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Prognostic role of preoperative carcinoembryonic antigen levels in colorectal cancer: propensity score matching

Cho Shin Kim, Sohyun Kim

Department of surgery, Yeungnam University College of Medicine, Daegu, Korea

Background: This study was conducted to investigate preoperative carcinoembryonic antigen (CEA) as a prognostic factor in colorectal cancer.
Methods: Between January 2000 and July 2011, 1298 patients with primary adenocarcinoma colorectal cancer without metastasis, who underwent curative resection were retrospectively identified. The patients were divided into two groups according to serum CEA level at primary diagnosis: a high CEA (HCEA) group (serum CEA ≥6 ng/mL) and a normal CEA (NCEA) group (serum CEA <6 ng/mL). A 1:1 propensity score matching analysis was applied to reduce bias. Finally, 364 patients were enrolled in this study. Matched variables were age, gender, preoperative chemoradiotherapy, tumor site, cell differentiation and pathologic stage.
Results: The clinicopathological characteristics of the two groups did not differ significantly difference. The systemic metastasis rate was 16.5% (30/182) and 25.3% (46/182) in the NCEA and HCEA groups, respectively (p=0.039). There were no significant differences in local recurrence or metastatic sites between groups. The 5-year disease-free survival (DFS) rate of the HCEA group was worse than that of the NCEA group; however, there was no significant difference in overall survival between the two groups.
Conclusion: Elevated preoperative CEA was related to frequent systemic recurrence and low DFS. Therefore, elevated preoperative CEA could be considered a prognostic factor for worse clinical outcomes in patients with colorectal cancer.

Keywords: Carcinoembryonic antigen; Recurrence; Prognosis; Colorectal neoplasms

INTRODUCTION

Serum carcinoembryonic antigen (CEA) has been widely used as a tumor marker for colorectal cancer [1]. Serum CEA is usually tested at diagnosis, following treatment, and during surveillance. Serum CEA has been used as a predictive factor for early detection of recurrence after curative resection [2,3]. Although most colorectal tumors have been found to produce CEA, elevated CEA levels are not common upon at diagnosis of patients with colorectal cancer. Overall, studies have shown that 57-66% of patients with colorectal cancer have normal preoperative CEA levels, while 34-43% of patients present with elevated preoperative CEA levels [1,2]. Elevated serum CEA is usually related to advanced tumor stage [1]. However, patients with the same tumor stage have shown inconsistency in serum CEA levels, with only some patients presenting increased CEA levels [4].

Some studies have reported a prognostic role of preoperative CEA, with elevated preoperative CEA being a poor prognostic predictor [2,5]. Specially, Ozawa et al. showed that elevated preoperative CEA was associated with worse 5-year

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Corresponding Author: Sohyun Kim, Department of Surgery, Yeungnam University College of Medicine, 170, Hyeonchung-ro, Nam-Gu, Daegu 42415, Korea
Tel: +82-53-620-3594, Fax: +82-53-624-1213
E-mail: kshgs@yu.ac.kr

disease-free survival (DFS) and overall survival (OS) [5]. However, in these studies, the elevated preoperative CEA group showed higher pathologic tumor (T) and lymph node (N) stage than the normal preoperative CEA group. Thus, elevated preoperative serum CEA was correlated with advanced stage disease [6].

Pathologic stage has been used as strong prognostic factor in colorectal cancer [7,8]. However, a number of authors doubted that elevated preoperative CEA indicated advanced stage colorectal cancer instead of poor prognosis. Moreover, few previous reports have suggested a prognostic role of elevated preoperative CEA in colorectal cancer, regardless of pathologic stage. Therefore, this study was conducted to investigate the prognostic role of preoperative CEA levels across all stages of colorectal cancer by applying propensity score matching.

MATERIALS AND METHODS

We conducted a retrospective review using a database of 2069 patients between January 2000 and July 2011. The inclusion criteria were as follows: (1) histologic proven adenocarcinoma; (2) curative resection of primary tumor; (3) no histological or radiological proven distant metastasis at the time of primary diagnosis; and (4) no history of hereditary, metachronous colorectal cancer or other malignancies. We eventually reviewed the medical records of 1,569 patients who followed the inclusion criteria. Patients with carcinoma in situ (n=121) and those who did not have preoperative CEA (n=150) were excluded. Thus, 1,298 patients were enrolled in this study. Patients were divided into two groups according to serum CEA level at the time of primary diagnosis, with those having a preoperative CEA level greater than 6 ng/mL included in the High CEA (HCEA) group and patients with a CEA level of 6 ng/mL or less included in the Normal CEA (NCEA) group.

