone group (HR: 0.71, 95% CI: 0.53–0.98; Figure 2).

**Table 2. Multivariable Survival Analysis of Tumor Marker Combination Groups.**

| Tumor marker combination (N = 3,688) | Disease-free survival | Overall survival |
|-------------------------------------|-----------------------|-----------------|
|                                     | No. of cases | No. of events | Univariable HR (95% CI) | Multivariablea HR (95% CI) | No. of cases | No. of events | Univariable HR (95% CI) | Multivariablea HR (95% CI) |
| Group A b                          | 2,187      | 270          | 1 (reference)          | 1 (reference)               | 242        | 242          | 1 (reference)          | 1 (reference)               |
| Group B c                          | 1,226      | 223          | 1.62 (1.40–1.87)       | 1.47 (1.24–1.74)            | 221        | 221          | 1.71 (1.43–2.06)       | 1.59 (1.28–1.97)            |
| Group C d                          | 275        | 65           | 2.44 (1.97–3.01)       | 2.16 (1.67–2.79)            | 82         | 82           | 3.01 (2.35–3.87)       | 2.71 (2.01–3.67)            |
| P-trend                            | <0.0001    |              | <0.0001                | <0.0001                    |            |              | <0.0001                | <0.0001                    |

aThe multivariable Cox regression model was adjusted for age, sex, performance status, tumor location, lymph node dissection level, T-stage, tumor differentiation, venous invasion, lymphatic invasion, number of dissected lymph nodes, and postoperative adjuvant chemotherapy.

bGroup A: both serum CEA levels ≤ 5.0 ng/mL and serum CA19-9 levels ≤ 37.0 U/mL.

cGroup B: either serum CEA levels > 5.0 ng/mL or serum CA19-9 levels > 37.0 U/mL.

dGroup C: both serum CEA levels > 5.0 ng/mL and serum CA19-9 levels > 37.0 U/mL.

eP-trend was calculated by the linear trend across the ordinal categories of tumor marker combination (Group A, Group B, and Group C).

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio
Table 3. Clinical and Pathological Characteristics of Group C in Surgery-Alone and Surgery+AC Groups.

| Characteristics                      | Total No. (N = 3,688) | Group Ca (N = 275) | P-valueb | Group Ca (N = 275) | P-valueb |
|--------------------------------------|-----------------------|--------------------|----------|--------------------|----------|
| Age (years)                          |                       |                    |          |                    |          |
| <75                                  | 2,081 (67%)           | 1,027 (33%)        | <0.0001  | 2,069 (74%)        | 0.004    |
| ≥75                                  | 1,027 (33%)           | 74 (13%)           | 0.91     | 106 (47%)          | 0.53     |
| Sex                                  |                       |                    |          |                    |          |
| Male                                 | 1,856 (60%)           | 345 (60%)          | 0.10     | 119 (53%)          | 0.55     |
| Female                               | 1,251 (40%)           | 235 (40%)          |          | 106 (47%)          |          |
| Performance Status                   |                       |                    |          |                    |          |
| 0–1                                  | 2,366 (67%)           | 150 (67%)          | 0.0001   | 84 (3%)            | 0.48     |
| 2–4                                  | 84 (3%)               | 5 (2%)             |          |                    |          |
| Tumor location                       |                       |                    |          |                    |          |
| Colon                                | 2,012 (65%)           | 323 (56%)          |          | 1,065 (34%)        |          |
| Rectum                               | 1,065 (34%)           | 245 (42%)          |          |                    |          |
| Lymph node dissection level          |                       |                    |          |                    |          |
| D1, D2                               | 756 (24%)             | 91 (16%)           | <0.0001  | 2,330 (75%)        | 0.10     |
| D3                                   | 2,330 (75%)           | 485 (84%)          |          |                    |          |
| T-stage                              |                       |                    |          |                    |          |
| T3                                   | 2,345 (75%)           | 381 (66%)          | <0.0001  | 756 (24%)          | 0.09     |
| T4                                   | 756 (24%)             | 196 (34%)          |          |                    |          |
| Tumor differentiation                |                       |                    |          |                    |          |
| Well to moderate                     | 2,820 (91%)           | 513 (88%)          | 0.16     | 2,060 (66%)        | 0.02     |
| Poor                                 | 266 (9%)              | 60 (10%)           |          |                    |          |
| Venous invasion                      |                       |                    |          |                    |          |
| Negative                             | 940 (30%)             | 149 (26%)          | 0.04     | 2,060 (66%)        | 0.49     |
| Positive                             | 2,060 (66%)           | 404 (70%)          |          |                    |          |
| Lymphatic invasion                   |                       |                    |          |                    |          |
| Negative                             | 1,842 (59%)           | 244 (42%)          | <0.0001  | 1,017 (37%)        | 0.70     |
| Positive                             | 1,017 (37%)           | 313 (54%)          |          |                    |          |
| Number of dissected lymph nodes      |                       |                    |          |                    |          |
| <12                                 | 520 (17%)             | 94 (16%)           | 0.80     | 2,585 (83%)        | 0.69     |
| ≥12                                 | 2,585 (83%)           | 482 (83%)          |          |                    |          |

