ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2021.100.1.33
Annals of Surgical Treatment and Research

Prognostic value of carcinoembryonic antigen levels before and after curative surgery in colon cancer patients

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Purpose: CEA is a useful tumor marker for colon cancer. The aim of this study was to investigate the prognostic value of changes in CEA levels before and after surgery in colon cancer patients who underwent radical surgery.
Methods: A total of 601 colon cancer patients who underwent radical surgery from January 2007 to December 2017 at a single institution were evaluated. Patients were categorized according to preoperative and postoperative CEA levels. We adjusted patient characteristics using propensity score matched analysis between groups and compared survival outcomes according to changes in CEA levels before and after surgery.
Results: According to the preoperative and postoperative CEA levels, patients were classified into 3 groups: group 1, ≤5 and ≤5 ng/mL, respectively (n = 407); group 2, >5 and ≤5 ng/mL, respectively (n = 127); and group 3 (>5 and >5 ng/mL, respectively (n = 67). Postoperative CEA elevation was associated with adverse clinical features. Before and after matching, the patients in group 3 showed significantly lower disease-free survival and overall survival rates compared to the patients in group 1 and group 2. In multivariate analysis, changes in CEA levels were an independent prognostic factor of overall survival (P = 0.041).
Conclusion: The changes in CEA levels before and after surgery can be a useful prognostic factor for disease-free survival and overall survival in colon cancer patients.
[Ann Surg Treat Res 2021;100(1):33-39]

Key Words: Carcinoembryonic antigen, Colonic neoplasms, Prognosis

INTRODUCTION

Tumor markers have been used for the diagnosis of cancer, evaluation of response to therapy, prediction of prognosis, or detection of recurrence. CEA is a glycoprotein that was first described in 1965 and is one of the most widely used tumor markers for many cancers, especially colon cancer [1-3]. The diagnostic and prognostic value of CEA has been extensively evaluated. Thus, CEA has been measured prior to surgery and every 3–6 months during follow-up after surgery in colon cancer.

Many researchers have investigated the role of serum CEA as a prognostic indicator in colon cancer. Serum CEA level is widely studied and easy to assess during the preoperative or postoperative periods. In some studies, the focus was on CEA level before surgery [4-11], while others focused on CEA level after surgery [12,13]. Another study sought to determine whether preoperative or postoperative CEA was more prognostic [14-16]; specifically, they asked whether elevated preoperative CEA was more prognostic. However, these before or after surgery studies are often simple to analyze, and there are few studies on the mode of change. Also, the reliability of the results may be reduced due to confounding bias.

In this study, we investigated the prognostic value of changes

Received July 28, 2020, **Revised** August 31, 2020,
Accepted October 9, 2020

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in CEA levels before and after surgery using propensity score matched analysis in colon cancer patients who underwent radical surgery.

METHODS

Patients

A total of 601 records of colon cancer patients who underwent surgical resection from January 2007 to December 2017 at Hallym University Sacred Heart Hospital in Anyang, Korea were retrospectively reviewed. All had histologically confirmed stage I–III primary colonic adenocarcinoma and underwent radical surgery for the primary tumor. Patients were excluded if they had no data for preoperative or postoperative CEA, recurrent or metastatic disease, hereditary colon cancer, synchronous malignancies, local excision, palliative surgery, or previous treatment for cancer (Fig. 1). This study was approved by Institutional Review Board of Hallym University Sacred Heart Hospital (No. 2020-07-027), which waived the need for written informed consent from patients due to the retrospective nature of this study.

Measurement of serum CEA levels

The serum CEA levels were measured using a microparticle enzyme immunoassay (ARCHITECT CEA Reagent Kit, ref. 7K68-27; Abbott, Wiesbaden, Germany) preoperatively and postoperatively (within 3 months after surgery and before starting adjuvant treatments). The normal range of serum CEA level was defined as less than or equal to 5 ng/mL. According to changes in CEA level before and after surgery, patients were divided into 3 groups as follows: group 1, preoperative CEA level ≤ 5 ng/mL and postoperative CEA level ≤ 5 ng/mL; group 2, preoperative CEA level > 5 ng/mL and postoperative CEA level ≤ 5 ng/mL; and group 3, preoperative CEA level > 5 ng/mL and postoperative CEA level > 5 ng/mL.