Curative resection was defined as the absence of gross or microscopic residual tumors from the surgical bed and resection margin. Curative resection included lymph node resection at the origin of the feeding vessel. Of 1,298 patients, 682 patients underwent laparoscopic surgery and 610 patients underwent open surgery. Most patients of stage II and stage III with high risk were considered for adjuvant chemotherapy and were administered 5-fluorouracil (5-FU)/leucovorin (LV), capecitabine, or oxaliplatin. Some patients with locally advanced rectal cancer underwent radiotherapy. A total of 54 patients received preoperative radiotherapy.

All patients underwent preoperative examinations, including physical examination, laboratory tests, abdominopelvic computed tomography (CT), chest CT, and CEA blood level test. Serum CEA levels were measured using an immunoassay (Chemiluminescent Microparticle immunoassay, Abbott, USA). The normal range for serum CEA is 0-6 ng/mL. Blood samples were collected 2 weeks before and 1 week after surgery. Some patients also underwent rectal or liver ultrasonography (US) and F-18 fluorodeoxyglucose positron emission tomography scan (FDG-PET); specifically, those presenting with or suspected of recurrence underwent FDG-PET. Pathologic staging was defined by the American Joint Committee on Cancer (AJCC), 7th edition. All patients underwent regular intervals follow-up after surgery that included physical examination, abdominopelvic and chest CT, and CEA blood level tests. In particular, the patients underwent follow-up CEA evaluation every 3 months for 2 years, then every 6 months for 3 years. Follow-up radiologic evaluation was performed every 6 months for 2 years, then every 12 months for 3 years. Systemic metastases were defined as metastases of distant organs such as liver and lung or peritoneum except local recurrence. Local recurrence was defined as recurrence of the previous surgical site.

Categorical variables were compared using the Chi-squared test or Fisher's exact test in both the HCEA and NCEA groups. All data were analyzed using IBM SPSS version 22.0 (IBM Co., Armonk, NY, USA). Statistical significance was defined as a p-value <0.05. Propensity score matching was used to compare significant differences in the characteristics of patients and reduce selection bias. The model was applied to obtain a one-to-one match. The following variates were matched for: age, gender, preoperative chemoradiotherapy, tumor site, cell differentiation, and pathologic stage.

RESULTS

Of the 1,298 patients, 751 (57.8 %) were men. The mean age of the patients was 62.4 years (range, 22-88 years) in the NCEA group and 62.6 years (range, 22-87 years) in the HCEA group. In the NCEA group, 602 (61.9%) cases were colonic

tumors and 371 (38.1%) were rectal tumors. In the HCEA group, 192 (59.1%) cases were colonic tumors and 133 (40.9%) were rectal tumors. There were significant differences in preoperative chemoradiotherapy (PCRT), pathologic T stage, N stage, histology grade, lymphatic invasion, vascular invasion, neural invasion, and postoperative chemotherapy between the HCEA and NCEA groups (Table 1).

After propensity score matching, 364 patients (182 NCEA and 182 HCEA patients) were eligible for further study. Of the 364 patients, 228 (72.6%) were men. The mean age of the patients was 63.3 years (range, 33-83 years) in both groups. There were no significant differences in any variables between groups (Table 1).

One week postoperatively, 179 patients (98.4%, 179/182) in the NCEA group presented normal postoperative CEA values. In the HCEA group, 138 patients (75.8%, 138/182) presented normal postoperative CEA values ($p<0.0001$).

Overall recurrence was presented in 32 patients (17.6%, 32/182) in the NCEA group and 48 patients (26.4%, 48/182) in the HCEA group ($p=0.043$). For analysis of recurrence patterns, the site of recurrence was divided into systemic metastasis and local recurrence. Systemic metastasis presented in 30 (16.5%) patients and 46 (25.3%) patients in the NCEA and HCEA groups, respectively ($p=0.039$). There were no significant differences in local recurrences and metastatic sites between groups ($p=1.000$ and 0.829, respectively) (Table 2).