aGroup C: both serum CEA levels > 5.0 ng/mL and serum CA19-9 levels > 37.0 U/mL.
bTo compare categorical data between two groups, the chi-squared test was performed.

Abbreviations: AC, adjuvant chemotherapy; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; D1, paraintestinal lymph node dissection; D2, intermediate lymph node dissection; D3, main lymph node dissection; T-stage, pathological depth of tumor invasion stage; T3, depth of tumor invasion - subserosa; T4, depth of tumor invasion - serosa or other organs

Stage II CRC patients with at least one high-risk factor for recurrence accounted for 87% of all patients. No significant difference was observed in the DFS between the surgery-plus-AC and the surgery-alone group, whereas multivariable Cox regression analysis showed improvement in OS in the surgery-plus-AC group compared to the surgery-alone group (HR: 0.66, 95% CI: 0.51-0.98, P = 0.04).

Furthermore, among the groups classified according to tumor marker combination, Cox regression analyses were conducted to assess the interaction between tumor marker combinations and AC effects. Multivariable Cox regression analysis showed that the DFS in the surgery-plus-AC group was improved compared to the surgery-alone group in Group C than in Groups A and B (Pinteraction = 0.03, Group A: HR, 1.02; 95% CI, 0.73-1.42 vs. Group B: HR, 1.28; 95% CI, 0.92-1.79 vs. Group C: HR, 0.44; 95% CI, 0.21-0.96; Table 4).

The Kaplan-Meier curves showed that the 5-year DFS and OS were noted to be more improved in the surgery-plus-AC group than in the surgery-alone group in Group C (DFS: P = 0.02, OS: P = 0.003; Figure 3).

Discussion

In this present study, using the Japanese nationwide data-
Figure 3. Patient survival in surgery-alone vs. surgery-plus-AC in Group C.
Surgery-plus-AC group was associated with superior survival in DFS (A) and OS (B). Group C: both serum CEA levels >5.0 ng/mL and serum CA19-9 levels >37.0 U/mL. The table (bottom) shows the number of patients at risk.
AC, adjuvant chemotherapy; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; DFS, disease-free survival; OS, overall survival

Table 4. Multivariable Survival Analysis of Surgery-Alone vs. Surgery+AC Group.

