Ann Surg Oncol (2019) 26:1685–1694
https://doi.org/10.1245/s10434-019-07184-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

Preoperative Carcinoembryonic Antigen as a Poor Prognostic Factor in Stage I–III Colorectal Cancer After Curative-Intent Resection: A Propensity Score Matching Analysis

Shu-Huan Huang, MD[1], Wen-Sy Tsai, MD, PhD[1,2], Jeng-Fu You, MD[1], Hsin-Yuan Hung, MD[1], Chien-Yuh Yeh, MD[1], Pao-Shiu Hsieh, MD[1], Sum-Fu Chiang, MD[1], Cheng-Chou Lai, MD[1], Jy-Ming Chiang, MD[1], Reiping Tang, MD[1], and Jinn-Shiun Chen, MD[1]

[1]Division of Colon and Rectal Surgery, Chang Gung Memorial Hospital, Linkou, Taiwan; [2]College of Medicine, Chang Gung University, Taoyuan, Taiwan

ABSTRACT

Background. Preoperative carcinoembryonic antigen (CEA) has yet to be used as a prognostic or adjuvant chemotherapy factor for colorectal cancer (CRC).

Methods. This retrospective cohort study included all stage I–III CRC patients with different preoperative serum CEA levels ($\leq$ 5, 5–10, and $>$ 10 ng/ml) at a single center between 1995 and 2010. Propensity score matching was performed in a 1:1 ratio between the two elevated CEA groups (5–10 ng/ml and $>$ 10 ng/ml) and in a 1:2 ratio between the elevated and non-elevated groups ($\leq$ 5 ng/ml), with a caliper of 0.05.

Results. After exclusion and matching, 3857 patients had preoperative CEA levels $\leq$ 5 ng/ml, 1121 patients had CEA levels between 5 and 10 ng/ml, and 1121 patients had CEA levels $>$ 10 ng/ml. Elevated preoperative CEA showed an increased risk of overall survival (5–10 ng/ml: hazard ratio [HR] 1.376; $>$ 10 ng/ml: HR 1.523; both $p < 0.001$), cancer-specific survival (5–10 ng/ml: HR 1.404; $>$ 10 ng/ml: HR 1.712; both $p < 0.001$), and recurrence free interval (5–10 ng/ml: HR 1.190; $>$ 10 ng/ml: HR 1.468; both $p < 0.05$). Patients with negative lymph node staging (LNs) and CEA $>$ 10 ng/ml, as well as those with positive LNs and CEA $\leq$ 5 ng/ml, showed similar overall survival (5-year survival: 72% vs. 69%; $p = 0.542$) and recurrence free intervals (19.9 vs. 21.72 months; $p = 0.662$).

Conclusions. A preoperative CEA level can be an independent prognostic factor for stage I–III CRC after curative resection. Patients with negative LNs and preoperative CEA level $>$ 10 ng/ml should be considered for intensive follow-up or adjuvant chemotherapy.

Colorectal cancer (CRC) is the third most common cancer in men, the second most common cancer in women, and the fourth most common cause of cancer-related death worldwide.[1,2] Carcinoembryonic antigen (CEA) is a glycoprotein that was first described in 1965 as an antigen present in both fetal colon and colon adenocarcinoma.[3] It is a member of the immunoglobulin supergene family expressed in normal mucosa cells with the biological function of cell recognition or adhesion mechanisms.[4] In CRC patients, disruption of normal tissue structure and loss of polarization of neoplastic cells causes expression of CEA over the entire cell surface, causing its secretion into the blood, eventually increasing the serum CEA level.[5]

In earlier reports, elevated serum CEA levels $>$ 5.0 ng/ml have been shown to have an adverse impact on CRC prognosis.[6–8] Early in 2000, the American Joint Committee on Cancer (AJCC) proposed a C stage to indicate CEA levels $\geq$ 5 ng/ml, in addition to the TNM staging of CRC; [9] however, this proposal has not currently been adopted because of the lack of long-term data to estimate the survival of each AJCC stage with the inclusion of the C stage. Nonetheless, different cut-off values of preoperative CEA values were suggested, ranging from 2.5 to 50 ng/ml; 5 ng/ml was mainly used, with a mostly significant outcome difference.[10–21]

First Received: 17 August 2018;
Published Online: 26 March 2019

W.-S. Tsai, MD, PhD
e-mail: wensy@cgmh.org.tw; wensyt@gmail.com

CEA is also overexpressed in other cancers, including those of the pancreas, lung, prostate, urinary bladder, ovary, and breast,[5,22,23] and can also be elevated in some non-malignant conditions, such as cirrhosis, ulcerative colitis, chronic renal failure, hypothyroidism, and pancreatitis, and on cigarette smoking.[24–27] Therefore, it is suggested that the CEA level be adjusted for confounding factors before interpretation.

Although CEA is not a disease-specific marker, it is widely used as a tumor marker to monitor recurrence or to evaluate response to treatment in adenocarcinoma patients.[28] Serial CEA measurement has proven both safe and effective for detecting recurrence after curative resection of tumor, especially for CRC.[29] Moreover, changing between the preoperative and postoperative CEA levels is also suggested as an indicator of higher recurrence rate. Konishi et al.[30] reported that a cohort study on stage I–III CRC with curative surgery showed worst recurrence-free survival for both elevated preoperative and postoperative serum CEA, but similar recurrence survival between normalized postoperative CEA and the non-elevated group. However, another cohort study conducted by Tokodai et al.[31] showed preoperative rather than postoperative CEA elevation (5 ng/ml) was related to a higher recurrence rate in stage III CRC, but not stage II CRC.

