High postoperative carcinoembryonic antigen as an indicator of high-risk stage II colon cancer

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Abstract. Postoperative carcinoembryonic antigen (post-CEA) has recently been reported to be a reliable prognostic factor for colon cancer. However, most clinicians decide whether or not to conduct adjuvant chemotherapy (AC) for stage II colon cancer according to major guidelines, which do not include post-CEA in their high-risk criteria. The present study aimed to assess post-CEA in stage II colon cancer for which the significance of AC is unknown. The present study analyzed 199 consecutive patients with stage II colon cancer who underwent curative surgery between January 2007 and December 2016. The CEA value was considered high when it was ≥5.0 ng/ml. The prognostic value of high post-CEA values was assessed. Overall, 19 patients exhibited high post-CEA levels. Kaplan-Meier survival curve analysis demonstrated that patients with high post-CEA levels had significantly worse relapse-free survival (RFS) and overall survival (OS) than those with normal post-CEA [RFS, 63.5 (high post-CEA) vs. 88.0% (normal post-CEA), P=0.003; OS, 76.5 (high post-CEA) vs. 96.8% (normal post-CEA), P<0.001]. Multivariate analysis demonstrated that high post-CEA remained a significant independent risk factor for worse RFS [hazard ratio (HR), 3.98; P=0.006]. The same was also demonstrated for patients without AC (HR, 5.43; P=0.008). To the best of our knowledge, the present study was the first to demonstrate that high post-CEA levels may be an indicator of high-risk stage II colon cancer, even for patients without AC. These results highlight the need for a multicenter prospective study.

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Abbreviations: CEA, carcinoembryonic antigen; pre, preoperative; post, postoperative; AC, adjuvant chemotherapy; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; ESMO, European Society of Medical Oncology

Key words: CEA, postoperative carcinoembryonic antigen, colon cancer, high-risk stage II, AC, surgery

Introduction

Colon cancer is the third most commonly diagnosed cancer in males and the second most commonly diagnosed in females worldwide (1). Overall ~75% of patients are diagnosed with stage I-III colon cancer, at which curative resection can be performed (2). Although the use of adjuvant chemotherapy (AC) in patients with stage III colon cancer is widely recognized, whether AC is recommended or not for stage II patients should be considered on an individual basis (3).

Carcinoembryonic antigen (CEA) is a commonly examined low-cost biomarker for colon cancer (4-6). Margalit *et al* (2) analyzed 45,449 patients with stage I-II colon cancer and determined that preoperative (pre)-CEA could be a potential prognostic factor. Furthermore, postoperative (post)-CEA has recently been identified as a reliable prognostic factor. Konishi *et al* (7) reported that post-CEA, and not pre-CEA, is an important prognostic factor for patients with stage I-III colon cancer. Auclin *et al* (8) performed a post-hoc analysis of the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, which indicated that high post-CEA is an independent prognostic factor in patients with stage II colon cancer. Furthermore this study reported that the addition of oxaliplatin to fluorouracil and leucovorin as AC is only a benefit to stage II patients with a high risk (T4, tumor perforation, or <12 examined lymph nodes) and high post-CEA levels. Patients with <10 ng/ml post-CEA were included in this previous study and all patients received AC.

However, AC is usually prescribed for patients with stage II colon cancer using the guidelines published by the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO), which do not include post-CEA levels among the high-risk criteria (3,9-11). However, this may be because, to the best of our knowledge, there are no

studies assessing high post-CEA as an independent risk factor of recurrence in patients with stage II colon cancer without AC.

Therefore, the aim of the present study was to assess post-CEA in patients with stage II colon cancer for which the significance of AC is unknown.

Materials and methods

Study population. The present study included patients with stage II primary colon cancer who underwent curative surgery, with appropriate lymphadenectomy, at the institute between January 2007 and December 2016. Patients with cancer in other organs were excluded. All patients provided informed consent and patient anonymity was preserved. The present study was approved by the ethics committee at the institution (Approval number: 15144-6).

Definitions. Pre-CEA was defined as the last CEA value examined before surgery and post-CEA was defined as the first CEA value examined after surgery. The CEA value was considered high when it was ≥5.0 ng/ml, which had previously been determined as a cut-off value (7,12).

Data collection. Clinicopathological and demographic data, including sex, age, BMI, pre- and post-CEA values, tumor location, bowel obstructions caused by a tumor, tumor histology, pathological T/N stage, and lymphovascular invasion, were collected retrospectively. The right side of the colon was defined as ascending and transverse, whereas the left side of the colon was defined as descending and sigmoid. Furthermore, retrospective data were acquired about the surgical procedure (laparoscopic or open surgery), the number of harvested lymph nodes, postoperative complications (Clavien-Dindo grade ≥3) and AC.