| Group               | No. of cases | Disease-free survival | Overall survival |
|---------------------|--------------|-----------------------|------------------|
|                     | No. of events | Univariable HR (95% CI) | Multivariable HR (95% CI) | No. of events | Univariable HR (95% CI) | Multivariable HR (95% CI) |
| All population (N = 3,688) |              |                       |                   |              |                       |                   |
| Surgery-alone       | 3,108        | 429                   | 1 (reference)     | 1 (reference) | 483                   | 1 (reference)     |
| Surgery+AC          | 580          | 129                   | 1.04 (0.87–1.25)  | 0.99 (0.80–1.25) | 62                    | 0.67 (0.52–0.88)  |
| **P-value**         |              | 0.62                  | 0.99              |               | 0.003                  | 0.04              |
| High-risk population (N = 3,219) |              |                       |                   |              |                       |                   |
| Surgery-alone       | 2,669        | 409                   | 1 (reference)     | 1 (reference) | 454                   | 1 (reference)     |
| Surgery+AC          | 550          | 124                   | 0.96 (0.79–1.16)  | 0.97 (0.77–1.22) | 58                    | 0.60 (0.47–0.82)  |
| **P-value**         |              | 0.65                  | 0.79              |               | 0.0004                 | 0.02              |
| Group A* (N = 2,187) |              |                       |                   |              |                       |                   |
| Surgery-alone       | 1,863        | 211                   | 1 (reference)     | 1 (reference) | 215                   | 1 (reference)     |
| Surgery+AC          | 324          | 59                    | 1.03 (0.78–1.35)  | 1.02 (0.73–1.42) | 27                    | 0.73 (0.49–1.08)  |
| Group B* (N = 1,226) |              |                       |                   |              |                       |                   |
| Surgery-alone       | 1,020        | 163                   | 1 (reference)     | 1 (reference) | 191                   | 1 (reference)     |
| Surgery+AC          | 206          | 60                    | 1.20 (0.92–1.57)  | 1.28 (0.92–1.79) | 30                    | 0.73 (0.50–1.07)  |
| Group C (N = 275)   |              |                       |                   |              |                       |                   |
| Surgery-alone       | 225          | 55                    | 1 (reference)     | 1 (reference) | 77                    | 1 (reference)     |
| Surgery+AC          | 50           | 10                    | 0.47 (0.25–0.88)  | 0.44 (0.21–0.96) | 5                     | 0.27 (0.11–0.67)  |
| **P_interaction**   |              | 0.02                  | 0.03              |               |                       | 0.13              |

*aThe multivariable Cox regression model was adjusted for age, sex, performance status, tumor location, lymph node dissection level, T-stage, tumor differentiation, venous invasion, lymphatic invasion, and the number of dissected lymph nodes.
*bHigh risk population was T4 depth of invasion, dissected lymph nodes <12, positive lymphatic or venous invasion, and poorly differentiated histology.
*cGroup A: both serum CEA levels ≤ 5.0 ng/mL and serum CA19-9 levels ≤ 37.0 U/mL.
*dGroup B: either serum CEA levels > 5.0 ng/mL or serum CA19-9 levels > 37.0 U/mL.
*eGroup C: both serum CEA levels > 5.0 ng/mL and serum CA19-9 levels > 37.0 U/mL.
*fP_interaction was calculated using the Wald test for the interaction between adjuvant chemotherapy (negative and positive) and combinations of tumor markers (Group A, Group B, and Group C) in the Cox regression model.
Abbreviations: AC, adjuvant chemotherapy; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio
base, we showed that the 5-year DFS and OS were shorter in patients with both preoperative serum CEA levels >5.0 ng/mL and serum CA19-9 levels >37.0 U/mL (Group C) compared to those with both preoperative serum CEA levels ≤5.0 ng/mL and serum CA19-9 levels ≤37.0 U/mL (Group A) and either preoperative serum CEA levels >5.0 ng/mL or serum CA19-9 levels >37.0 U/mL (Group B). Furthermore, in Group C, the 5-year DFS rate was improved in the surgery-plus-AC group compared to the surgery-alone group. These results suggest that an assessment considering the tumor marker combination can be as useful to predict prognosis as other high-risk factors for recurrence. In addition, AC can be an effective treatment for stage II CRC patients with high levels of both tumor markers.

For subgroups with different prognoses in stage II CRC, the ASCO, ESMO, JSCCR, and NCCN guidelines provide high-risk factors for recurrence and recommend considering AC for those cases. A high preoperative CEA level, which is considered as a high-risk factor for recurrence in the ESMO guidelines[7], has been reported to be a poor prognostic factor for recurrence in stage II CRC treated with curative resection[15,16]. Moreover, previous studies reported that a high level of preoperative serum CA19-9 was a poor prognostic factor for recurrence in CRC[17,18]. Additionally, monitoring postoperative serum CEA and CA19-9 levels was found to be useful in identifying the recurrence of CRC[19]. Thus, preoperative and postoperative serum CEA and CA19-9 levels would be important as predictive factors for recurrence and prognosis of CRC. However, in clinical settings, both tumor markers may not necessarily show a simultaneous increase in all cases.