Recently, the prognostic impact of preoperative CEA elevation on CRC was re-evaluated according to recent population-based studies, with significantly increased overall and cancer-specific mortality in patients with a preoperative CEA level > 5 ng/ml or up to two times the normal cut-off value.[21,32,33] Our previous report also showed that a CEA level > 5 ng/ml was an independent prognostic factor for poor overall survival (OS) in 8861 consecutive stage I–IV CRC patients.[15]

This current study aimed to evaluate the prognostic impact of CEA levels in patients with stage I–III CRC who underwent curative surgery, with adjustment of other non-malignant conditions associated with the influence of CEA levels.

MATERIALS AND METHODS

Data were collected from our prospective database based on a single medical center (Chang Gung Memorial Hospital, Linkou, Taiwan). Between 1 January 1995 and 31 December 2010, all consecutive stage I–III CRC patients were included and analyzed. All patients underwent routine preoperative evaluations, such as computerized tomography of the chest, abdomen, and pelvis, and their CEA data were collected. Postoperative follow-up visits were arranged on the basis of a standardized protocol. All recurrence and other primary cancer sites were recorded prospectively, along with disease status, date, and cause of mortality. Patients were classified into three different groups on the basis of their serum CEA levels (≤ 5 ng/ml, 5–10 ng/ml, and > 10 ng/ml). This study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 201601423B0).

Statistical significance was analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Pearson's Chi square test was used to analyze categorical variables, and an independent samples *t* test was used to analyze the mean variables. Propensity score matching was carried out using covariates such as age, sex, diabetes, smoking, serum creatinine > 2 mg/dl, liver cirrhosis, adjuvant chemotherapy, TNM stage, histological type, and tumor diameter > 4.5 cm. The Kaplan–Meier method was used to analyze OS and recurrence free interval (RI) in patients with recurrence, and a log-rank test p-value < 0.05 was considered a statistically significant difference in survival between groups. The Cox proportional hazards model was used for multivariate analyses of clinicopathological factors, with a p-value < 0.05 defined as statistically significant.

RESULTS

A total of 9634 patients with stage I–III CRC were included in this study. Non-curative resection cases that were not new or were secondary primary cases, were of non-colorectal origin or pathology, and that lacked preoperative CEA or preoperative serum creatinine data were excluded. For the remaining cases, propensity score matching was performed twice, with a 1:1 ratio between the two elevated CEA groups (5–10 ng/ml and > 10 ng/ml) and a 1:2 ratio between the matched elevated and non-elevated groups, with a caliper of 0.05. After exclusion and matching, 6099 matched cases were identified, with a mean follow-up 82.61 months and a maximal follow-up 183 months (Fig. 1). With the exception of advanced age, diabetes, serum creatinine level > 2 mg/dl, and a higher rate of mucinous adenocarcinoma, the elevated preoperative CEA levels were still significantly related to advanced age, TNM staging, smoking habits (including previous smokers and current smokers), and tumor diameter > 4.5 cm after matching (Table 1). Poor OS was proportional to CEA elevation in both lymph node staging (LNs) groups (5-year OS of patients with negative LNs: CEA ≤ 5 ng/ml: 83%, CEA 5–10 ng/ml: 77%, CEA $>$ 10 ng/ml: 72%; 5-year OS of patients with positive LNs: CEA ≤ 5 ng/ml: 69%, CEA 5–10 ng/ml: 56%, CEA $>$ 10 ng/ml: 50%), but a significant difference was only found between CEA ≤ 5 ng/ml and CEA > 10 ng/ml within both LNs groups. Moreover, similar OS was found