Statistical analysis. Demographic data are presented as the absolute count and proportion of patients, the mean ± SD, or the median and interquartile range (IQR). An unpaired Student's t-test was used for comparing quantitative variables, and Pearson χ^2 test or Fisher's exact test was used to compare categorical data depending on sample size. The association between different factors, including pre-CEA or post-CEA and 3-year overall survival (OS) or 3-year relapse-free survival (RFS), was assessed using Kaplan-Meier survival analysis followed by the log-rank test. Bonferroni correction was used to adjust the P-values for statistical comparison tests among more than two groups, including for the statistical comparison of survival curves. The RFS was defined as the time between surgery and relapse, second colon occurrence, or death, whichever occurred first. Patients without relapse, second colon cancer, or death were recorded at the last date of their follow-up. The OS was defined as the time between surgery and death from any cause. Patients who survived were recorded at the last date of their follow-up. The relationship of demographic, clinicopathological, and therapeutic factors to survival was assessed using the univariate Cox proportional-hazards model. Risk factors with P<0.05 in univariate analyses and certain high-risk factors reported by ASCO, NCCN, or ESMO, were included in the multivariate Cox regression model. The factors included in the multivariate analysis were determined based on Akaike's Information Criterion (13). These data are presented as the hazard ratio (HR) and 95% confidence interval (CI). All data analysis was performed using JMP Pro 14.1.0 (JMP Statistical Discovery, LLC). P-values were two-sided. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient clinicopathological characteristics. In the present study there were 207 patients with stage II primary colon cancer who underwent surgery between January 2007 and December 2016. In total 8 patients with cancer in other organs and 10 patients who underwent AC were excluded, which resulted in 189 patients being analyzed in the present study (Fig. S1). The clinicopathological characteristics of all the patients are presented in Table I. Moreover, 89.9% of the patients underwent laparoscopic surgery, 37.7% of the patients had high pre-CEA levels and 9% had high post-CEA levels. The median (IQR) follow-up was 5.0 (3.6-5.6) years. Furthermore, 5% of the patients had postoperative complications (Clavien-Dindo grade ≥3), consisting of seven anastomotic leakages, one ureteral stricture, one intraperitoneal hemorrhage and one bowel obstruction.

High post-CEA is associated with a worse prognosis. Patients were divided into the following three groups: i) Normal pre-CEA; ii) normalized (high pre-CEA and normal post-CEA); and iii) high post-CEA. The 3-year RFS rates of these three groups were 85.6, 91.4 and 60.0%, respectively. A statistical comparison of the 3-year RFS of these three groups demonstrated that there was no significant difference between the 122 patients in the normal pre-CEA group and the 59 patients in the normalized group. However, the 3-year RFS of the 18 patients in the high post-CEA group was significantly worse compared with the normal pre-CEA group (P=0.011) and the normalized group (P=0.003) (Fig. 1A). The 3-year OS rates of these groups were 96.7, 94.8 and 77.8%, respectively (Fig. 1B). A statistical comparison of the 3-year OS of these three groups demonstrated that there was no significant difference between the normal pre-CEA group and the normalized group. However, the OS in the high post-CEA group was significantly worse compared with the high pre-CEA group (P=0.003) and was also markedly worse compared with the normalized group (P=0.072). These results indicated that post-CEA levels, not pre-CEA levels, may be an optimal potential prognostic factor for 3-year RFS and OS of patients with stage II colon cancer.

High post-CEA patients have a worse prognosis compared with normal post-CEA patients. The clinicopathological characteristics of high post-CEA patients and normal post-CEA patients are presented in Table II. The results demonstrated that there were no significant differences between these two groups. The relationship between post-CEA status and survival of patients with stage II colon cancer was determined using Kaplan-Meier survival curves (Fig. 2). The results demonstrated that patients with high post-CEA levels had significantly worse 3-year RFS

Table I. Clinicopathological characteristics of patients (stage II; n=199).

