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Prognostic Reappraisal of Postoperative Carcinoembryonic Antigen in T1-2N0 Colorectal Cancer

GUANGZHE PIAN[1,2,3], JUN SANG SHIN[1], SUNSEOK YOON[1] and SEUNG YEOP OH[1]

[1]*Department of Surgery, Ajou University School of Medicine, Suwon, Republic of Korea;*
[2]*Department of Surgery, Ajou University Graduate School of Medicine, Suwon, Republic of Korea;*
[3]*Department of Surgery, Yanbian University Hospital, Jilin, P.R. China*

Abstract. *Background/Aim: The purpose of this study was to compare the prognostic value of preoperative carcinoembryonic antigen (CEA), preoperative CEA/tumor size and postoperative CEA in stage I colorectal cancer. Patients and Methods: We analyzed a total of 305 consecutive stage I colorectal cancer patients who underwent a radical surgery at our Department. The patients were divided into low and high preoperative CEA groups, low and high preoperative CEA/tumor size groups, and low and high postoperative CEA groups according to the optimal cut-off values. Results: Multivariate analysis showed that postoperative CEA was independently associated with OS and DFS. However, the preoperative CEA and preoperative CEA/tumor size were not. Conclusion: The prognostic value of postoperative CEA is better than preoperative CEA and preoperative CEA/tumor size in patients with stage I colorectal cancer. Moreover, the common 5 ng/ml cut-off was not optimal for risk stratification in stage I colorectal cancer.*

Colorectal cancer (CRC) is one of the most common causes of cancer death in the world. Seventy-five percent of patients can receive radical treatment, due to diagnosis with non-metastatic disease (1, 2).

In colorectal cancer, after radical surgery, adjuvant chemotherapy is the standard treatment for patients with stage II disease with risk factors for recurrence, *i.e.*, poorly differentiated, lymphatic/vascular invasion, lymph nodes harvested (<12), perineural invasion, obstruction, perforation, and T4 lesions. However, in stage I disease, although the chance of recurrence still exists, adjuvant therapy is usually not provided, and there are few reports about the risk factors for recurrence (3). Therefore, it is necessary to identify patients at high risk for recurrence in stage I colorectal cancer because such individuals may benefit from adjuvant treatment.

Carcinoembryonic antigen (CEA), a complex glycoprotein involved in cell adhesion, has been widely used as a biological tumor marker in clinical practices since 1965 (4). Previous studies have shown that elevated preoperative CEA, preoperative CEA/tumor size and postoperative CEA were significantly associated with worse outcome in patients with colorectal cancer (5-9). Marglit *et al*. reported that in stage I and II colon cancers, the optimal cuff-off value of preoperative CEA was 2.35 ng/ml, and patients with CEA >2.35 ng/ml had worse outcome compared to those with CEA <2.35 ng/ml (5). Auclin *et al*. also suggested that postoperative CEA is a strong risk factor in stage II colon cancer, and reported that high-risk stage II colon cancer patients with postoperative CEA >2.35 ng/ml benefited from the addition of oxaliplatin to LV5FU2 (6). Another study has shown that preoperative CEA/tumor size was an independent risk factor in stage I-III rectal cancers, where patients with high CEA/tumor size had worse outcome compared to those with low CEA/tumor size (7). Most of these studies evaluated the prognostic value of CEA in stage II-III diseases and there were few reports about stage I. In addition, to the best of our knowledge, the comparison of prognostic value between preoperative CEA, preoperative CEA/tumor size and postoperative CEA has never been reported. The aim of this study was to compare the prognostic value of preoperative CEA, preoperative CEA/tumor size, and postoperative CEA in stage I colorectal cancer.

Patients and Methods

Patients. The medical records of 367 patients who were diagnosed with stage I colorectal cancer and underwent a radical surgery at Ajou University Hospital from January 2010 to December 2015 were studied. We excluded patients with the following criteria: 1) history of other primary cancers (n=39); 2) received preoperative

Correspondence to: Seung Yeop Oh, MD, Department of Surgery, Ajou University School of Medicine, 164, World cup-ro, Yeongtong-gu, Suwon 16499, Republic of Korea. Tel: +82 312194450, Fax: +82 312195755, e-mail: kgsosy@ajou.ac.kr

Key Words: Colorectal cancer, stage I, preoperative CEA, preoperative CEA/tumor size, postoperative CEA.

chemoradiation therapy (n=12); 3) dead within 1 month after surgery (n=2); and 4) non-adenocarcinoma or unknown histology (n=9). Thus, a total of 305 patients were finally enrolled in the study.