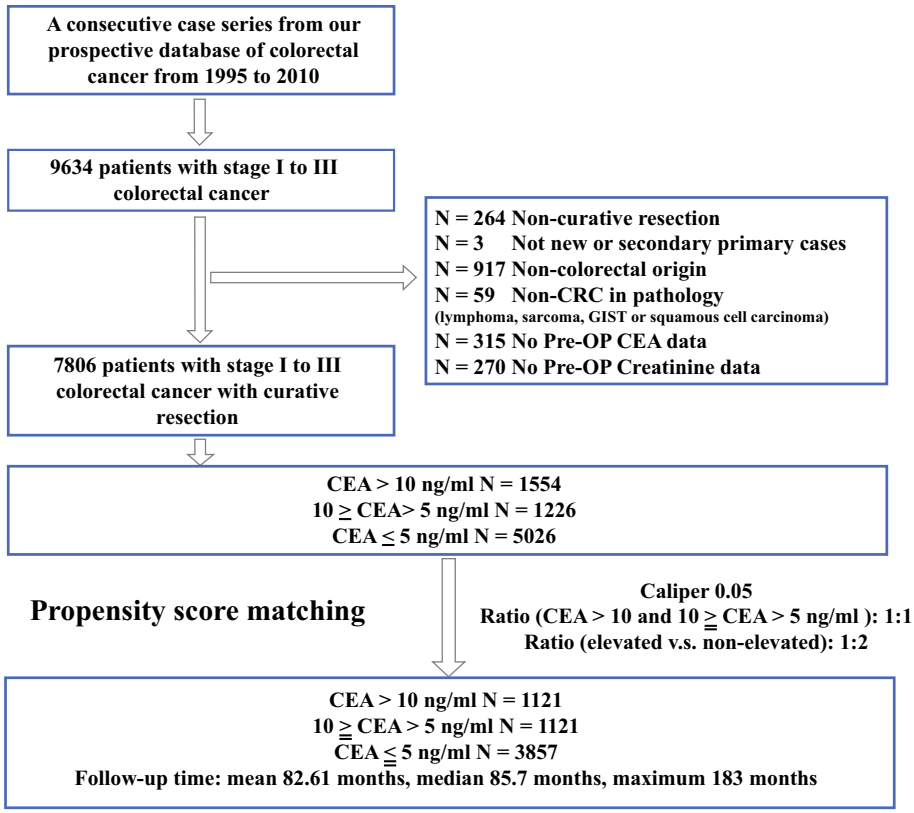


FIG. 1 Study population. *CEA* carcinoembryonic antigen

between patients with positive LNs and CEA ≤ 5 ng/ml, and patients with negative LNs and CEA > 10 ng/ml ($p = 0.542$) (Fig. 2a). Poor oncologic outcome was also correlated to CEA elevation. There was a significant difference in cancer-specific survival (CSS) among different CEA levels for both the positive and negative LN groups (5-year CSS of patients with negative LNs: CEA ≤ 5 ng/ml: 92%, CEA 5–10 ng/ml: 87%, CEA > 10 ng/ml: 82%; 5-year CSS of patients with positive LNs: CEA ≤ 5 ng/ml: 75%, CEA 5–10 ng/ml: 65%, CEA > 10 ng/ml: 56%), except between the groups with CEA levels of 5–10 ng/ml and > 10 ng/ml in the positive LNs group ($p = 0.064$) (Fig. 2b). For patients with recurrence, the recurrence free interval of patients with positive LNs was significantly shorter in proportion to CEA levels (CEA ≤ 5 ng/ml: 21.72, CEA 5–10 ng/ml: 18.17, and CEA > 10 ng/ml: 13.58 months; $p < 0.05$ between each group), but was only significant in the negative LNs group between CEA ≤ 5 ng/ml and CEA > 10 ng/ml (24.65 vs. 19.90 months; $p = 0.036$). As with OS, the RI was similar between the groups of patients with negative LNs and CEA > 10 mg/ml, and patients with positive LNs and CEA < 5 ng/ml (19.9 vs. 21.72 months; $p = 0.662$) [Fig. 2c]. With regard to first metastatic sites and their correlation to CEA levels, a higher rate of bone metastasis was found in the group of patients with non-elevated CEA than the two groups of patients with elevated CEA (8.1% vs. 5.8% and 5.5%; $p = 0.027$) [Table 2].

After adjusting for other clinicopathological factors, multivariate regression analysis showed a significantly higher hazard ratio (HR) associated with elevated serum CEA levels in OS (HR 1.376 and 1.523), CSS (HR 1.404 and 1.712), and RI (HR 1.190 and 1.468), with a p-value < 0.01 (Table 3).

DISCUSSION

In our results, preoperative CEA elevation is an independent factor for poor prognosis, even after adjusting for benign factors related to CEA elevation. Our results also revealed that patients with a CEA level > 10 ng/ml had significantly shorter RI on recurrence, indicating that CEA-producing tumors had higher metastatic potential. Animal experiments showed that metastatic ability was decreased by > 50% in mice following CEA knockdown, which implied its influence on metastatic progression.[34] Our data supported other findings that, in addition to other oncological factors, CEA elevation was also an independent risk factor of metastasis, indicating the feasibility of using adjuvant chemotherapy for CRC patients after curative surgery.

TABLE 1 Clinicopathological factors between different CEA levels before and after propensity score matching