Characteristics	Value
Sex, n (%)	
Female	94 (47.2)
Male	105 (52.8)
Mean age, years (SD)	67.9 (11.4)
Age, n (%)	
<75 years	146 (73.4)
≥75 years	53 (26.6)
Mean body mass index (SD)	22.3 (3.3)
Tumor location, n (%)	
Right-sided colon	94 (47.2)
Left-sided colon	105 (52.8)
Surgical procedure, n (%)	
Open	22 (11.1)
Laparoscopic	177 (88.9)
Histology, n (%)	
tub1, tub2	179 (89.9)
por, muc	20 (10.1)
pT stage, n (%)	
T3	190 (95.5)
T4	9 (4.5)
Lymphovascular invasion, n (%)	
Yes	134 (67.3)
No	65 (32.7)
Harvested lymph nodes, n (%)	
<12	42 (21.1)
≥12	157 (78.9)
Bowel obstruction, n (%)	
Yes	9 (4.5)
No	190 (95.5)
Postoperative complications, n (%)	
Yes	10 (5.0)
No	189 (95.0)
Adjuvant chemotherapy, n (%)	
Yes	10 (5.0)
No	189 (95.0)
Preoperative CEA, n (%)	
<5 ng/ml	124 (62.3)
≥5 ng/ml	75 (37.7)
Postoperative CEA, n (%)	
<5 ng/ml	181 (91.0)
≥5 ng/ml	18 (9.0)
Median time between surgery and CEA measurement, days (IQR)	36 (27-93)
Median follow-up, years (IQR)	5.0 (3.6-5.6)

Data are presented as n (%), mean (SD), or median (IQR). tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous carcinoma; CEA, carcinoembryonic antigen; IQR, interquartile range.

or 3-year OS compared with patients in the normal post-CEA group (RFS, 60.0 vs. 87.5%, P<0.001; and HR, 77.8 vs. 96.1%, P<0.001, respectively).

High post-CEA levels are an independent risk factor. Univariate analysis demonstrated that an age of ≥75 years, pT4 stage and high post-CEA levels were significant risk factors for RFS (Table III). Multivariate analysis demonstrated that high post-CEA levels remained a significant independent risk factor for worse RFS (HR, 4.47; 95% CI, 1.83-10.96; P=0.001).

Furthermore, univariate analysis revealed that an age of ≥75 years, pT4 stage, and high post-CEA levels were significant risk factors for OS (Table SI). Multivariate analysis demonstrated that high post-CEA remained a significant independent risk factor for worse OS (HR, 5.62; 95% CI, 1.62-19.53; P=0.007).

High post-CEA levels are an independent risk factor for patients without AC. Subsequently the significance of post-CEA as a prognostic factor for patients with stage II colon cancer who did not undergo AC, were assessed. The 3-year RFS was determined to be 85.9% and the 3-year OS was 94.1%. Overall 19 patients had high post-CEA levels. The relationship between post-CEA levels and patient survival without AC was determined (Fig. 3). Kaplan-Meier survival curves demonstrated that patients with high post-CEA levels had significantly worse RFS or OS compared with the normal post-CEA group (RFS, 63.5 vs. 88.0%, P=0.003; and OS, 76.5 vs. 96.8%, P<0.001, respectively).

Univariate analysis revealed that in males, an age of ≥75 years, pT4 stage, with a number of harvested lymph nodes <12 and high post-CEA levels were significant risk factors for RFS (Table IV). Multivariate analysis demonstrated that high post-CEA remained a significant independent risk factor for a worse RFS (HR, 3.98; 95% CI, 1.48-10.70; P=0.006).

Furthermore, univariate analysis revealed that an age of ≥75 years, pT4 stage, and high post-CEA levels were significant risk factors for OS (Table SII). Multivariate analysis demonstrated that high post-CEA levels remained a significant independent risk factor for a worse OS (HR, 5.43; 95% CI, 1.55-18.98; P=0.008).

Discussion

To the best of our knowledge this is the first study that has demonstrated that high post-CEA levels, more than high pre-CEA levels, may be an independent risk factor for patients with stage II primary colon cancer who do not undergo AC following curative resection. These results strongly suggested that high post-CEA is a potential indicator of AC for stage II colon cancer following surgery.

Previous studies have demonstrated that pre-CEA can be a risk factor for the recurrence of stage II colon cancer (2,14). In the present study the 3-year RFS and OS of high pre-CEA patients were not significantly different from those of low pre-CEA patients when the CEA level normalized following surgery. However, the 3-year RFS and OS of high post-CEA patients were significantly worse than those of normal post-CEA patients. This result is consistent with a previous report of 1,027 patients with stage I-III

Table II. Clinicopathological characteristics of patients in the high and normal post-CEA groups.