Data collection. The clinicopathological data analyzed included gender (male *vs*. female), age (median, ≤63 *vs*. >63), body mass index (BMI, <25 *vs*. ≥25 kg/m^2), location (colon *vs*. rectum), histology (well *vs*. moderately *vs*. poorly), tumor size (median, ≤2 *vs*. >2 cm), T stage (T1 *vs*. T2), number of retrieved lymph nodes (<12 *vs*. ≥12), lymphatic invasion (negative *vs*. positive) and perineural invasion (negative *vs*. positive). Preoperative CEA was defined as the CEA value closest to the time of surgery and postoperative CEA was defined as the CEA value closest to the time of surgery.

Patients were regularly followed-up every 3-6 months for the first 2 years after surgery, every 6 months for the next 3 years, and every year thereafter. Routine physical examinations and serum CEA assays were performed at each follow-up. Abdominopelvic computed tomography scan, chest X-ray, and colonoscopy were performed every year and when recurrence was suspected. Recurrence was detected by a combination of radiographic examinations and/or histological confirmation through biopsy.

The last follow-up was in July 2020, and the median follow-up period was 87.0 months (range=3-125 months). During the follow-up period, there were twenty-one patients (6.89 %) who died and sixteen patients (5.25 %) who had recurrence. Overall survival (OS) was defined as the period from the date of surgery to the date of death from any cause or to the last follow-up date. Disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence, death, or last follow-up. This study had full ethical approval from the Institutional Review Board of Ajou University School of Medicine.

Statistical analysis. The tumor size was defined as the maximum diameter in the maximum cross section, which was measured by pathologists (7). The X-tile 3.6.1 software (Yale University, New Haven, CT, USA) was used to determine the optimal cut-off value of preoperative CEA, preoperative CEA/tumor size and postoperative CEA, which were identified from the minimum *p*-value according to the OS. A Pearson's x^2 or Fisher's exact test was used to evaluate differences between postoperative CEA and clinicopathological features. Survival curves were estimated using the Kaplan–Meier method. The log-rank test was performed to compare the survival curves affected by univariate factors. Multivariate Cox regression analyses were used to evaluate the prognostic factors in OS and DFS. In the multivariate analysis, the variables that had $p<0.20$ in univariate analysis were included. $p<0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS software program, version 25.0 (IBM, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software Inc, La Jolla, USA).

Results

Clinicopathological features. Table I shows the clinicopathological features of 305 patients who underwent a radical surgery from January 2010 to December 2015. The median age was 63 (range=25-87 years) and the patient group included 183 men and 122 women. Among the total patient group, 279 (91.48%) patients had preoperative CEA ≤5.0 ng/ml and 26 (8.52%) patients had preoperative CEA > 5.0 ng/ml. There were 299 (98.03%) patients with postoperative CEA ≤5.0 ng/ml and 6 (1.97%) patients with postoperative CEA >5.0 ng/ml.

Table I. *Clinicopathological features of patients*.

Variables	N (%)
Gender	
Male	183 (60.00)
Female	122 (40.00)
Median age (range,y)	63 (25-87)
BMI	
<25 kg/m^2	209 (68.52)
≥25 kg/m^2	96 (31.48)
Location	
Colon	176 (57.70)
Rectum	129 (42.30)
Histology	
Well	104 (34.10)
Moderately	190 (62.30)
Poorly	11 (3.60)
Tumor size	
≤2 cm	156 (51.15)
>2 cm	149 (48.85)
T stage	
T1	164 (53.77)
T2	141(46.23)
Number of retrieved LN	
<12	95 (31.15)
≥12	210 (68.85)
Lymphatic invasion	
Negative	274 (89.84)
Positive	31 (10.16)
Perineural invasion	
Negative	303 (99.34)
Positive	2 (0.66)
Preoperative CEA	
≤5.0 ng/ml	279 (91.48)
>5.0 ng/ml	26 (8.52)
Postoperative CEA	
≤5.0 ng/ml	299 (98.03)
>5.0 ng/ml	6 (1.97)

BMI: Body mass index; LN: lymph node; CEA: carcinoembryonic antigen.

Survival analysis based on the preoperative and postoperative CEA cut-off value of 5.0 ng/ml. There were no significant differences in OS or DFS between the preoperative CEA >5.0 ng/ml and CEA ≤5.0 ng/ml groups ($p=0.351$ and $p=0.112$, respectively) (Figure 1A and C). The patients with postoperative CEA >5.0 ng/ml compared to those with ≤5.0 ng/ml also showed no significant differences in OS or DFS ($p=0.383$ and $p=0.164$, respectively) (Figure 1B and D).