There were significant differences in DFS between groups ($p=0.006$, Fig. 1A). In the NCEA and HCEA groups, the 5-year DFS was 80.4% and 67.5%, respectively. However, there was no significant difference in OS between groups ($p=0.092$, Fig. 1B). The 5-year OS rate of the NCEA and HCEA groups was 84.4% and 78.6%, respectively.

DISCUSSION

In this study, elevated preoperative CEA was associated with more frequent overall recurrence and systemic metastases regardless of tumor stage, and subsequently, with worse 5-year DFS. During the same stage, elevated preoperative CEA level was a relevant risk factor for recurrence, especially systemic metastasis. However, there was no significant difference in local recurrence and OS. Overall, the results of this study suggested that elevated preoperative CEA level is an independent prognostic factor in patients with colorectal cancer of the same stage.

Serum CEA has been shown to be affected by various factors including stage, tumor grade, site of origin in the colon and ploidy [9]. In particular, elevated serum CEA levels have been shown to be correlated with advanced stage, with mean serum concentrations of CEA were 4.2, 6.4, 23, and 102 ng/mL in Duke's A, B, C, and D stage tumors, respectively [10]. In a previous study, the rate of an abnormal preoperative CEA (>5 ng/mL) for UICC stage I, II, and III patients was 10%, 47.3%, and 48.6%, respectively [1]. Well-differentiated colorectal cancers produce higher CEA than poorly differentiated tissues [9]. According to Bhatnagar et al., the mean CEA levels in well-differentiated, moderately-differentiated, and poorly-differentiated colorectal adenocarcinomas were 18.0, 5.5, and 2.2 μg/g of protein, respectively [10]. Moreover, patients with colon tumor of the left side have been shown to have a significantly higher incidence of elevated CEA levels than those with tumors on the right side [9,11]. Furthermore, high levels produced by aneuploidy versus diploid patterns in colorectal tumors have been reported [9]. This study applied propensity score matching to reduce the effects of those factors on serum CEA levels and showed clinical effects of serum CEA.

Elevated preoperative CEA has been associated with overall recurrence, which has been shown in over 40% of patients with increased CEA, and 15% of patients with low preoperative CEA [2,12]. In the present study, after controlling pathologic stage, patients with elevated preoperative CEA showed more frequent overall recurrence than those with normal preoperative CEA. Thus, elevated preoperative CEA could be considered a prognostic factor for recurrence in the same stage.

Many previous studies have reported that elevated preoperative CEA was related to worse DFS and OS in colorectal cancer [13,14]. Becerra et al. demonstrated that elevated preoperative CEA was associated with a 48-78% increase in death hazard [2]. Huh, et al. reported that 5-year DFS and OS were 82.4% and 81.7% in the normal CEA group and 70.6% and 69.9% in the high CEA groups, respectively [13]. In those previous studies, the elevated preoperative CEA group was found to have a larger tumor size, and more advanced T and N stage [2,13,15]. Moreover, T stage, N stage, cell differentiation, and high preoperative CEA were associated with worse oncologic outcomes on multivariate analysis [2,16]. However, another study failed to confirm the correla