Characteristics	High post-CEA (n=18)	Normal post-CEA (n=181)	P-value
Sex, n (%)			
Male	9 (50.0)	96 (53.0)	0.806
Female	9 (50.0)	85 (47.0)	
Age, n (%)			
≥75	6 (33.3)	47 (26.0)	0.500
<75 years	12 (66.7)	134 (74.0)	
Mean body mass index (SD)	21.3 (3.6)	22.4 (3.3)	0.192
Tumor location, n (%)			
Right-sided colon	9 (50.0)	85 (47.0)	0.806
Left-sided colon	9 (50.0)	96 (53.0)	
Surgical procedure, n (%)			
Open	1 (5.6)	21 (11.6)	0.699[a]
Laparoscopic	17 (94.4)	160 (88.4)	
Histology, n (%)			
por, muc	2 (11.1)	18 (9.9)	0.699[a]
tub1, tub2	16 (88.9)	163 (90.1)	
pT stage, n (%)			
T4	1 (5.6)	8 (4.4)	0.582[a]
T3	17 (94.4)	173 (95.6)	
Lymphovascular invasion, n (%)			
Yes	12 (66.7)	122 (67.4)	0.949
No	6 (33.3)	59 (32.6)	
Harvested lymph nodes, n (%)			
<12	2 (11.1)	40 (22.1)	0.373[a]
≥12	16 (88.9)	141 (77.9)	
Bowel obstruction, n (%)			
Yes	1 (5.6)	8 (4.4)	0.582[a]
No	17 (94.4)	173 (95.6)	
Postoperative complications, n (%)			
Yes	1 (5.6)	9 (5.0)	>0.990[a]
No	17 (94.4)	172 (95.0)	
Adjuvant chemotherapy, n (%)			
Yes	1 (5.6)	9 (5.0)	>0.990[a]
No	17 (94.4)	172 (95.0)	
Median time between surgery and CEA measurement, days (IQR)	28 (22-131)	37 (28-92)	0.512

An unpaired Student's t-test was used to compare quantitative variables and Pearson χ^2 test was used to compare categorical data unless otherwise noted. [a]Fisher's exact test. Data are presented as n (%), mean (SD) or median (IQR). tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous carcinoma; CEA, carcinoembryonic antigen; post, postoperative; IQR, interquartile range.

colon cancer, but this previous study did not determine the significance of post-CEA for stage II colon cancer (7). Other studies have also demonstrated that post-CEA is a high-risk factor for stage II colon cancer. Lin *et al* (15) reported that high post-CEA patients had a worse 5-year RFS compared with normal post-CEA patients. However, multivariate analysis for patients with stage II colon cancer was not performed as part of this previous study. Tsai *et al* (12) reported that high post-CEA can be a risk factor for early relapse (within 12 months following surgery) in patients with stage II colon cancer, but multivariate analysis was not performed and 46.1% of the patients underwent AC. As previously stated, a post-hoc analysis of the MOSAIC trial demonstrated that patients with high post-CEA have a 50% increased risk of death or recurrence compared with those who have low post-CEA levels determined via multivariate

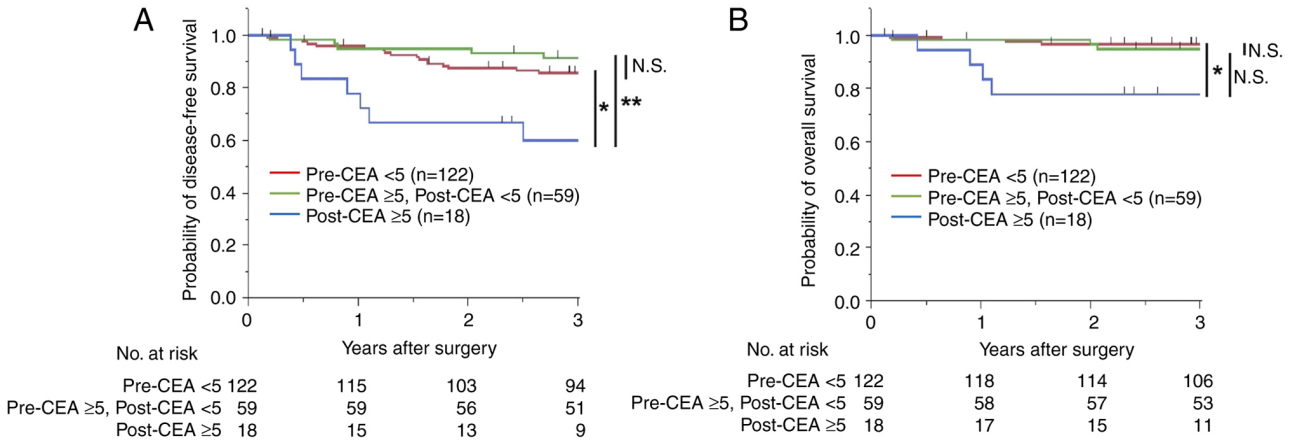

Figure 1. (A) Comparison of disease-free survival in the normal pre-CEA group, normalized (high pre-CEA and normal post-CEA) group and high post-CEA group. *P=0.011; **P=0.003. (B) Comparison of overall survival in the three groups. *P=0.003. CEA, carcinoembryonic antigen; N.S., not significant; post, postoperative; pre, preoperative.