Re-determined the cut-off value of preoperative and postoperative CEA. Using the X-tile software, the cut-off

Table II. *Univariate analysis for overall survival and disease-free survival.*

	Univariate analysis for overall survival			Univariate analysis for disease-free survival		
	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Gender						
(Male *vs.* Female)	1.118	0.471-2.654	0.800	0.666	0.231-1.917	0.451
Age						
(≤63 *vs.* >63)	4.846	1.630-14.405	0.005	1.862	0.677-5.124	0.229
BMI						
(<25 *vs.* ≥25 kg/m^2)	0.661	0.242-1.806	0.420	1.286	0.467-3.539	0.626
Histology			0.116			0.047
Well	1			1		
Moderately	0.495	0.201-1.219	0.126	0.264	0.090-0.774	0.015
Poorly	2.038	0.446-9.311	0.358	1.045	0.134-8.160	0.967
Location						
(Colon *vs.* Rectum)	1.848	0.778-4.385	0.164	2.336	0.849-6.427	0.100
Tumor size						
(≤2 *vs.* >2 cm)	1.368	0.576-3.248	0.477	0.631	0.229-1.737	0.373
T stage						
(T1 *vs.* T2)	1.580	0.666-3.750	0.299	1.537	0.572-4.126	0.394
Number of retrieved LN						
(<12 *vs.* ≥12)	0.780	0.323-1.886	0.582	0.742	0.270-2.042	0.564
Lymphatic invasion						
(Negative *vs.* Positive)	1.488	0.438-5.053	0.524	2.081	0.593-7.304	0.252
Perineural invasion						
(Negative *vs.* Positive)	10.461	1.380-79.304	0.023	18.461	2.432-140.108	0.005
Preoperative CEA						
(≤2.3 *vs.* >2.3 ng/ml)	2.836	1.100-7.311	0.031	1.901	0.691-5.230	0.214
Preoperative CEA/tumor Size						
(≤0.8 *vs.* >0.8 ng/ml per cm)	1.956	0.716-5.339	0.190	2.646	0.754-9.286	0.129
Postoperative CEA						
(≤2.6 *vs.* >2.6 ng/ml)	4.435	1.868-10.526	0.001	6.078	2.281-16.200	<0.001

BMI: Body mass index LN: lymph node; CEA: carcinoembryonic antigen.

values for preoperative and postoperative CEA were re-determined as 2.3 and 2.6 ng/ml, respectively. We also determined that the cut-off value of preoperative CEA/tumor size was 0.8 ng/ml per cm. The patients were then divided into low (n=159) and high (n=146) preoperative CEA groups, low (n=113) and high (n=192) preoperative CEA/tumor size groups, and low (n=258) and high (n=47) postoperative CEA groups according to the new cut-off values.

Survival analysis according to the new cut-off values. The high preoperative CEA group had significantly worse OS compared to the low preoperative CEA group (p=0.024). In DFS, there was no significant difference between the two groups (p=0.206). There were no differences in OS or DFS between the high and low preoperative CEA/tumor size groups (p=0.182 and p=0.114, respectively). However, the high postoperative CEA group had significantly worse OS and DFS compared to the low postoperative CEA group (p<0.001 and p<0.001, respectively) (Figure 2A and B).

Univariate and multivariate analyses for OS and DFS. The univariate analysis for OS showed that p-values for age, histology, location, perineural invasion, preoperative CEA, preoperative CEA/tumor size, and postoperative CEA were less than 0.2 (Table II). In the multivariate analysis, both age (HR=4.342, 95%CI=1.427-13.211; p=0.010) and postoperative CEA (HR=3.550, 95%CI=1.451-8.685; p=0.006) were independently associated with OS (Model 1, Table III).

The univariate analysis for DFS showed that p-values for the histology, location, perineural invasion, preoperative CEA/tumor size and postoperative CEA were less than 0.2 (Table II). In the multivariate analysis, location (HR=2.873, 95%CI=1.007-8.194; p=0.048), perineural invasion (HR=23.318, 95%CI=2.332-233.163; p=0.007), and postoperative CEA (HR=5.851, 95%CI=2.132-16.052; p=0.001) were independently associated with DFS (Model 4, Table III).