	Before propensity score matching				After propensity score matching			
	CEA ≤ 5 ng/ml	5 < CEA ≤ 10 ng/ml	CEA > 10 ng/ml	*p*-Value	CEA ≤ 5 ng/ml	5 < CEA ≤ 10 ng/ml	CEA > 10 ng/ml	*p*-Value
No. of cases	5026	1226	1554		3857	1121	1121	
Age (± SD)	62 (13.34)	65.1 (12.59)	64.1 (13.32)	< 0.001	63.28 (13.19)	64.95 (12.80)	63.96 (13.17)	0.001
Sex								
Male	2773 (55.2)	738 (60.2)	797 (51.3)	< 0.001	2174 (56.4)	648 (57.8)	631 (56.3)	0.673
Female	2553 (44.8)	488 (39.8)	757 (48.7)		1683 (43.6)	473 (42.2)	490 (43.7)	
Smoking[a]	1812 (36.1)	534 (43.6)	592 (38.1)	< 0.001	495 (12.8)	177 (15.8)	167 (14.9)	0.019
Diabetes	561 (11.2)	193 (15.7)	301 (19.4)	< 0.001	1274 (33)	405 (36.1)	404 (36)	0.053
Serum creatinine > 2 mg/dl	94 (1.9)	54 (4.4)	52 (3.3)	< 0.001	1503 (39.0)	476 (42.5)	450 (40.1)	0.106
Liver cirrhosis	31 (0.6)	20 (1.6)	12 (0.8)	0.002	79 (2)	34 (3)	34 (3)	0.054
Cardiac disease	387 (7.7)	119 (9.7)	124 (8.0)	0.068	24 (0.6)	9 (0.8)	11 (1)	0.430
Stroke	176 (3.5)	52 (4.2)	61 (3.9)	0.410	318 (8.2)	105 (9.4)	88 (7.9)	0.382
Organ								
Colon	2523 (50.2)	597 (48.7)	804 (51.7)	0.203	1998 (51.8)	555 (49.5)	567 (50.6)	0.130
Rectum	2372 (47.2)	599 (48.9)	699 (45.0)		1758 (45.6)	545 (48.6)	517 (46.1)	
Both	131 (2.6)	30 (2.4)	51 (3.3)		101 (2.6)	21 (1.9)	37 (3.3)	
TNM stage								
I	1125 (22.4)	129 (10.5)	57 (3.7)	< 0.001	308 (8)	81 (7.2)	53 (4.7)	< 0.001
II	1993 (39.7)	491 (40)	644 (41.4)		1674 (43.4)	442 (39.4)	515 (45.9)	
III	1908 (38.0)	606 (49.4)	853 (54.9)		1875 (48.6)	598 (53.3)	553 (49.3)	
T stage								
T0	2	0	0					
T1	497 (9.9)	45 (3.7)	11 (0.7)	< 0.001	155 (4)	27 (2.4)	11 (1)	< 0.001
T2	878 (17.5)	108 (8.8)	63 (4.1)		400 (10.4)	78 (7)	54 (4.8)	
T3	2214 (44.1)	573 (46.7)	754 (48.5)		1995 (51.7)	543 (48.4)	553 (49.3)	
T4	1435 (28.6)	500 (40.8)	726 (46.7)		1307 (33.9)	473 (42.2)	503 (44.9)	
N stage								
N0	3107 (61.8)	620 (50.6)	701 (45.1)		1977 (51.3)	523 (46.7)	567 (50.6)	
N1	1241 (24.7)	364 (29.7)	479 (30.8)	< 0.001	1222 (31.7)	358 (31.9)	302 (26.9)	< 0.001
N2	678 (13.5)	242 (19.7)	374 (24.1)		658 (17.1)	240 (21.4)	252 (22.5)	
Histological type								
Adenocarcinoma	4697 (93.5)	1144 (93.3)	1411 (90.8)		3566 (92.5)	1039 (92.7)	1038 (92.6)	
Signet ring cell carcinoma	35 (0.7)	10 (0.8)	11 (0.7)	0.005	32 (0.8)	10 (0.9)	7 (0.6)	0.948
Mucinous adenocarcinoma	294 (5.8)	72 (5.9)	132 (8.5)		259 (6.7)	72 (6.4)	76 (6.8)	
Tumor diameter > 4.5 cm	1891 (37.6)	543 (44.3)	866 (55.7)	< 0.001	1748 (45.3)	534 (47.6)	566 (50.5)	0.007

TABLE 1 continued

	Before propensity score matching				After propensity score matching			
	CEA ≤ 5 ng/ml	5 < CEA ≤ 10 ng/ml	CEA > 10 ng/ml	*p*-Value	CEA ≤ 5 ng/ml	5 < CEA ≤ 10 ng/ml	CEA > 10 ng/ml	*p*-Value
Poor differentiation	316 (6.3)	71 (5.8)	107 (6.9)	0.491	279 (7.2)	69 (6.2)	71 (6.3)	0.333
Lymph nodes < 12[b]	1097 (21.8)	257 (21)	267 (17.2)	< 0.001	727 (18.8)	209 (18.6)	213 (19)	0.977
Chemotherapy[c]	1675 (33.3)	476 (38.8)	712 (45.8)	< 0.001	158 (4.1)	48 (4.3)	42 (3.7)	0.804