Assessment of clinical outcomes

Postoperative surveillance was performed every 3 months for the first 2 years after surgery, and then every 6 months for up 5 years. Most patients were evaluated with a physical examination, serum CEA level, and chest X-ray at each visit. Abdominopelvic CT and chest CT were performed every 6 months. Colonoscopy was performed after the first year and then biennially. Patients were categorized according to CEA levels as previously described. We adjusted patient characteristics between groups and compared survival outcomes. The primary endpoint of this study was disease-free survival and overall survival according to changes in CEA levels before and after surgery.

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics for Windows ver. 22.0 (IBM Corp., Armonk, NY, USA) and R software ver. 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Categorical variables were compared using the chi-square test or linear by linear association. A propensity score matched analysis was performed to minimize confounding bias for oncologic outcomes between the 3 groups. Survival rates were analyzed using the Kaplan-Meier method and the log-rank test. Multivariate analyses for

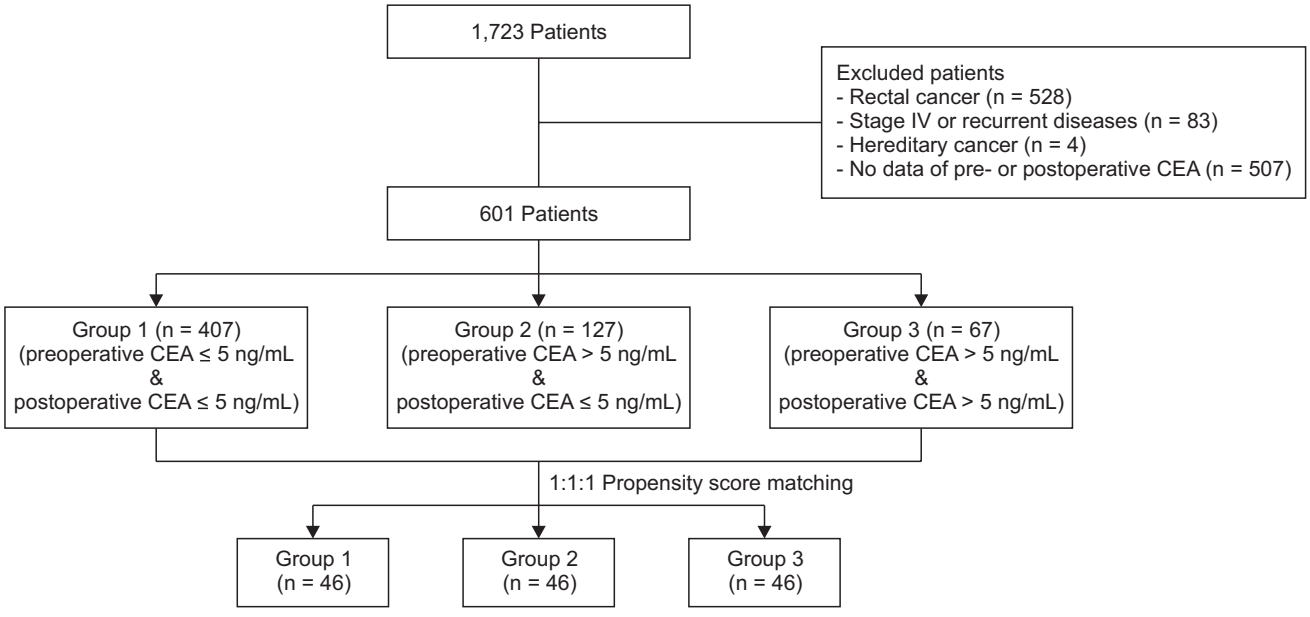

Fig. 1. Flow chart of this study.