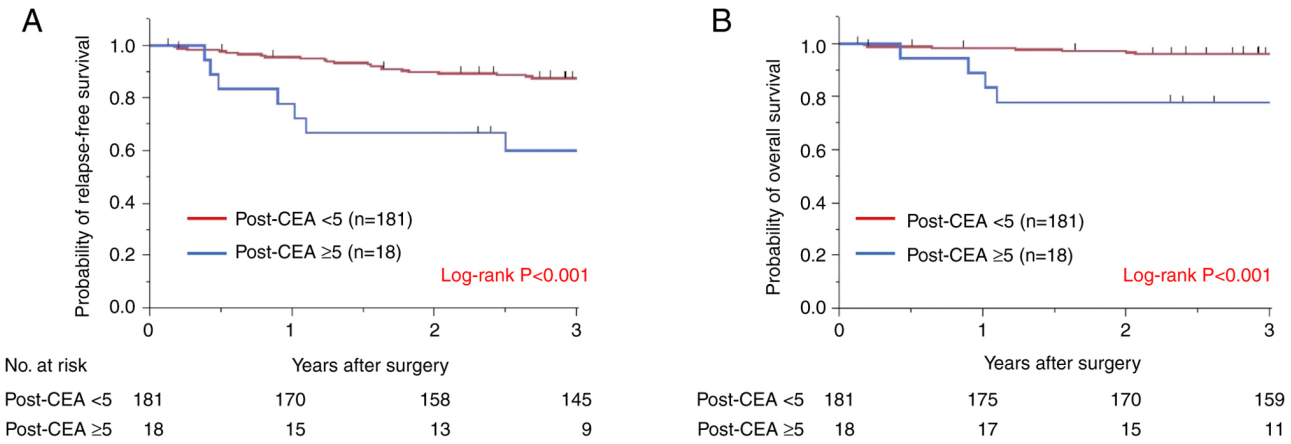

Figure 2. Kaplan-Meier survival curves for (A) relapse-free survival and (B) overall survival of patients with high post-CEA and normal post-CEA. CEA, carcinoembryonic antigen; post, postoperative.

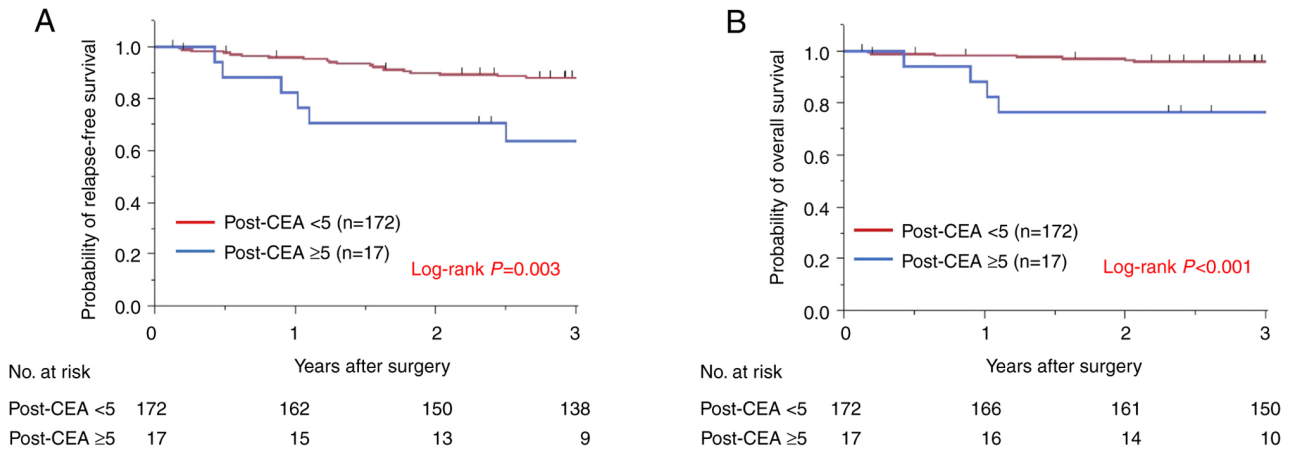

Figure 3. Kaplan-Meier survival curves for (A) relapse-free survival and (B) overall survival of patients with high post-CEA and normal post-CEA who did not undergo adjuvant chemotherapy. CEA, carcinoembryonic antigen; post, postoperative.

analysis, although all patients received AC (8). Therefore, to the best of our knowledge the present study was the first to have demonstrated the significance of high post-CEA as an indicator of AC for stage II colon cancer.

The decision to perform AC should be made cautiously because it can cause adverse effects in patients (16-18). Therefore, it is essential to precisely assess a patients risk factors for relapse. Previous studies have reported

Table III. Univariate and multivariate analysis of risk factors for relapse-free survival (n=199).