Data are expressed as *n* (%) unless otherwise specified

CEA carcinoembryonic antigen, *SD* standard deviation

[a]Including ex-smokers and current smokers

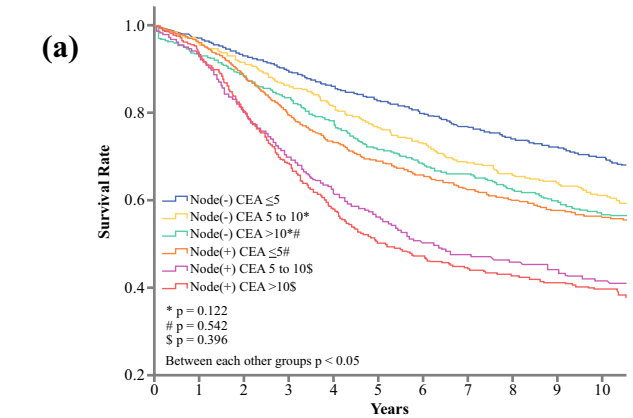
[b]Retrieved lymph nodes

[c]Adjuvant chemotherapy

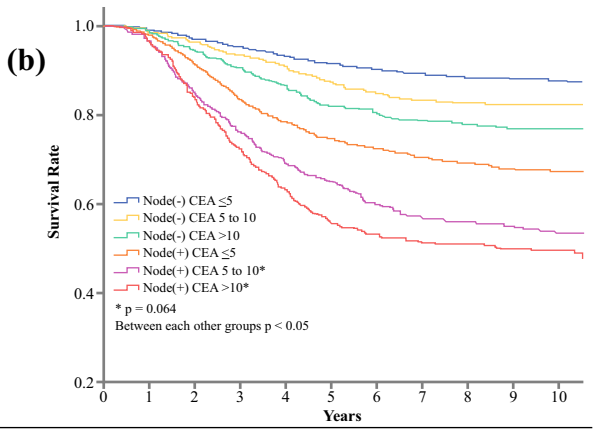
A population-based study with a total of 16,619 CRC patients reported that patients with preoperative CEA > 5 ng/ml were independently associated with an increased risk of cancer-specific mortality and poorer prognosis in each AJCC stage;[32] however, that study had some limitations, such as the lack of adjustment for benign factors of CEA elevation, heterogeneity of staging, and type of operation (including curative or palliative resection), with no mention of RI. Another population-based study with 137,381 stage I–III colon cancer patients also showed that an elevated CEA level had a 62% increase in the hazard of death compared with patients with a normal CEA level, but nearly 50% of enrolled patients lacked preoperative CEA data.[21] Ozawa et al.[33] reported a 144% increase in the hazard of recurrence with stage I CRC, 42% with stage II CRC, and 67% with stage III CRC, with elevation of the CEA level after curative resection; however, the cut-off value was different between each participating institute. After all, these three observational studies were all supportive of the inclusion of CEA level as another high-risk feature that clinicians can use to counsel patients regarding adjuvant chemotherapy, especially for stage II patients.[21,32,33]

Generally, the cut-off level of 5 ng/mL was used to define CEA elevation, but some studies showed different optimal cut-off levels for recurrence prediction at different stages. Takagawa et al.[35] reported that the optimal cut-off value for preoperative serum CEA levels was 10 ng/ml in 638 stage I–III CRC patients. Relapse-free survival between CEA levels > 10 ng/ml and < 10 ng/ml significantly differed in patients with stage II and III CRC, but not in stage I CRC patients after curative surgery. Kim et al.[17] reported an optimal cut-off level of 6 ng/ml for stage IIa CRC patients who underwent curative surgery, with poor 5-year disease-free survival and OS. Moreno García et al. reported a cut-off value of 2.5 ng/ml in stage I–III rectal cancer patients who underwent both chemoradiotherapy and surgery, which showed an insignificant HR in OS and cancer-free survival;[10] however, both cut-off values were limited to certain subgroups, which limits their application.

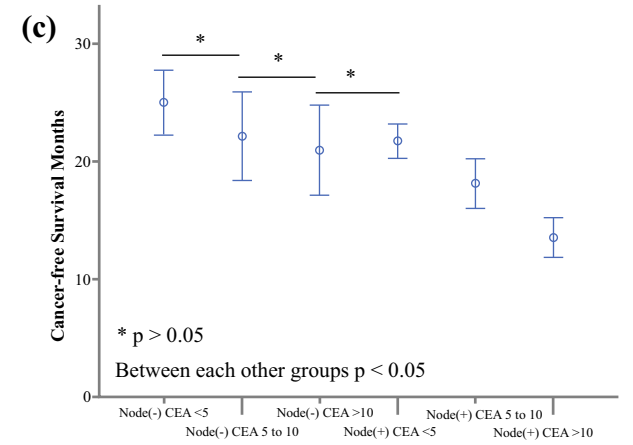
In the current study focused on stage I–III patients who underwent curative surgery between 1995 and 2010, we collected 7806 consecutive cases, with less bias caused by cross-sectional heterogeneity of treatment, follow-up interval, and CEA measurements compared with those studies based on nationwide cancer databanks. Our findings not only revealed that preoperative CEA was an independent prognostic factor of OS and CSS, but that the HR also significantly increased gradually from normal CEA levels, CEA levels between 5 and 10 ng/ml, to CEA levels > 10 ng/ml. CEA levels > 10 ng/ml were significantly associated with shorter poor OS and RI of patients and were



Node(-) CEA ≤5	1982	1917	1837	1703	1685	1595	1442	1244	1123	991	783
Node(-) CEA 5 to 10	522	498	476	448	418	382	338	291	253	228	193
Node(-) CEA >10	568	530	500	470	437	394	340	308	277	229	187
Node(+) CEA ≤5	1875	1796	1654	1482	1360	1235	1063	904	790	682	552
Node(+) CEA 5 to 10	598	551	479	415	363	321	256	226	202	175	140
Node(+) CEA >10	553	515	440	373	313	254	229	190	164	144	119



Node(-) CEA ≤5	1982	1917	1837	1703	1685	1595	1442	1244	1123	991	783
Node(-) CEA 5 to 10	522	498	476	448	418	382	338	291	253	228	193
Node(-) CEA >10	568	530	500	470	437	394	340	308	277	229	187
Node(+) CEA ≤5	1875	1796	1654	1482	1360	1235	1063	904	790	682	552
Node(+) CEA 5 to 10	598	551	479	415	363	321	256	226	202	175	140
Node(+) CEA >10	553	515	440	373	313	254	229	190	164	144	119



Mean Months	**24.65**	**22.21**	**19.90**	**21.72**	**18.17**	**13.58**
95% CI	22.09-27.17	18.69-26.03	16.46-23.67	20.21-23.31	16.12-20.16	12.12-15.30