prognostic factors were performed using a Cox proportional hazard model. Variables that were significant P-values in univariate analysis were entered into the multivariate model. The P-values were derived from two-tailed tests and $P \leq 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 601 patients with stage I–III colon cancer were included in this study. Among the total of 601 patients, preoperative CEA levels were normal in 407 and elevated in 194. Of the 194 patients with elevated preoperative CEA levels, 127 presented normalized CEA levels after surgery and 67 remained elevated in CEA levels after surgery. The median value of preoperative and postoperative CEA levels were 3.2 ng/mL (range, 1.0–1,252.0 ng/mL) and 1.9 ng/mL (range, 0.1–736.3 ng/mL), respectively. According to preoperative and postoperative CEA levels, patients were classified into 3 groups; 407 were in group 1, 127 were in group 2, and 67 were in group 3. There were no differences between groups in age or sex. Advanced stage, presence of lymphatic invasion, vascular invasion, or perineural invasion, and cases with adjuvant treatment were more common by group in the order of 3, 2, and 1 (Table 1). Therefore, patient characteristics were adjusted using propensity score matched analysis. We adjusted the patients at a 1-to-1 ratio with 46 patients in each group and determined that all variables were equally distributed (Table 2).

Table 1. Patient characteristics before matching

Variable	Group 1 (n = 407)	Group 2 (n = 127)	Group 3 (n = 67)	P-value
Age (yr)				0.422
<65	183 (45.0)	52 (40.9)	25 (37.3)	
≥65	224 (55.0)	75 (59.1)	42 (62.7)	
Sex				0.130
Male	217 (53.3)	80 (63.0)	40 (59.7)	
Female	190 (46.7)	47 (37.0)	27 (40.3)	
Cancer obstruction				<0.001
Yes	100 (24.6)	56 (44.1)	36 (53.7)	
No	307 (75.4)	71 (55.9)	31 (46.3)	
Cancer perforation				0.001
Yes	10 (2.5)	5 (3.9)	8 (11.9)	
No	397 (97.5)	122 (96.1)	59 (88.1)	
Pathologic stage				<0.001
I	141 (34.6)	17 (13.4)	5 (7.5)	
II	139 (34.2)	55 (43.3)	26 (38.8)	
III	127 (31.2)	55 (43.3)	36 (53.7)	
Cell type				0.383
WD/MD	380 (93.4)	115 (90.6)	60 (89.6)	
PD/MUC/SRC	27 (6.6)	12 (9.4)	7 (10.4)	
Lymphatic invasion				0.015
Yes	106 (26.0)	38 (29.9)	29 (43.3)	
No	301 (74.0)	89 (70.1)	38 (56.7)	
Vascular invasion				<0.001
Yes	42 (10.3)	19 (15.0)	19 (28.4)	
No	365 (89.7)	108 (85.0)	48 (71.6)	
Perineural invasion				<0.001
Yes	30 (7.4)	18 (14.2)	15 (22.4)	
No	377 (92.6)	109 (85.8)	52 (77.6)	
Adjuvant treatment				<0.001
Yes	152 (37.3)	65 (51.2)	40 (59.7)	
No	255 (62.7)	62 (48.8)	27 (40.3)	

Values are presented as number (%).
WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; MUC, mucinous carcinoma; SRC, signet ring cell carcinoma.