Table 1. Clinical characteristics of this study patients

Variable	Unmatched			Matched		
	NCEA (n=973)	HCEA (n=325)	*p*-value	NCEA (n=182)	HCEA (n=182)	*p*-value
Age (year)	62.4 (22-88)	62.6 (22-87)	0.333	63.3 (33-83)	63.3 (33-83)	1.000
Gender			0.701			1.000
Male	560 (57.6)	191 (58.5)		114 (72.6)	114 (72.6)	
Female	413 (42.4)	134 (41.2)		68 (37.4)	68 (37.4)	
ASA			0.356			1.000
1-2	907 (93.2)	298 (91.7)		170 (93.4)	168 (92.3)	
3-4	66 (6.8)	27 (8.3)		12 (6.6)	14 (7.7)	
PCRT			<0.001			1.000
No	907 (93.2)	245 (75.4)		155 (85.2)	155 (85.2)	
Yes	66 (6.8)	80 (24.6)		27 (14.8)	27 (14.8)	
Tumor site			0.371			1.000
Col on	602 (61.9)	192 (59.1)		126 (69.2)	126 (69.2)	
Rectum	371 (38.1)	133 (40.9)		56 (30.8)	56 (30.8)	
T stage			<0.001			0.137
yp Tis	24 (2.5)	7 (2.2)		2 (1.1)	3 (1.6)	
T1	152 (15.6)	7 (2.2)		8 (4.4)	7 (3.8)	
T2	162 (16.6)	16 (4.9)		20 (11.0)	8 (4.4)	
T3	553 (56.8)	237 (72.9)		130 (71.4)	133 (73.1)	
T4	82 (8.4)	58 (17.8)		22 (12.1)	31 (17.0)	
N stage			<0.001			0.873
0	634 (65.2)	158 (48.6)		89 (48.9)	89 (48.9)	
1	259 (26.6)	116 (35.7)		73 (40.1)	70 (38.5)	
2	80 (8.2)	51 (15.7)		20 (11.0)	23 (12.6)	
Histologic grade			0.003			1.000
G1-2	916 (94.1)	290 (89.2)		179 (98.4)	179 (98.4)	
G3	57 (5.9)	35 (10.8)		3 (1.6)	3 (1.6)	
Lymphatic invasion			0.015			0.818
No	592 (60.8)	178 (54.8)		97 (53.3)	93 (51.1)	
Yes	360 (37.0)	145 (44.6)		83 (45.6)	87 (47.8)	
Indeterminate	21 (2.2)	2 (0.6)		2 (1.1)	2 (1.1)	
Vascular invasion			0.026			0.560
No	875 (89.9)	285 (87.7)		166 (91.2)	160 (87.9)	
Yes	77 (7.9)	38 (11.7)		15 (8.2)	20 (11.0)	
Indeterminate	21 (2.2)	2 (0.6)		1 (0.5)	2 (1.1)	
Neural invasion			<0.001			0.900
No	744 (76.5)	216 (66.5)		128 (70.3)	124 (68.1)	
Yes	204 (21.0)	107 (32.9)		52 (28.6)	56 (30.8)	
Indeterminate	25 (2.5)	2 (0.6)		2 (1.1)	2 (1.1)	
Harvested lymph node	19.9±14.0	22.7±13.0	0.993	20.1±10.9	23.6±13.1	0.013
Postoperative chemotherapy			<0.001			0.457
No	229 (23.5)	43 (13.2)		29 (15.9)	24 (13.2)	
Yes	744 (76.5)	282 (86.8)		153 (84.1)	158 (86.8)	
Stage			<0.001			1.000
0	21 (2.2)	6 (1.8)		2 (1.1)	2 (1.1)	
I	252 (25.9)	18 (5.5)		11 (6.0)	11 (6.0)	
II	362 (37.2)	136 (41.9)		76 (41.8)	76 (41.8)	
III	338 (34.7)	165 (50.8)		93 (51.1)	93 (51.1)	

Values are presented as mean±standard deviation or number (%).
NCEA, normal carcinoembryonic antigen; HCEA, high carcinoembryonic antigen; ASA, American Society of Anesthesiologists; PCRT, preoperative chemoradiotherapy.

Table 2. Patterns of recurrence

	CEA <6 (n=182)	CEA ≥6 (n=182)	*p*-value
Systemic metastasis			0.039
No	152 (83.5)	136 (74.7)	
Yes	30 (16.5)	46 (25.3)	
Local recurrence			1.000
No	180 (98.9)	180 (98.9)	
Yes	2 (1.1)	2 (1.1)	
Metastases according to organ			
Hepatic	11 (6)	12 (6.6)	0.829
Pulmonary	7 (3.8)	16 (8.8)	0.083
Peritoneal	5 (2.7)	5 (2.7)	1.000
Etc	10 (5.5)	13 (7.1)	0.518

Values are presented as number (%).
CEA, carcinoembryonic antigen; Etc, et cetera.