FIG. 2 **a** Overall survival, **b** cancer-specific survival, and **c** recurrence free interval between patients with different levels of CEA after propensity score matching. *CEA* carcinoembryonic antigen, *CI* confidence interval

comparable with the reports by Ozawa et al. and Takagawa et al.[33,35] Tumors with a higher preoperative CEA level had more rapid development of metastasis if occurred. Although National Comprehensive Cancer Network guidelines did not include elevated serum CEA levels as a high-risk factor because previous randomized trials did not account for CEA levels in risk stratification for adjuvant therapy,[36–38] recent studies, as well as our findings, have provided more evidence to support the inclusion of C stage into stage-specific prognostic data that can be applied to intensive postoperative follow-up and aggressive adjuvant chemotherapy. In stage I and II CRC patients, the standard treatment is surgical resection alone, while adjuvant therapy is reserved for patients with high-risk factors, including tumors with poorly differentiated histology, lymphovascular invasion, obstruction, perforation, < 12 LNs examined, and close/positive margins.[39] Besides these traditional clinicopathological factors, preoperative CEA elevation should also be considered a high-risk factor of metastasis, especially CEA levels > 10 ng/ml; however, further randomized trials are necessary to prove the application of adjuvant chemotherapy, depending on pre-operative CEA levels.

CEA elevation also occurs in benign conditions. Several recent studies have investigated the association of CEA with multiple non-malignant factors for the improvement

TABLE 2 First metastatic site between patients with different serum CEA levels after propensity score matching

	CEA ≤ 5	5 < CEA ≤ 10	CEA > 10	*p*-Value
No. of cases	896	378	440	
Multiple metastasis	228 (25.4)	94 (24.9)	98 (22.3)	0.440
Lung	280 (31.3)	114 (30.2)	133 (30.2)	0.263
Liver	318 (35.5)	145 (38.4)	151 (34.3)	0.873
Anastomosis	103 (11.5)	45 (11.9)	51 (11.6)	0.218
Pelvic organ	136 (15.2)	56 (14.8)	66 (15.0)	0.305
Intra-abdominal	67 (7.5)	28 (7.4)	25 (5.7)	0.756
Retroperitoneum	70 (7.8)	21 (5.6)	40 (9.1)	0.535
Bone	73 (8.1)	22 (5.8)	24 (5.5)	0.027
Brain	25 (2.8)	12 (3.2)	4 (0.9)	0.189
Kidney	5 (0.6)	2 (0.5)	2 (0.5)	0.298

Data are expressed as *n* (%)

CEA carcinoembryonic antigen

TABLE 3 Multivariate regression analysis of survival

	Overall survival		Cancer-specific survival		Recurrence free interval	
	HR	*p*-Value	HR	*p*-Value	HR	*p*-Value
CEA level						
CEA ≤ 5 ng/ml	Ref		Ref		Ref	
5 < CEA ≤ 10 ng/ml	1.376	< 0.001	1.404	< 0.001	1.190	0.006
CEA > 10 ng/ml	1.523	< 0.001	1.712	< 0.001	1.468	< 0.001
T stage						
1	Ref		Ref		Ref	
2	1.171	0.337	1.792	0.193	1.234	0.538
3	1.550	0.003	3.754	< 0.001	1.196	0.577
4	2.150	< 0.001	5.811	< 0.001	1.470	0.230
N stage						
0	Ref		Ref		Ref	
1a	1.796	< 0.001	2.265	< 0.001	1.333	< 0.001
1b	2.057	< 0.001	2.820	< 0.001	1.289	0.001
2a	2.745	< 0.001	4.226	< 0.001	1.312	0.001
2b	4.280	< 0.001	7.083	< 0.001	1.667	< 0.001
Histological type						
Adenocarcinoma	Ref		Ref		Ref	
Signet ring cell carcinoma	1.751	0.002	2.214	< 0.001	0.708	0.083
Mucinous adenocarcinoma	0.954	0.581	1.051	0.633	0.790	0.017
Poor differentiation	1.140	0.129	1.191	0.095	1.622	< 0.001
Chemotherapy[a]	0.519	< 0.001	0.634	< 0.001	0.833	0.001
Lymph nodes < 12[b]	1.574	< 0.001	1.580	< 0.001	1.130	0.049
Tumor diameter > 4.5 cm	0.925	0.073	0.806	< 0.001	1.043	0.420
Smoking[c]	1.273	< 0.001	1.184	0.002	0.899	0.033
Creatinine > 2 mg/dl	1.951	< 0.001	1.010	0.958	0.909	0.581
Liver cirrhosis	2.018	< 0.001	1.343	0.379	1.591	0.146

TABLE 3 continued

	Overall survival		Cancer-specific survival		Recurrence free interval	
	HR	*p*-Value	HR	*p*-Value	HR	*p*-Value
Diabetes	1.254	< 0.001	0.947	0.506	0.984	0.833

CEA carcinoembryonic antigen, *HR* hazard ratio

[a]Adjuvant chemotherapy

[b]Retrieved lymph nodes

[c]Including ex-smokers and current smokers

of CEA measurement accuracy. A retrospective, cross-sectional study that included 18,131 healthy non-smokers reported that a CEA level ≥ 1.6 ng/ml, compared with a CEA level < 0.8 ng/ml, had a positive correlation with age, creatinine, and glycosylated hemoglobin.[40] Another study that was also based on a healthy population reported a positive association between the elevation of serum CEA and age, fasting glucose, cigarette smoking, and alcohol consumption. The average CEA level was 3.86 ng/ml, with a range of 0.10–61.20 ng/ml in that study.[41] Both studies indicated that these metabolic factors, as well as lifestyle, influenced CEA levels, but the elevation of CEA levels by benign factors was rarely > 10 ng/ml, which also implied that non-malignant conditions did not influence the prognostic impact of preoperative CEA, especially for CEA levels > 10 ng/ml.