Table 2. Patient characteristics after matching

Variable	Group 1 (n = 46)	Group 2 (n = 46)	Group 3 (n = 46)	P-value
Age (yr)				0.869
<65	14 (30.4)	12 (26.1)	14 (30.4)	
≥65	32 (69.6)	34 (73.9)	32 (69.6)	
Sex				0.520
Male	30 (65.2)	31 (67.4)	26 (56.5)	
Female	16 (34.8)	15 (32.6)	20 (43.5)	
Cancer obstruction				>0.999
Yes	22 (47.8)	22 (47.8)	22 (47.8)	
No	24 (52.2)	24 (52.2)	24 (52.2)	
Cancer perforation				0.208
Yes	1 (2.2)	1 (2.2)	4 (8.7)	
No	45 (97.8)	45 (97.8)	42 (91.3)	
Pathologic stage				0.542
I	4 (8.7)	5 (10.9)	5 (10.9)	
II	13 (28.3)	20 (43.5)	18 (39.1)	
III	29 (63.0)	21 (45.7)	23 (50.0)	
Cell type				0.924
WD/MD	41 (89.1)	41 (89.1)	42 (91.3)	
PD/MUC/SRC	5 (10.9)	5 (10.9)	4 (8.7)	
Lymphatic invasion				0.465
Yes	16 (34.8)	16 (34.8)	21 (45.7)	
No	30 (65.2)	30 (65.2)	25 (54.3)	
Vascular invasion				0.871
Yes	9 (19.6)	8 (17.4)	10 (21.7)	
No	37 (80.4)	38 (82.6)	36 (78.3)	
Perineural invasion				0.434
Yes	5 (10.9)	9 (19.6)	9 (19.6)	
No	41 (89.1)	37 (80.4)	37 (80.4)	
Adjuvant treatment				0.679
Yes	25 (54.3)	29 (63.0)	26 (56.5)	
No	21 (45.7)	17 (37.0)	20 (43.5)	

WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; MUC, mucinous carcinoma; SRC, signet ring cell carcinoma.