Several studies have evaluated the prognostic potential of the combination of preoperative serum CEA and CA19-9 levels in CRC, suggesting that the high levels of these tumor markers were associated with reduced cumulative survival, DFS, and OS[20,21]. Consistent with these results, this study further showed that the 5-year DFS and OS were shorter in patients with high levels of both preoperative serum CEA and CA19-9. Furthermore, the C-index for DFS in this group was comparable to the other high-risk factors for recurrence reported in the guidelines. These results indicate that combining these two tumor markers can predict recurrence and prognosis in stage II CRC. In addition, this group may be at a high risk for recurrence with an increased necessity for AC.

International multicenter randomized controlled trials for stage II CRC, the International Multicenter Pooled Analysis of B2 Colon Cancer Trials[3], and the QUick And Simple And Reliable trial[22] have shown that AC could neither suppress recurrence nor improve OS in all patients regardless of high-risk factors for recurrence[23]. In addition, the Surgical Adjuvant Chemotherapy with UFT for Curatively Resected Stage II Colon Cancer (SACURA) trial[24] - the world’s first randomized controlled trial for only stage II CRC patients conducted in Japan - has failed to show the superiority of AC (oral tegafur-uracil) in terms of DFS compared to surgery-alone. However, a large-scale retrospective study using the US National Cancer Database showed improvement in OS after AC (single or multi-agent) in stage II CRC patients with high-risk factors for recurrence, which suggested the beneficial effects of AC on the prognosis[25]. Furthermore, the Japanese Foundation for Multidisciplinary Treatment of Cancer 46-1201 trial, which was conducted in Japan on stage II CRC patients with high-risk factors for recurrence, showed that AC (UFT/LV) improved DFS compared to surgery-alone[26]. In contrast, a large-scale retrospective study using the Surveillance, Epidemiology, and End Results Program showed that AC for stage II CRC with high-risk factors for recurrence did not improve OS compared to surgery-alone[11]. Even with a limited sample size, Hatano et al. demonstrated less beneficial effects of AC (UFT/LV) on DFS for stage II CRC patients at high risk for recurrence[27]. Thus, the beneficial effect of AC on DFS and OS in high-risk stage II CRC patients remains to be limited, and further in-depth analysis is warranted.

According to the study by Kumar et al., 76% of the patients had stage II CRC with at least one high-risk factor for recurrence (obstruction, perforation, T4 depth of invasion, dissected lymph nodes <12, lymphatic or venous invasion, perineural invasion, and poorly differentiated histology)[12]. Similarly, in our study, 87% of the patients had been diagnosed with high-risk stage II CRC and were considered eligible for AC according to the current guidelines. In this study, the effectiveness of AC was classified based on a combination of preoperative serum CEA and CA19-9 levels in stage II CRC patients. The patients with high levels of both preoperative serum CEA and CA19-9 who had prolonged DFS because of AC comprised 7.5% of all stage II CRC patients. Thus, combining these tumor markers could generate a widely available and beneficial tool to predict the prognosis and select very high-risk stage II CRC patients who might need AC.

The strength of our study was the use of large, multicenter sample data on clinicopathological features contributing to high generalizability. In addition, preoperative serum CEA and CA19-9 tests assessed in this study could be performed minimally invasively and inexpensively in many hospitals. Furthermore, they can be determined objectively. This may be an advantage of utilizing tumor markers in terms of screening high-risk cases compared with high-risk factors previously described in several guidelines. However, this study has several limitations. First, serum CA19-9 is a carbohydrate antigen, and its level does not increase even in advanced cancer in Lewis antigen a (Le-a)-negative individuals (approximately 7% of the Japanese population) who have a deficiency of the Lewis enzyme necessary for the
synthesis of the Lewis carbohydrate. Therefore, cases with extremely low serum CA19-9 levels may have included Lewis-negative patients. Second, multiple types of chemotherapy were used in the adjuvant setting in a non-randomized manner, and UFT/LV was the most frequent regimen, whereas capcitabine or CAPOX, which has higher treatment intensities than UFT/LV [28], was less frequent in this study. However, the surgery-plus-AC group had longer DFS than the surgery-alone group in Group C, indicating that a capcitabine-based regimen can also have prognostic benefits. Furthermore, as this study was derived from large-scale multicenter retrospective data, our findings could be considered to have only exploratory consequences. In addition, various confounding factors, such as oncology factors, patients’ social backgrounds, and physicians’ factors for performing AC, were not included. Moreover, regarding stratified analyses, statistical power may have been limited. Therefore, data derived from prospective studies in multicenter cohorts are warranted to consider selection bias involved in treatment determination for AC.