According to our study, the main locations of metastasis showed no obvious difference between patients with different CEA levels, except for bone metastasis, which was higher in patients with normal CEA levels. Studies on CRC bone metastasis and CEA are limited, and the small number of cases of bone metastasis may cause statistical bias in our study. A retrospective study that enrolled 516 CRC patients who underwent curative surgery reported that a higher risk of metachronous bone metastasis was observed in patients with LN involvement and tumors of rectal origin. However, patients with a serum CEA level of > 5 ng/ml showed no difference ($p = 0.600$) in bone metastasis, and data for patients with a CEA level of > 10 ng/ml was lacking in this study.[42] Therefore, further studies are necessary to elucidate the relationship between CEA and bone metastasis.

There are several limitations to this study. Although matched using the propensity score method, a retrospective study may still cause bias during data collection and as a result of factors not considered during enrolment. Although a longer period of collection (1995–2010) may ensure a larger sample and long-term outcome, the treatment method and staging classification may be different across the entire duration of collection due to changes in treatment modalities, such as the addition of oxaliplatin to the 5-fluorouracil-based regimen as adjuvant chemotherapy, the introduction of various minimally invasive methods of resection, and the different staging systems, such as N1c staging.

CONCLUSION

Elevation of preoperative CEA levels is an independent prognostic factor in both overall and oncological outcomes of CRC patients after curative intent surgery. Therefore, a more intense follow-up, or adjuvant chemotherapy, should be considered, particularly in patients with negative LN staging and preoperative CEA > 10 ng/ml.

AUTHOR CONTRIBUTIONS WST and SHH had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: WST Acquisition of data: All authors. Drafting of the manuscript: WST and SHH. Critical revision of the manuscript for important intellectual content: WST and SHH. Statistical analysis: WST and SHH. Administrative, technical, or material support: WST. Study supervision: WST.

FUNDING This work was supported by the Chang Gung Medical Research Fund (CORPG3F032).

DISCLOSURES Part of the data included in this study was presented as an oral presentation at the International Digestive Disease Forum held in Hong Kong, 9–10 June 2018.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int. J. Cancer.* 2010;127(12):2893–917.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J. Clin.* 2011;61(2):69–90.
3. Goldstein MJ, Mitchell EP. Carcinoembryonic antigen in the staging and follow-up of patients with colorectal cancer. *Cancer Invest.* 2005;23(4):338–51.
4. Thompson JA, Grunert F, Zimmermann W. Carcinoembryonic antigen gene family: molecular biology and clinical perspectives. *J. Clin. Lab. Anal.* 1991;5(5):344–366.
5. Hammarstrom S. The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. *Semin. Cancer Biol.* 1999;9(2):67–81.
6. Wanebo HJ, Rao B, Pinsky CM, et al. Preoperative carcinoembryonic antigen level as a prognostic indicator in colorectal cancer. *New Engl. J. Med.* 1978;299(9):448–451.