Survival analysis of postoperative CEA in colon and rectal cancer. In colon cancer, the high postoperative CEA group had significantly worse OS and DFS compared to the low

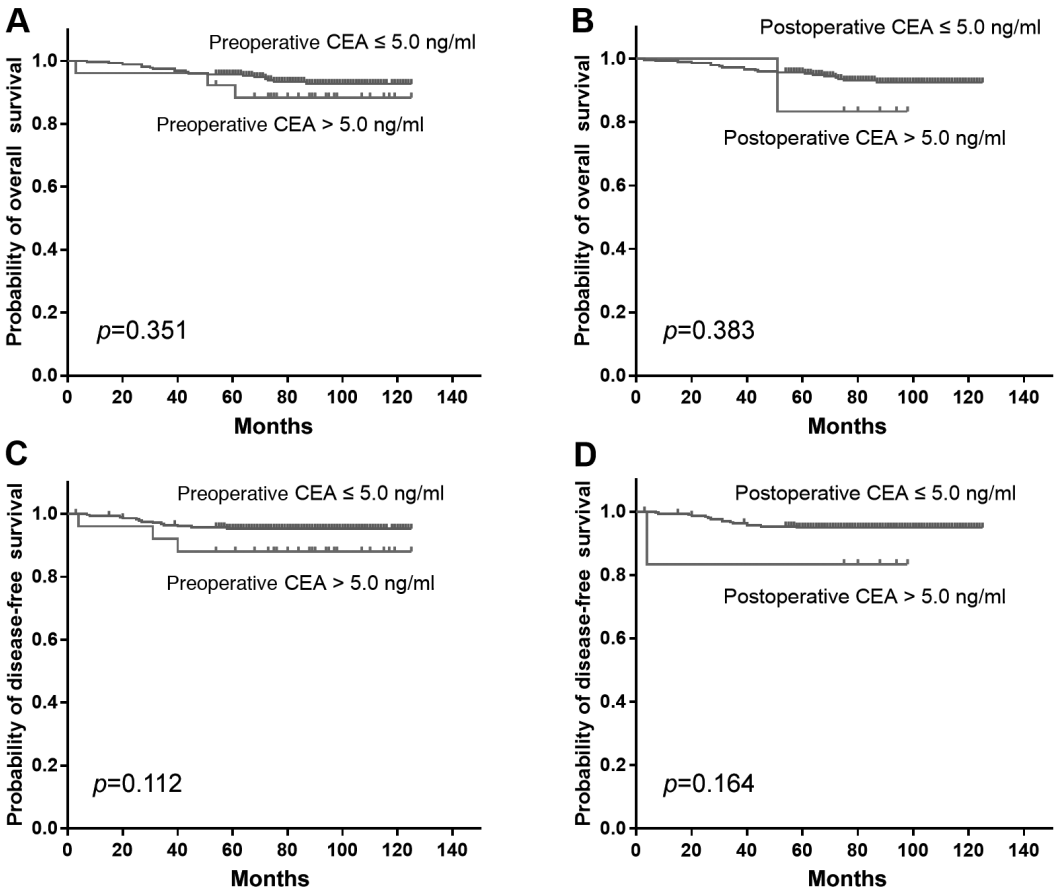

Figure 1. *Survival analysis based on the preoperative and postoperative CEA cut-off value of 5.0 ng/ml. A) Overall survival (OS) in the preoperative CEA ≤5.0 ng/ml and CEA >5.0 ng/ml groups. B) OS in postoperative CEA ≤5.0 ng/ml and CEA >5.0 ng/ml groups. C) Disease-free survival (DFS) in the preoperative CEA ≤5.0 ng/ml and CEA>5.0 ng/ml groups. D) DFS in the postoperative CEA ≤5.0 ng/ml and CEA >5.0 ng/ml groups.*