	Univariate analysis		Multivariate analysis	
Variables	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Sex (male/female)	1.53 (0.72-3.23)	0.269	1.62 (0.76-3.44)	0.212
Age (≥75/<75 years)	2.14 (1.02-4.48)	0.044	1.82 (0.86-3.85)	0.116
Left-sided/right-sided	1.32 (0.63-2.77)	0.458		
Obstruction (+/-)	1.63 (0.39-6.86)	0.505		
Histology (por, muc/tub1, tub2)	0.66 (0.16-2.78)	0.573		
pT stage (T4/T3)	3.41 (1.03-11.29)	0.045	2.92 (0.87-9.78)	0.083
Lymphovascular invasion (+/-)	0.95 (0.44-2.04)	0.888		
Harvested lymph nodes (<12/≥12)	1.89 (0.86-4.16)	0.112	2.20 (0.97-4.98)	0.059
Surgical procedure (open/laparoscopic)	1.81 (0.69-4.74)	0.228		
Postoperative CEA (≥5/<5 ng/ml)	3.96 (1.69-9.29)	0.001	4.47 (1.83-10.96)	0.001
Adjuvant chemotherapy (+/-)	2.34 (0.71-7.72)	0.164		

tub1, well differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous carcinoma; CEA, carcinoembryonic antigen.

Table IV. Univariate and multivariate analysis for relapse-free survival among patients without adjuvant chemotherapy (n=189).

	Univariate analysis		Multivariate analysis	
Variables	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Sex (male/female)	2.09 (0.91-4.80)	0.084	2.45 (1.05-5.73)	0.039
Age (≥75/<75 years)	2.43 (1.13-5.26)	0.024	1.83 (0.82-4.07)	0.138
Left-sided/right-sided	1.30 (0.60-2.84)	0.504		
Obstruction (+/-)	1.74 (0.41-7.37)	0.452		
Histology (por, muc/tub1, tub2)	0.39 (0.05-2.87)	0.354		
pT stage (T4/T3)	7.83 (2.33-26.38)	<0.001	6.10 (1.67-22.33)	0.006
Lymphovascular invasion (+/-)	1.01 (0.45-2.27)	0.979		
Harvested lymph nodes (<12/≥12)	2.27 (1.01-5.09)	0.047	2.86 (1.22-6.71)	0.016
Surgical procedure (open/laparoscopic)	2.23 (0.84-5.92)	0.107		
Postoperative CEA (≥5/<5 ng/ml)	3.58 (1.44-8.93)	0.006	3.98 (1.48-10.70)	0.006

tub1, well differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous carcinoma; CEA, carcinoembryonic antigen.

that circulating tumor cells and circulating tumor DNA are potential indicators of a high risk of recurrence for stage II-III colorectal cancer (19-22). However, detection of circulating tumor cells and DNA requires special techniques, equipment and is expensive. Therefore, these tests are not yet commonly used to examine patients with colon cancer. The CEA value, on the other hand, is commonly determined perioperatively and at low cost. Furthermore, because CEA half life is reported to be 3-7 days (23) its levels can normalize within a few weeks following complete tumor resection. Therefore, if the CEA level does not normalize after apparent curative resection this may indicate that there are some residual micrometastases. The 3-year RFS of high post-CEA patients in the present study was worse than that in the post hoc analysis of the MOSAIC study, whereby all patients underwent AC, and the cutoff CEA value in the present study was more severe (high post-CEA was defined as ≥5 ng/ml) (8). Taken together, these results indicated that high post-CEA levels may be a good indicator for AC or more intensive follow-up treatment than patients with normal CEA levels. However, this should be validated by a multicenter prospective trial.

In the present study multivariate analyses for patients without AC revealed that being male was an independent risk factor, which is consistent with previous reports (8,24). However, the underlying reason for this remains to be investigated. Pathological T4 stage and the number of harvested lymph nodes (<12) were also independent risk factors for relapse and are well-known high-risk stage II indicators as suggested by the ASCO, ESMO and NCCN.