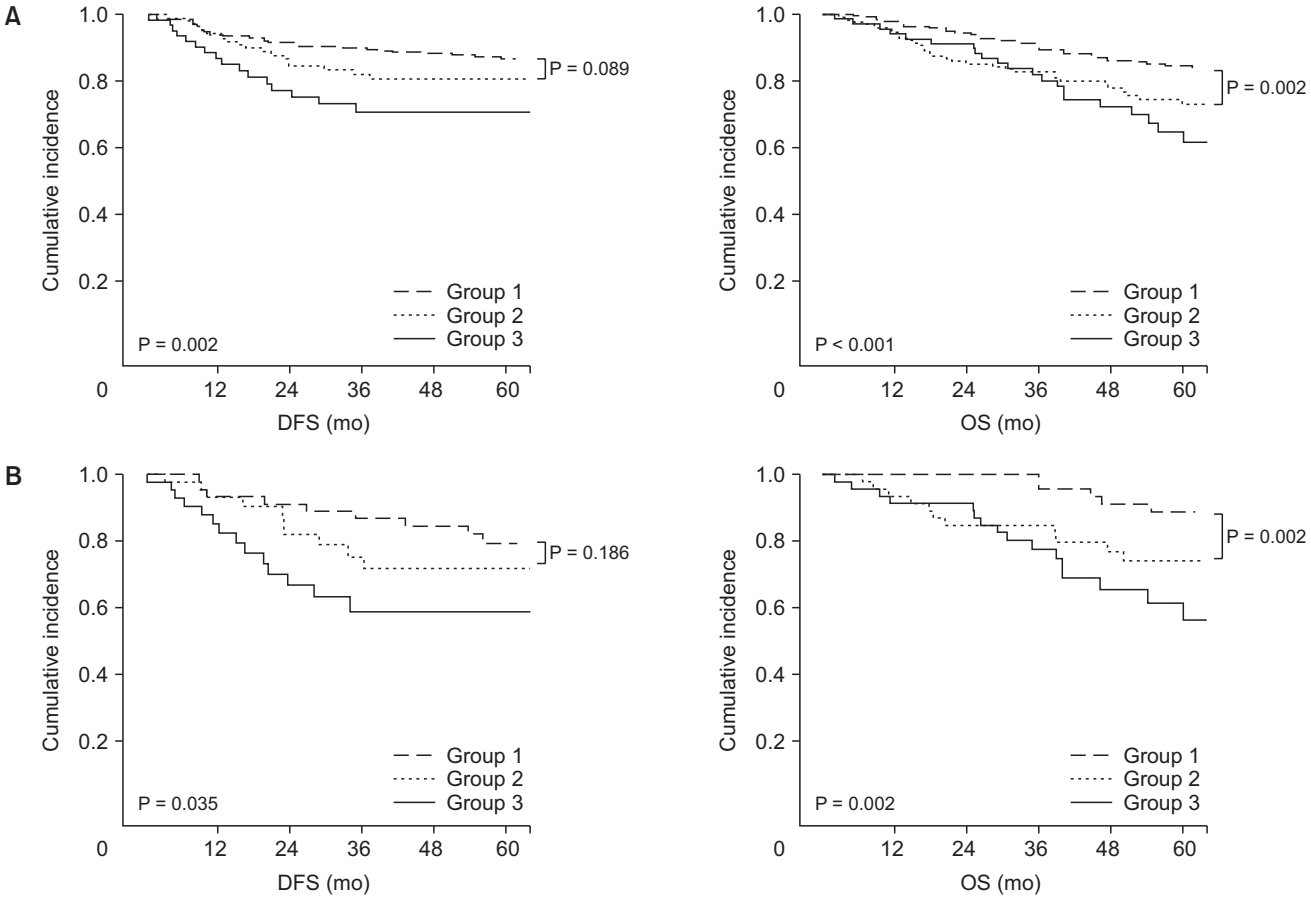

Fig. 2. Survival according to CEA before and after matching. (A) Before matching, disease-free survival (DFS) and overall survival (OS) were significantly worse in group 3 than in group 1 and group 2 (P = 0.002 and P < 0.001, respectively). (B) After matching, DFS and OS were still worse in group 3 than in group 1 and group 2 (P = 0.035 and P = 0.002, respectively).

Survival outcomes according to changes in CEA levels

In order to identify oncologic outcomes according to changes in CEA levels before and after surgery, disease-free survival and overall survival for each group were analyzed. Median follow-up duration was 43.4 months (range, 0.2–180.7 months). Before matching, disease-free survival was significantly worse in group 3 (76.6 ± 5.4 months) than in group 1 (144.0 ± 8.1 months) and group 2 (94.0 ± 1.7 months) (P = 0.002). Overall survival was significantly worse in group 3 (85.4 ± 5.8 months) than in group 1 (136.9 ± 12.5 months) and group 2 (106.5 ± 1.9 months) (P < 0.001) (Fig. 2A). After matching, there were still differences in disease-free survival and overall survival between groups (P = 0.035 and P = 0.002, respectively) (Fig. 2B).

To identify whether change in CEA levels before and after surgery was an independent prognostic factor for survival outcomes in colon cancer patients, a Cox proportional hazard model was performed. In multivariate analysis, change in CEA level was an independent prognostic factor for overall survival (P = 0.041) (Table 3).

DISCUSSION

In this study, we investigated the prognostic value of changes in CEA levels before and after surgery in colon cancer patients who underwent radical surgery. We observed an association between continuing CEA level elevation postoperatively and other adverse features such as bowel obstruction or perforation, advanced cancer stage, and presence of lymphatic invasion, vascular invasion, or perineural invasion. We adjusted these features to properly evaluate the prognostic value of changes in CEA levels in colon cancer patients pre- and postoperatively. Before and after matching, we observed that patients with continuing CEA level elevation after surgery showed significantly poorer survival outcomes compared to patients with lower CEA level postoperatively.

Many studies have investigated the role of serum CEA as a prognostic indicator in colon cancer. Many observational studies revealed preoperative CEA level was a significant indicator for recurrence and survival, while different studies found that postoperative CEA was an independent prognostic factor [8,12,14-20]. Also, population-based studies with large cohorts