In conclusion, patients with both preoperative high levels of serum CEA and CA19-9 may have a poor prognosis. In addition, combination assessment of preoperative serum CEA and CA19-9 could be useful for predicting prognosis in patients with stage II CRC. AC may need to be considered in these patients. However, establishing the efficacy of AC in high-risk patients with stage II CRC awaits results of future clinical trials.

Acknowledgements

This study was based on the data from the following referral institutions in the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer: Sapporo Medical University (I. Takemasa), Hirosaki University (K. Hakamada), Niigata University (Y. Shimada), Niigata Cancer Center Hospital (Y. Takii), National Defense Medical College (H. Ueno), Tochigi Cancer Center (H. Ozawa), Tokyo University (S. Ishihara), Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (K. Takahashi), National Cancer Center Hospital (Y. Kanemitsu), Tokyo Women’s Medical University (M. Itabashi), National Center for Global Health and Medicine (T. Kiyomatsu), Tokyo Medical and Dental University (Y. Kinugasa), Keio University (K. Okabayashi), Teikyo University (Y. Hashiguchi), Kyorin University (E. Sumami), Kitazato University (M. Watanabe), Shizuoka Cancer Center (A. Shiomi), Fujita Health University (T. Hanai), Aichi Cancer Center Hospital (K. Komori), Kyoto University (K. Hida), Osaka International Cancer Institute (M. Ohue), Osaka Rosai Hospital (S. Noura), Hyogo College of Medicine (M. Ikeda), and Kurume University (Y. Akagi). We would like to thank Editage (www.editage.jp) for English language editing.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Study concept and design, analysis and interpretation of data, drafting and revising of the article: Ogata S, Fujita F, Fujiyoshi K, Sudo T, and Akagi Y. Acquisition of data, concept and design, revision of the manuscript: Ogata S, Fujita F, Fujiyoshi K, and Sudo T. Computational analysis and interpretation of data, revision of the manuscript: Murotani K. Provided important suggestions on the study, revision of the manuscript: Yoshida T, and Koushi K. Study concept and design, interpretation of data, revision of the article: Sugihara K and Yamauchi S. All the authors read and approved the final manuscript.

Approval by Institutional Review Board (IRB)