The present study has several limitations. First, it is a retrospective study conducted in one institute. The sample size of 189 patients without AC was considered to be sufficient because the minimum sample size was 65 patients, which was determined using an α-error value of 0.05 and statistical power of 0.8 (25). Moreover, there were no significant differences in clinicopathological characteristics between the high and normal post-CEA groups without any adjustments. Second, the interval between surgery and the first CEA examination after operation was not controlled. Given that AC should be performed within 8 weeks (26,27), post-CEA levels must be examined within 8 weeks after surgery at the latest. As the present study included high post-CEA patients whose CEA values were obtained more than 8 weeks following resection, there is a possibility that the CEA values were once less than 5 ng/ml after surgery and later exceeded the cutoff. However, it is also possible that the CEA values remained high after surgery; the median value of this interval was 36 days, which is within 8 weeks. In order to deal with this limitation, a well-designed prospective study should be performed in the future. Third, no data was included on smoking history, a factor that is associated with higher CEA levels, and other factors which can also have an affect, such as gastritis, diverticulitis, pancreatitis, liver diseases, diabetes and inflammatory bowel disease (28-30). Therefore, these false-positive-CEA-related factors should be considered when using the post-CEA value as a high-risk indicator. Despite these limitations, the present study, to the best of our knowledge, is the first report to analyze patients without AC and to demonstrate that the post-CEA value could be a potential indicator of AC for patients with stage II colon cancer.

In conclusion, the present study demonstrated the importance of high post-CEA as a prognostic factor for stage II colon cancer. Even though it is not included in the major guidelines, data from previous multicenter and large-scale studies support these findings. On the basis of the present study, a prospective multicenter study with more patients should be performed to validate the significance of the post-CEA value.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YM was responsible for the conceptualization, the acquisition and analysis of data, interpretation of data, methodology, project administration, resources, validation, visualization and writing of the first draft of the manuscript. YM and HT confirm the authenticity of all the raw data. HT, YD and HE were responsible for the conceptualization, the acquisition and analysis of data, methodology, project administration, resources, supervision, validation, visualization and reviewing and editing of the manuscript. AA and HI performed the acquisition and analysis of data and helped with validation and visualization. MF was also involved in the acquisition and analysis of data, and validation. YS, TH, SF and NM were responsible for the interpretation of data, methodology, project administration, resources, validation, visualization and reviewing and editing of the manuscript. TO was responsible for the interpretation of data, methodology, project administration, resources, validation and visualization. MU, CM, HY and TM were responsible for the interpretation of data, methodology, project administration, resources, supervision, validation, visualization and the reviewing and editing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All patients provided written informed consent and patient anonymity was preserved. The present study was approved by the Ethics Board of Osaka University Hospital (Suita, Osaka, Japan).

Patient consent for publication

Not applicable.

Competing interests

TM was supported by donations from Kinshukai Medical Corporation. The other authors declare that they have no competing interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
2. Margalit O, Mamtani R, Yang YX, Reiss KA, Golan T, Halpern N, Aderka D, Giantonio B, Shacham-Shmueli E and Boursi B: Assessing the prognostic value of carcinoembryonic antigen levels in stage I and II colon cancer. Eur J Cancer 94: 1-5, 2018.
3. Kannarkatt J, Joseph J, Kurniali PC, Al-Janadi A and Hrinczenko B: Adjuvant Chemotherapy for Stage II Colon Cancer: A Clinical Dilemma. J Oncol Pract 13: 233-241, 2017.
4. Gold P and Freedman SO: Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med 121: 439-462, 1965.
5. Takagawa R, Fujii S, Ohta M, Nagano Y, Kunisaki C, Yamagishi S, Osada S, Ichikawa Y and Shimada H: Preoperative serum carcinoembryonic antigen level as a predictive factor of recurrence after curative resection of colorectal cancer. Ann Surg Oncol 15: 3433-3439, 2008.
6. Araujo RL, Gönen M, Allen P, DeMatteo R, Kingham P, Jarnagin W, D'Angelica M and Fong Y: Positive postoperative CEA is a strong predictor of recurrence for patients after resection for colorectal liver metastases. Ann Surg Oncol 22: 3087-3093, 2015.
7. Konishi T, Shimada Y, Hsu M, Tufts L, Jimenez-Rodriguez R, Cercek A, Yaeger R, Saltz L, Smith JJ, Nash GM, *et al*: Association of preoperative and postoperative serum carcinoembryonic antigen and colon cancer outcome. JAMA Oncol 4: 309-315, 2018.
8. Auclin E, André T, Taieb J, Banzi M, Van Laethem JL, Tabernero J, Hickish T, de Gramont A and Vernerey D: Association of post-operative CEA with survival and oxaliplatin benefit in patients with stage II colon cancer: A post hoc analysis of the MOSAIC trial. Br J Cancer 121: 312-317, 2019.