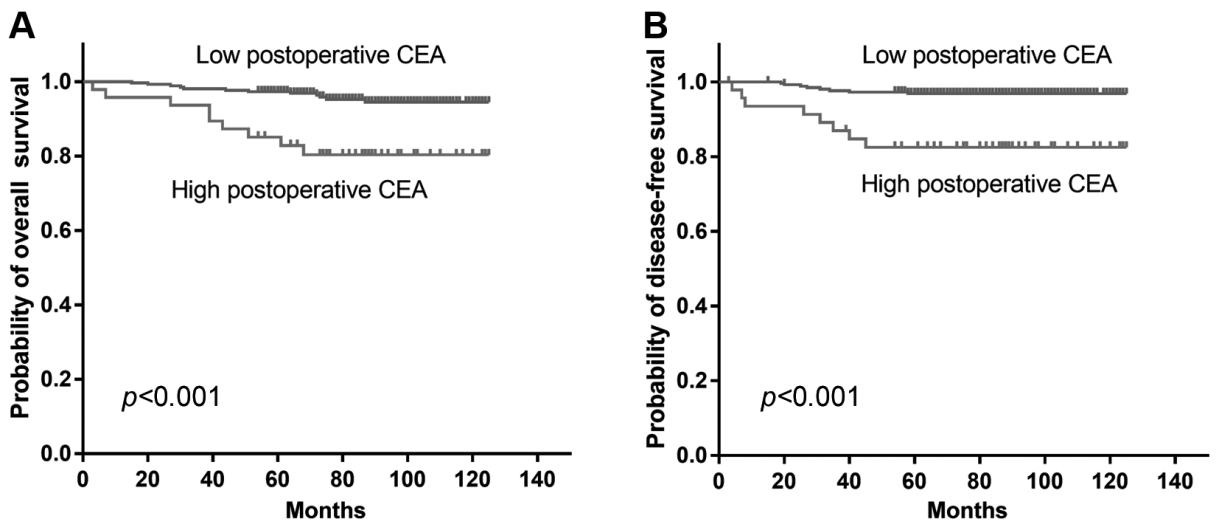

Figure 2. *Survival rates between high and low postoperative CEA groups. A) Overall survival in the two groups. B) Disease-free survival in the two groups.*

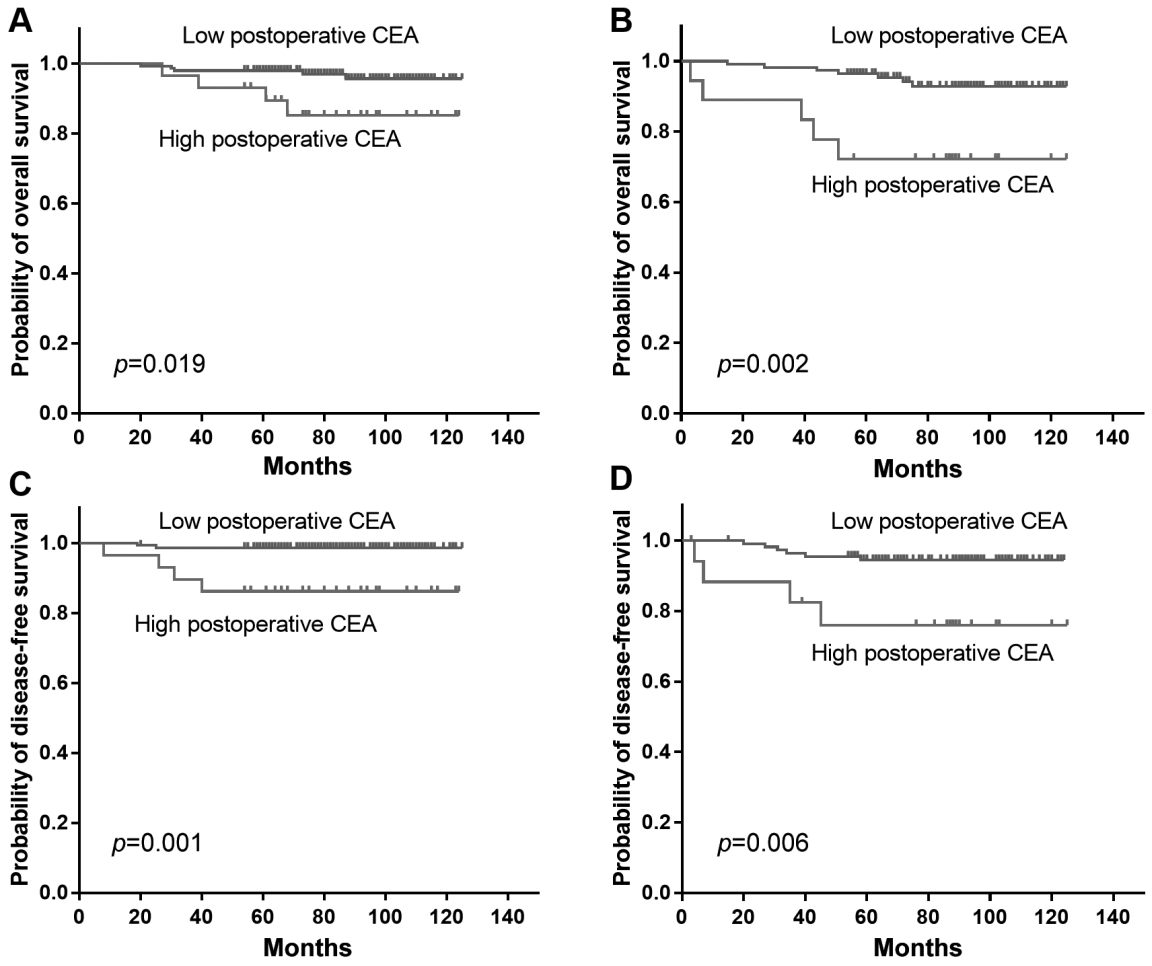

Figure 3. *Survival rates between high and low postoperative CEA groups in colon and rectum cancers. A) Overall survival (OS) in the two groups in colon cancer. B) OS in the two groups in rectum cancer. C) Disease-free survival (DFS) in the two groups in colon cancer. D) DFS in the two groups in rectum cancer.*