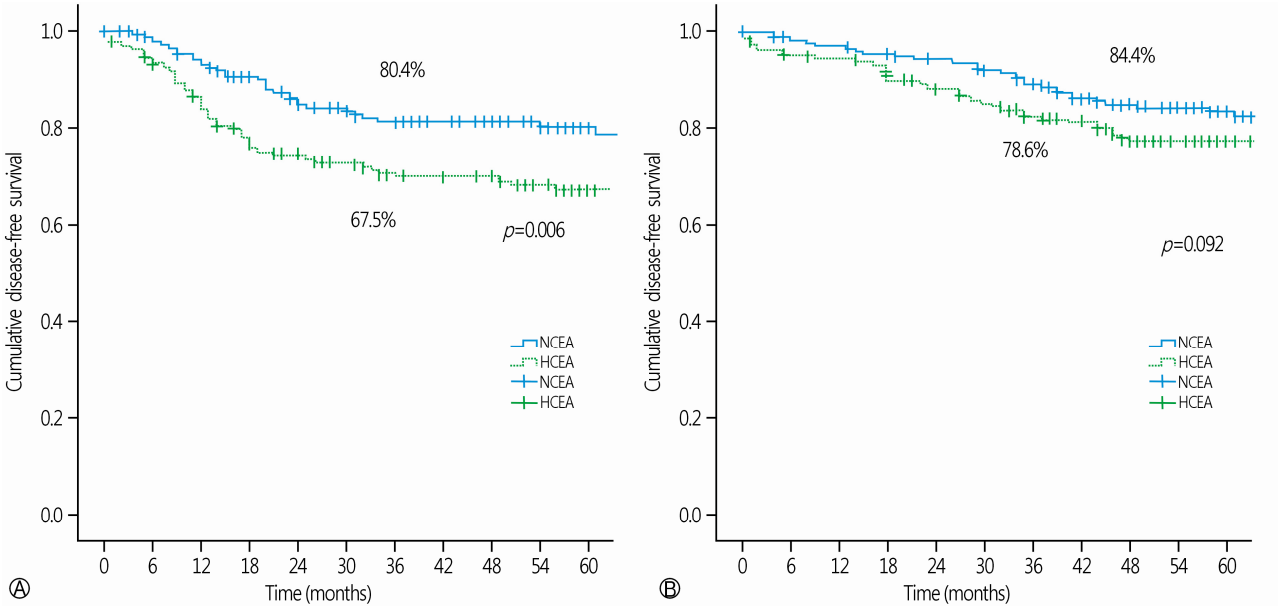

Fig. 1. (**A**) Five-year disease-free survival (p=0.006). (**B**) Five-year overall survival (p=0.092). NCEA, normal carcinoembryonic antigen; HCEA, high carcinoembryonic antigen.

tion between high preoperative CEA and worse clinical outcomes [15]. As previously discussed, T and N stages are important prognostic factors, while elevated preoperative serum CEA as a prognostic factor remains controversial. This study reduced the clinical effect of T and N stages, and elevated preoperative serum CEA was found to be related to worse DFS. The current study demonstrated that elevated preoperative serum CEA was not a marker for advanced tumor stage, but rather a poor prognostic factor.

In the current study, DFS was worse in the elevated preoperative CEA group, while OS was not worse after controlling T and N stages. The authors suggest the T and N stages were more influential to OS than elevated preoperative CEA. In a previous study, a steady decrease in OS with increasing T stage (T1-2, 75%; T3, 60%; T4, 47%; p<0.001) in rectal cancer has been observed [17]. Moreover, the N stage has been shown to affect the 5-year OS (N0, 74%; N1, 64%; N2, 48%; p<0.001) [17].

It should be noted that this study has several limitations. Although the study used propensity score matching to reduce

various biases, it is a retrospective study. The cutoff value of serum CEA was several levels according to study design [14,16]. Moreover, the size of this study was small. Additionally, serum CEA was likely influenced by smoking [18]; however, because of the study's retrospective nature, we could not consider the effects of smoking. We need further large-scale study to evaluated role of preoperative CEA.

To conclude, our study suggests that elevated preoperative CEA level is related to high systemic recurrence and poor DFS. Moreover, elevated preoperative CEA could be a prognostic factor for worse clinical outcomes in the same stage.

CONFLICT OF INTEREST

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

ORCID

Sohyun Kim, http://orcid.org/0000-0002-8625-329X

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