Table 3. Prognostic factors for survival

Variable	Disease-free survival			Overall survival		
	Univariate	Multivariate		Univariate	Multivariate	
	P-value	HR (95% CI)	P-value	P-value	HR (95% CI)	P-value
CEA	0.003		0.071	<0.001		0.041
Group 2 *vs.* 1		1.503 (0.908–2.487)	0.113		1.362 (0.991–2.917)	0.058
Group 3 *vs.* 1		1.531 (1.021–2.295)	0.039		2.021 (1.518–3.115)	0.026
Age (yr), ≥65 *vs.* <65	0.153			<0.001	3.144 (2.088–4.733)	<0.001
Sex, female *vs.* male	0.987			0.482		
Cancer obstruction, yes *vs.* no	0.025	0.962 (0.604–1.534)	0.872	<0.001	1.370 (0.946–1.985)	0.096
Cancer perforation, yes *vs.* no	<0.001	3.156 (1.519–6.559)	0.002	0.042	1.922 (0.911–4.055)	0.086
Pathologic stage	<0.001		0.014	<0.001		0.008
II *vs.* I		3.047 (1.109–8.376)	0.031		0.912 (0.521–1.596)	0.748
III *vs.* I		4.739 (1.622–13.844)	0.004		1.720 (0.992–2.982)	0.053
Cell type, PD/MUC/SRC *vs.* WD/MD	0.615			0.460		
Lymphatic invasion, yes *vs.* no	<0.001	1.381 (0.824–2.312)	0.220	0.001	1.137 (0.746–1.733)	0.551
Vascular invasion, yes *vs.* no	0.017	0.910 (0.496–1.670)	0.760	0.002	1.211 (0.746–1.966)	0.440
Perineural invasion, yes *vs.* no	0.001	1.869 (1.216–2.900)	0.019	<0.001	2.050 (1.251–3.358)	0.004
Adjuvant treatment, yes *vs.* no	<0.001	1.359 (0.768–2.406)	0.292	0.263		

HR, hazard ratio; CI, confidence interval; PD, poorly differentiated; MUC, mucinous carcinoma; SRC, signet ring cell carcinoma; WD, well differentiated; MD, moderately differentiated.

reported that preoperative CEA level was an independent poor prognostic factor [14,21]. However, these studies showed insufficient CEA data, lack of adjustment for clinical features, and inclusion of patients with palliative surgery. In other studies, there were no significant CEA findings with respect to oncologic outcomes [22]. Konish et al. [23] reported similar results to ours. They suggested patients with elevated postoperative CEA are increased risk for recurrence compared to ones with elevated preoperative CEA that normalizes after resection. We further supported the results by adjusting the patient characteristics that may affect oncologic outcomes.

CEA is a 201 kDa highly glycosylated antigen expressed on the apical surface of colonic epithelial cells and that is excreted via the colonic lumen [1,14,17,24]. With the disruption of normal tissue architecture in malignancy and loss of polarization of neoplastic cells located deep inside the tumor glandular tissue, CEA may be expressed on the whole cell surface and is eventually shed into the bloodstream leading to a rise in serum CEA levels [17]. Elevated preoperative CEA levels are associated with advanced cancer stage, the incidence of recurrence, and survival. Also, high postoperative CEA levels are associated with residual disease and/or distant metastasis [24,25]. In colon cancer, it is important to predict patient prognosis and detect any early recurrence, thus efforts are being made to identify prognostic factors [22,26,27]. Measurement of serum CEA is simple, fast, inexpensive, and repeatable, thus it is likely to be widely used if the prognostic significance of CEA is established in colon cancer patients [28]. In this study, we confirmed changes in CEA levels were associated with clinical features and oncologic outcomes. These results may be useful in predicting recurrence and establishing treatment strategies, especially in patients with continued CEA level elevation after surgery.

There were some limitations in our study. This study was conducted retrospectively in a single institution. There was a lack of consideration of other factors contributing to false-positive CEA elevation, i.e., smoking, chronic obstructive pulmonary disease, acute or chronic inflammation, or benign tumor, etc. We did not analyze the effect of adjuvant treatment regimen. In addition, we did not compare other cut-off values for CEA. Despite these limitations, our study had the strength of using a propensity score matched analysis to evaluate the prognostic value of CEA level while overcoming the confounding bias between groups. Also, we evaluated CEA levels both before and after surgery to assess direction of any changes in this key metric.

In conclusion, preoperative and postoperative CEA levels can be reliable prognostic factors of disease-free survival and overall survival in colon cancer patients. It is necessary to measure CEA level not only preoperatively but also postoperatively. Close observation and active treatment are needed in patients whose CEA levels do not decrease after surgery.

ACKNOWLEDGEMENTS

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Investigation: HRK, JIJ
Methodology: JIJ, SWL
Project Administration: BYO
Writing – Original Draft: HRK, JIJ
Writing – Review & Editing: BYO, SWL

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