7. Wolmark N, Fisher B, Wieand HS, et al. The prognostic significance of preoperative carcinoembryonic antigen levels in colorectal cancer. Results from NSABP (National Surgical Adjuvant Breast and Bowel Project) clinical trials. *Ann. Surg.* 1984;199(4):375.
8. Scott NA, Wieand HS, Moertel CG, Cha SS, Beart RW, Lieber MM. Colorectal cancer: Dukes' stage, tumor site, preoperative plasma CEA level, and patient prognosis related to tumor DNA ploidy pattern. *Arch. Surg.* 1987;122(12):1375–1379.
9. Compton C, Fenoglio-Preiser CM, Pettigrew N, Fielding LP. American joint committee on cancer prognostic factors consensus conference: colorectal working group. *Cancer*. 2000; 88(7):1739–57.
10. Moreno García V, Cejas P, Codesido MB, et al. Prognostic value of carcinoembryonic antigen level in rectal cancer treated with neoadjuvant chemoradiotherapy. *Int. J. Colorectal Dis.* 2009;24(7):741–748.
11. Park IJ, Choi G-S, Lim KH, Kang BM, Jun SH. Serum carcinoembryonic antigen monitoring after curative resection for colorectal cancer: clinical significance of the preoperative level. *Ann. Surg. Oncol.* 2009;16(11):3087–3093.
12. Sun L-C, Chu K-S, Cheng S-C, et al. Preoperative serum carcinoembryonic antigen, albumin and age are supplementary to UICC staging systems in predicting survival for colorectal cancer patients undergoing surgical treatment. *BMC Cancer*. 2009;9(1):288.
13. Huh JW, Oh BR, Kim HR, Kim YJ. Preoperative carcinoembryonic antigen level as an independent prognostic factor in potentially curative colon cancer. *J. Surg. Oncol.* 2010;101(5):396–400.
14. Kim TH, Chang HJ, Kim DY, et al. Pathologic nodal classification is the most discriminating prognostic factor for disease-free survival in rectal cancer patients treated with preoperative chemoradiotherapy and curative resection. *Int. J. Radiat. Oncol. Biol. Phys.* 2010;77(4):1158–1165.
15. Yeh CY, Hsieh PS, Chiang JM, et al. Preoperative carcinoembryonic antigen elevation in colorectal cancer. *Hepatogastroenterology*. 2011;58(109):1171–6.
16. Kirat HT, Ozturk E, Lavery IC, Kiran RP. The predictive value of preoperative carcinoembryonic antigen level in the prognosis of colon cancer. *Am. J. Surg.* 2012;204(4):447–52.
17. Kim CW, Yoon YS, Park IJ, Lim S-B, Yu CS, 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.* 2013;20(9):2914–2920.
18. Lee SY, Jo JS, Kim HJ, et al. Clinicopathologic features and oncologic outcomes of colorectal cancer patients with extremely high carcinoembryonic antigen. *Int. J. Colorectal Dis.* 2015;30(1):63–69.
19. Thirunavukarasu P, Talati C, Munjal S, Attwood K, Edge SB, Francescutti V. Effect of incorporation of pretreatment serum carcinoembryonic antigen levels into AJCC staging for colon cancer on 5-year survival. *JAMA Surg*. 2015;150(8):747–755.
20. Li Destri G, Rubino AS, Latino R, et al. Preoperative carcinoembryonic antigen and prognosis of colorectal cancer. An independent prognostic factor still reliable. *Int. Surg.* 2015;100(4):617–625.
21. Becerra AZ, Probst CP, Tejani MA, et al. Evaluating the prognostic role of elevated preoperative carcinoembryonic antigen levels in colon cancer patients: results from the National Cancer Database. *Ann. Surg. Oncol.* 2016;23(5):1554–1561.
22. Booth S, King J, Leonard J, Dykes P. Serum carcinoembryonic antigen in clinical disorders. *Gut*. 1973;14(10):794–799.
23. Fang M, Wang S, Zheng Y, et al. Prognostic and predictive significance of plasma hepatocyte growth factor and carcinoembryonic antigen in non-small lung cancer after surgery. *Eur. Rev. Med. Pharmacol. Sci.* 2014;18(3):398–403.
24. Ruibal MA. CEA serum levels in non-neoplastic disease. *Int. J. Biol. Mark*. 1991;7(3):160–166.
25. Fukuda I, Yamakado M, Kiyose H. Influence of smoking on serum carcinoembryonic antigen levels in subjects who underwent multiphasic health testing and services. *J. Med. Syst.* 1998;22(2):89–93.
26. Bulut, I., P. Arbak, A. Coskun, et al., Comparison of serum CA 19.9, CA 125 and CEA levels with severity of chronic obstructive pulmonary disease. *Med. Princ. Pract.*, 2009. 18(4): p. 289–293.
27. Sturgeon C, Lai L, Duffy M. Serum tumour markers: how to order and interpret them. *BMJ*. 2009;339(7725):852–858.
28. Graham RA, Wang S, Catalano PJ, Haller DG. Postsurgical surveillance of colon cancer: preliminary cost analysis of physician examination, carcinoembryonic antigen testing, chest x-ray, and colonoscopy. *Ann. Surg.* 1998;228(1):59.
29. Pfister DG, Benson AB III, Somerfield MR. Surveillance strategies after curative treatment of colorectal cancer. *New Engl. J. Med.* 2004;350(23):2375–2382.
30. Konishi T, Shimada Y, Hsu M, et al., Association of preoperative and postoperative serum carcinoembryonic antigen and colon cancer outcome. *JAMA Oncol.* 2018;4(3):309–315.
31. Tokodai K, Narimatsu H, Nishida A, et al. Risk factors for recurrence in stage II/III colorectal cancer patients treated with curative surgery: the impact of postoperative tumor markers and an infiltrative growth pattern. *J. Surg. Oncol.* 2016;114(3):368–74.
32. Thirunavukarasu P, Talati C, Munjal S, Attwood K, Edge SB, Francescutti V. Effect of incorporation of pretreatment serum carcinoembryonic antigen levels into AJCC staging for colon cancer on 5-year survival. *JAMA Surg*. 2015;150(8):747–55.
33. Ozawa H, Kotake K, Hosaka M, et al. Incorporation of serum carcinoembryonic antigen levels into the prognostic grouping system of colon cancer. *Int. J. Colorectal Dis.* 2017;32(6):821–829.
34. Dallas MR, Liu G, Chen W-C, et al. Divergent roles of CD44 and carcinoembryonic antigen in colon cancer metastasis. *FASEB J.* 2012;26(6):2648–2656.
35. Takagawa R, Fujii S, Ohta M, et al. Preoperative serum carcinoembryonic antigen level as a predictive factor of recurrence after curative resection of colorectal cancer. *Ann. Surg. Oncol.* 2008;15(12):3433–9.
36. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J. Clin. Oncol.* 2009;27(19):3109–3116.
37. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol.* 2004;22(10):1797–806.
38. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *The Lancet*. 2007;370(9604):2020–2029.
39. Benson AB III, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J. Clin. Oncol.* 2004;22(16):3408–3419.
40. Kang HY, Choe EK, Park KJ, Lee Y. Factors requiring adjustment in the interpretation of serum carcinoembryonic antigen: a cross-sectional study of 18,131 healthy nonsmokers. *Gastroenterol. Res. Pract.* 2017;2017:9858931.
41. Sun L, MingjieXu LW, Wang Y, Wang Y. Increase of carcinoembryonic antigen level in serum is associated with metabolic factors and lifestyle. *Int. J. New Technol. Res*. 2016;2(4):79–84.

42. Sun C, Deng Y, Zhou H, Hu ZQ. Risk factors for the development of metachronous bone metastasis in colorectal cancer patients after curative resection. *Int. J. Surg*. 2015;21:145–9.