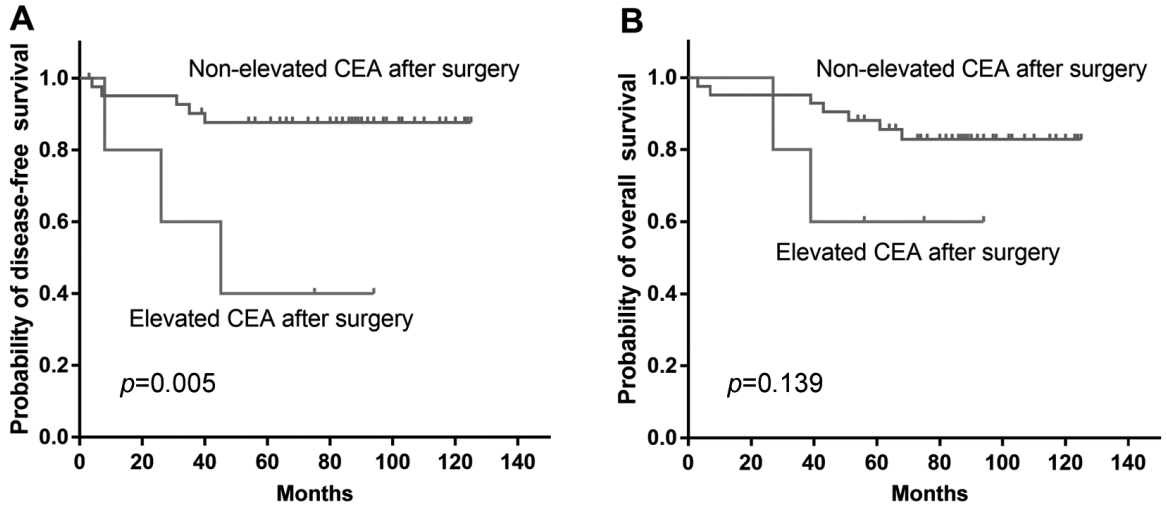

Figure 4. *Survival analysis in the high postoperative CEA group. A) Disease-free survival in the patients with elevated CEA after surgery and patients with non-elevated CEA after surgery. B) Overall survival in the two groups.*

Table III. *Multivariate analysis for overall survival and disease-free survival.*

	Hazard ratio	95%CI	*p*-Value
Model 1 – Overall survival			
Age (≤63 *vs.* >63)	4.342	1.427-13.211	0.010
Histology			0.242
Well	1		
Moderately	0.491	0.191-1.262	0.140
Poorly	1.295	0.276-6.073	0.743
Location (Colon *vs.* Rectum)	2.193	0.879-5.467	0.092
Perineural invasion (Negative *vs.* Positive)	2.119	0.240-18.691	0.499
Postoperative CEA (≤2.6 *vs.* >2.6 ng/ml)	3.550	1.451-8.685	0.006
Model 2 – Overall survival			
Age (≤63 *vs.* >63)	4.251	1.400-12.905	0.011
Histology			0.177
Well	1		
Moderately	0.454	0.180-1.145	0.094
Poorly	1.238	0.265-5.788	0.786
Location (Colon *vs.* Rectum)	2.139	0.868-5.274	0.099
Perineural invasion (Negative *vs.* Positive)	3.514	0.418-29.507	0.247
Preoperative CEA (≤2.3 *vs.* >2.3 ng/ml)	2.431	0.932-6.338	0.069
Model 3 – Overall survival			
Age (≤63 *vs.* >63)	4.833	1.595-14.643	0.005
Histology			0.186
Well	1		
Moderately	0.466	0.185-1.176	0.106
Poorly	1.301	0.277-6.103	0.739
Location (Colon *vs.* Rectum)	2.128	0.863-5.248	0.101
Perineural invasion (Negative *vs.* Positive)	3.791	0.455-31.587	0.218
Preoperative CEA/tumor size (≤0.8 *vs.* >0.8 ng/ml per cm)	2.050	0.741-5.672	0.167
Model 4 – Disease-free survival			
Histology			0.054
Well	1		
Moderately	0.260	0.085-0.791	0.018
Poorly	1.051	0.133-8.294	0.962
Location (Colon *vs.* Rectum)	2.873	1.007-8.194	0.048
Perineural invasion (Negative *vs.* Positive)	23.318	2.332-233.163	0.007
Postoperative CEA (≤2.6 *vs.* >2.6 ng/ml)	5.851	2.132-16.052	0.001
Model 5 – Disease-free survival			
Histology			0.036
Well	1		
Moderately	0.236	0.078-0.718	0.011
Poorly	0.949	0.121-7.469	0.961
Location (Colon *vs.* Rectum)	2.491	0.884-7.018	0.084
Perineural invasion (Negative *vs.* Positive)	41.405	3.949-434.079	0.002
Preoperative CEA/tumor size (≤0.8 *vs.* >0.8 ng/ml per cm)	3.152	0.818-12.146	0.095