9. Benson AB III, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, Krzyzanowska MK, Maroun J, McAllister P, Van Cutsem E, *et al*: American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 22: 3408-3419, 2004.
10. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A and Arnold D; ESMO Guidelines Working Group: Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24 (Suppl 6): vi64-vi72, 2013.
11. National Comprehensive Cancer Network: Colon Cancer (Version 2.2017). https://www2.tri-kobe.org/nccn/guideline/colorectal/english/colon.pdf. Accessed August 25, 2020.
12. Tsai HL, Huang CW, Chen CW, Yeh YS, Ma CJ and Wang JY: Survival in resected stage II colorectal cancer is dependent on tumor depth, vascular invasion, postoperative CEA level, and the number of examined lymph nodes. World J Surg 40: 1002-1009, 2016.
13. Akaike H: Information theory and an extension of the maximum likelihood principle. In: 2nd International Symposium on Information Theory, Tsahkadsor, Armenia, USSR, September 2-8, 1971. Petrov BN and Caski F (eds). Akadémiai Kiadó, Budapest, pp 267-281, 1973.
14. Kim CW, Yoon YS, Park IJ, Lim SB, Yu CS and Kim JC: Elevation of preoperative s-CEA concentration in stage IIA colorectal cancer can also be a high risk factor for stage II patients. Ann Surg Oncol 20: 2914-2920, 2013.
15. Lin JK, Lin CC, Yang SH, Wang HS, Jiang JK, Lan YT, Lin TC, Li AF, Chen WS and Chang SC: Early postoperative CEA level is a better prognostic indicator than is preoperative CEA level in predicting prognosis of patients with curable colorectal cancer. Int J Colorectal Dis 26: 1135-1141, 2011.
16. Akagi T and Inomata M: Essential advances in surgical and adjuvant therapies for colorectal cancer 2018-2019. Ann Gastroenterol Surg 4: 39-46, 2020.
17. Gelibter AJ, Caponnetto S, Urbano F, Emiliani A, Scagnoli S, Sirgiovanni G, Napoli VM and Cortesi E: Adjuvant chemotherapy in resected colon cancer: When, how and how long? Surg Oncol 30: 100-107, 2019.
18. Matsuda T, Yamashita K, Hasegawa H, Oshikiri T, Hosono M, Higashino N, Yamamoto M, Matsuda Y, Kanaji S, Nakamura T, *et al*: Recent updates in the surgical treatment of colorectal cancer. Ann Gastroenterol Surg 2: 129-136, 2018.
19. Peach G, Kim C, Zacharakis E, Purkayastha S and Ziprin P: Prognostic significance of circulating tumour cells following surgical resection of colorectal cancers: A systematic review. Br J Cancer 102: 1327-1334, 2010.
20. Lu CY, Uen YH, Tsai HL, Chuang SC, Hou MF, Wu DC, Juo SH, Lin SR and Wang JY: Molecular detection of persistent postoperative circulating tumour cells in stages II and III colon cancer patients via multiple blood sampling: Prognostic significance of detection for early relapse. Br J Cancer 104: 1178-1184, 2011.
21. Lecomte T, Berger A, Zinzindohoué F, Micard S, Landi B, Blons H, Beaune P, Cugnenc PH and Laurent-Puig P: Detection of free-circulating tumor-associated DNA in plasma of colorectal cancer patients and its association with prognosis. Int J Cancer 100: 542-548, 2002.
22. Tie J, Wang Y, Tomasetti C, Li L, Springer S, Kinde I, Silliman N, Tacey M, Wong HL, Christie M, *et al*: Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med 8: 346ra92, 2016.
23. Yakabe T, Nakafusa Y, Sumi K, Miyoshi A, Kitajima Y, Sato S, Noshiro H and Miyazaki K: Clinical significance of CEA and CA19-9 in postoperative follow-up of colorectal cancer. Ann Surg Oncol 17: 2349-2356, 2010.
24. Burdy G, Panis Y, Alves A, Nemeth J, Lavergne-Slove A and Valleur P: Identifying patients with T3-T4 node-negative colon cancer at high risk of recurrence. Dis Colon Rectum 44: 1682-1688, 2001.
25. Freedman LS: Tables of the number of patients required in clinical trials using the logrank test. Stat Med 1: 121-129, 1982.
26. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD and Booth CM: Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: A systematic review and meta-analysis. JAMA 305: 2335-2342, 2011.
27. Des Guetz G, Nicolas P, Perret GY, Morere JF and Uzzan B: Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. Eur J Cancer 46: 1049-1055, 2010.
28. Alexander JC, Silverman NA and Chretien PB: Effect of age and cigarette smoking on carcinoembryonic antigen levels. JAMA 235: 1975-1979, 1976.
29. Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. Adopted on May 17, 1996 by the American Society of Clinical Oncology. J Clin Oncol 14: 2843-2877, 1996.
30. Litvak A, Cercek A, Segal N, Reidy-Lagunes D, Stadler ZK, Yaeger RD, Kemeny NE, Weiser MR, Pessin MS and Saltz L: False-positive elevations of carcinoembryonic antigen in patients with a history of resected colorectal cancer. J Natl Compr Canc Netw 12: 907-913, 2014.