This study was approved by the Institutional Review Board or Ethics Committee of Tokyo Medical and Dental University (approval number: M2017-268).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Gertler R, Rosenberg R, Schuster T, et al. Defining a high-risk subgroup with colon cancer stages I and II for possible adjuvant therapy. Eur J Cancer. 2009 Nov; 45(17): 2992-9.
2. Efficacy of adjuvant fluorouracil and folic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet. 1995 Apr; 345(8955): 939-44.
3. Efficacy of adjuvant fluorouracil and folic acid in B2 colon cancer. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators. J Clin Oncol. 1999 May; 17(5): 1356-63.
4. Kannarkatt J, Joseph J, Kurniali PC, et al. Adjuvant chemotherapy for stage II colon cancer: a clinical dilemma. J Oncol Pract. 2017 Apr; 13(4):233-41.
5. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020 Jan; 25(1): 1-42.
6. Benson AB 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004 Aug; 22(16): 3408-19.
7. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct; 24 Suppl 6: vi64-72.
8. Colon cancer [Internet]. Version 3. National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology. 2018 [cited 2021 Dec 14]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
9. Yoshida M, Ishiguro M, Ikjiri K, et al. S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). Ann Oncol. 2014 Sep; 25(9): 1743-9.
10. Meropol NJ. Ongoing challenge of stage II colon cancer. J Clin Oncol. 2011 Sep; 29(25): 3346-8.
11. O’Connor ES, Greenblatt DY, LoConte NK, et al. Adjuvant chemotherapy for stage II colon cancer with poor prognostic features. J Clin Oncol. 2011 Sep; 29(25): 3381-8.
12. Kumar A, Kennecke HF, Renouf DJ, et al. Adjuvant chemotherapy use and outcomes of patients with high-risk versus low-risk stage II colon cancer. Cancer. 2015 Feb; 121(4): 527-34.
13. Chen PJ, Li TL, Sun TT, et al. Clinical decision support for high-risk stage II colon cancer: a real-world study of treatment concordance and survival. Dis Colon Rectum. 2020 Oct; 63(10): 1383-92.
14. Wilhelmsen M, Christensen B, Rasmussen L, et al. Detection of colorectal neoplasia: combination of eight blood-based, cancer-associated protein biomarkers. Int J Cancer. 2017 Mar; 140(6): 1436-46.
15. Ogata Y, Murakami H, Sasatomi T, et al. Elevated preoperative serum carcinoembryonic antigen level may be an effective indicator for needing adjuvant chemotherapy after potentially curative resection of stage II colon cancer. J Surg Oncol. 2009 Jan; 99(1): 65-70.
16. Nagata H, Ishihara S, Oba K, et al. Development and validation of a prediction model for organ-specific recurrences after curative resection of colon cancer. Dis Colon Rectum. 2019 Sep; 62(9): 1043-54.
17. Zheng CX, Zhan WH, Zhao JZ, et al. The prognostic value of preoperative serum levels of CEA, CA 19-9 and CA72-4 in patients with colorectal cancer. World J Gastroenterol. 2001 Jun; 7(3): 431-9.
18. Filella X, Molina R, Grau JJ, et al. Prognostic value of CA 19.9 levels in colorectal cancer. Ann Surg. 1992 Jul; 216(1): 55-9.
19. Kawamura YJ, Tokumitsu A, Mizokami K, et al. First alert for recurrence during follow-up after potentially curative resection for colorectal carcinoma: CA 19-9 should be included in surveillance programs. Clin Colorectal Cancer. 2010 Jan; 9(1): 48-51.
20. Basbug M, Arikangolu Z, Bulbuller 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.
21. Shibutani M, Maeda K, Nagahara H, et al. Significance of CEA and CA 19-9 combination as a prognostic indicator and for recurrence monitoring in patients with stage II colorectal cancer. Anticancer Res. 2014 Jul; 34(7): 3753-8.
22. Quasar Collaborative Group, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised trial. Lancet. 2007 Dec; 370(9604): 2020-9.
23. Mayer RJ. Oxaliplatin as part of adjuvant therapy for colon cancer: more complicated than once thought. J Clin Oncol. 2012 Sep; 30(27): 3325-7.
24. 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. Eur J Cancer. 2018 Jun; 96: 54-63.
25. Casadaban L, Rauscher G, Akilu M, et al. Adjuvant chemotherapy is associated with improved survival in patients with stage II colon cancer. Cancer. 2016 Nov; 122(21): 3277-87.
26. Sadahiro S, Morita S, Sasaki K, et al. Treatment rationale and study design for clinical trial on the efficacy of UFT/LV for stage II colorectal cancer with risk factors for recurrence (JFMC46-1201). Clin Colorectal Cancer. 2015 Dec; 14(4): 277-80.
27. Hatano S, Kumamoto K, Ishibashi K, et al. Study on risk factors for recurrence in patients with stage II colon cancer: verification of Western Guidelines in Japanese clinical practice. JJCS. 2013 Jan; 38(4): 738-45.
28. Schmoll HJ, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. J Clin Oncol. 2015 Nov; 33(32): 3733-40.

Supplementary Files
Supplementary Table S1.
Please find supplementary file(s); http://dx.doi.org/10.23922/jarc.2022-020