BMI: Body mass index; LN: lymph node; CEA: carcinoembryonic antigen.

postoperative CEA group (p=0.019 and p=0.001, respectively) (Figure 3A and C). Similarly, in rectal cancer patients, the high postoperative CEA group had significantly worse OS and DFS compared to the low postoperative CEA group (p=0.002 and p=0.006, respectively) (Figure 3B and D).

Survival analysis based on CEA changes. Among the patients in the low postoperative CEA group, the patients with elevated CEA after surgery compared to the patients with non-elevated CEA showed no differences in OS or DFS (p=0.591 and p=0.511, respectively). Among the

Table IV. *The relationship between preoperative CEA and clinicopathological features.*

Variables	Postoperative CEA ≤2.6 ng/ml (N=258)	Postoperative CEA >2.6 ng/ml (N=47)	*p*-Value
Gender			0.060
Male	149 (57.75)	34 (72.34)	
Female	109 (42.25)	13 (27.66)	
Age			0.168
≤63	138 (53.49)	20 (42.55)	
>63	120 (46.51)	27 (57.45)	
BMI			0.340
<25 kg/m^2	174 (67.44)	35 (74.47)	
≥25 kg/m^2	84 (32.56)	12 (25.53)	
Location			0.546
Colon	147 (56.98)	29 (61.70)	
Rectum	111 (43.02)	18 (38.30)	
Histology			0.070
Well	83 (32.17)	21 (44.68)	
Moderately	167 (64.73)	23 (48.94)	
Poorly	8 (3.10)	3(6.38)	
Tumor size			0.518
≤2 cm	134 (51.94)	22 (46.81)	
>2 cm	124 (48.06)	25 (53.19)	
T stage			0.386
T1	136 (52.71)	28 (59.57)	
T2	122 (47.29)	19 (40.43)	
Number of retrieved LN			0.012
<12	73 (28.29)	22 (46.81)	
≥12	185 (71.71)	25 (53.19)	
Lymphatic invasion			0.290
Negative	234 (90.70)	40 (85.11)	
Positive	24 (9.30)	7 (14.89)	
Perineural invasion			0.285
Negative	257 (99.61)	46 (97.87)	
Positive	1 (0.39)	1 (2.13)	

BMI: Body mass index; LN: lymph node; CEA: carcinoembryonic antigen.

patients in the high postoperative CEA group, the patients with elevated CEA after surgery had significantly worse DFS compared to the patients with non-elevated CEA after surgery (p=0.005) (Figure 4A). However, there was no difference in OS between the two groups (p=0.139) (Figure 4B).

The relationship between postoperative CEA and clinicopathological features. There was no significant difference in gender, age, BMI, location, histology, tumor size, T stage, lymphatic invasion, and perineural invasion between the high and low postoperative CEA groups. However, the number of retrieved lymph nodes was significantly different between the two groups (p=0.012) (Table IV).

Discussion

It was reported that the use of adjuvant chemotherapy for stage II colorectal cancers could lead to a reduction in both local and distant recurrences and improved survival (10-12). For stage II colorectal cancer, several risks have been published that could justify adjuvant chemotherapy. However, adjuvant chemotherapy is not recommended in stage I colorectal cancer, and the risk factors for recurrence and optimal monitoring strategies have not been established, mainly due to the small percentage of patients with recurrence and death (13-15). The American Society for Clinical Oncology (ASCO) also noted that there was a lack of follow-up data for patients with stage I colorectal cancer (16). Therefore, we suggest that postoperative monitoring for stage I should be the same as in other stages of colorectal cancer.

CEA is considered to reliably detect the recurrence of colorectal cancer and is recommended as a prognostic factor for routine follow-up after surgery (17-19). Despite the fact that no agreement has been reached regarding cut-off values, many reports have demonstrated the prognostic value of CEA in colorectal cancer (5, 6, 20-22). Most of the previous studies evaluated the prognostic value of CEA in stage II-III colorectal cancer and few studies have been reported on stage I. To the best of our knowledge, this is the first report that evaluated the prognostic value of preoperative CEA, preoperative CEA/tumor size, and postoperative CEA in stage I colorectal cancer.

The results of this study indicated that the prognostic value of postoperative CEA was better than preoperative CEA and preoperative CEA/tumor size in stage I colorectal cancer. In the multivariate analysis, neither preoperative CEA nor preoperative CEA/tumor size was independently associated with OS or DFS. In practice, clinicians usually assume that the primary lesion is the source of high CEA levels when patients present with a high preoperative CEA and normal imaging examinations for surgery. Some may argue that the preoperative CEA is a prognostic factor in follow-up periods (23). That is, if patients have a high preoperative CEA, clinicians are more likely to assume the CEA is the result of metastasis. However, recurrence can be accompanied by normal or high CEA levels irrespective of preoperative CEA levels (24-27). In addition, some studies also suggest that postoperative CEA is a prognostic factor rather than preoperative CEA in patients with colorectal cancer. Konishi *et al*., who suggested that routine measurement of postoperative CEA rather than preoperative CEA was warranted in stage I to III colon cancer, showed that preoperative CEA was not a prognostic factor for recurrence if postoperative CEA was normalized (9). Lin *et al*. showed that the prognostic value of early postoperative CEA was better than that of the preoperative CEA in patients with curable colorectal cancer (28). Although these studies had demonstrated that the prognostic value of postoperative CEA was better than that of preoperative CEA,

neither compared the CEA/tumor size ratio. Therefore, as in a previous study (7), we used tumor size to adjust the confounding effect to improve the prognostic value of preoperative CEA, and found that the prognostic value of postoperative CEA was still better than that of the preoperative CEA/tumor size ratio. Thus, neither preoperative CEA nor preoperative CEA/tumor size influence surveillance guidelines in stage I colorectal cancer. Because tumor location was significantly associated with DFS in multivariate analysis, we conducted survival analysis according to the tumor location. We found the postoperative CEA was significantly associated with DFS both in colon and rectal cancer.

Moreover, the present study showed that the optimal cut-off value of postoperative CEA was 2.6 ng/ml. The patients with postoperative CEA >2.6 ng/ml had worse outcomes compared to those with CEA ≤2.6 ng/ml. However, when the cut-off value was 5 ng/ml, most patients (98.03%) reached normal levels, and there were no significant differences in OS or DFS. This low cut-off value is in line with previous studies, which indicate that the 5 ng/ml cut-off is not optimal for risk stratification in early-stage colorectal cancer (5, 6).

Previous studies have suggested that patients with elevated CEA after surgery had significantly worse outcomes compared to patients with non-elevated CEA in colorectal cancer (9, 29). This is consistent with our results showing that, among the high postoperative CEA group, the patients with elevated CEA after surgery had worse DFS compared to the non-elevated CEA group. On the other hand, among the low postoperative CEA patients, there were no differences in OS or DFS between the two groups. The results showed that, among the patients with high postoperative CEA, those with elevated CEA after surgery had a more prominent risk for recurrence.

In summary, routine measurement of postoperative CEA rather than preoperative CEA or preoperative CEA/tumor size is warranted in stage I colorectal cancer. During the postoperative follow-up period, a strong follow-up system should be provided for the patients with high postoperative CEA, and adjuvant treatment should be considered.

The present study had several limitations. First, because this was a single-center retrospective study with a small cohort, selection bias was hard to avoid. Therefore, large-scale studies are warranted to establish whether our risk stratification system is fully robust and to determine the optimal cut-off value of postoperative CEA. Second, we did not exclude patients who smoked or had other comorbidities such as liver disease and diabetes, which may affect the CEA levels (30-32). Finally, we did not separate colon and rectal cancers because in stage I colon and rectal cancer, radical surgery is the standard treatment and adjuvant chemotherapy is not recommended. Moreover, we demonstrated that the prognostic value of postoperative CEA was similar in colon and rectal cancers.

Conclusion

The present study showed that postoperative CEA is an independent risk factor in stage I colorectal cancer, while the preoperative CEA and preoperative CEA/tumor size are not. In addition, the common 5 ng/ml cut-off value was not optimal for risk stratification in stage I colorectal cancer. In the future, large-scale studies are warranted to establish the prognostic value of postoperative CEA in stage I colorectal cancer.

Conflicts of Interest

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

Authors' Contributions

Seung Yeop Oh and Guangzhe Pian collected data, designed this study, analysed data, revised this paper and gave the final approval. Jun Sang Shin and Sunseok Yoon collected data and revised this paper and gave final approval.

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