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Carcinoembryonic Antigen Clearance Rate May Be a Prognostic Indicator for Metastatic Colorectal Cancer Patients Receiving Chemotherapy

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To figure out the relationship between the tumor marker clearance rate during the treatment period and the disease prognosis. Carcinoembryonic antigen (CEA) is a glycoprotein that has been widely used as a tumor marker in colorectal cancer for more than 30 years. This study evaluated the role of the CEA clearance rate during treatment and determined its relationship with chemotherapy regimens, increased metastasectomy rate, and overall survival. The medical records of 442 metastatic colorectal cancer patients whose primary tumors were treated with surgery followed by systemic therapy at a single center from 2000 to 2012 were reviewed. The CEA clearance rate was calculated as a change in CEA after 6 courses of therapy divided by the treatment period [(posttherapy CEA – pretherapy CEA)/days between therapy], and classified into 4 groups for further evaluation. The CEA clearance rate during treatment of stage IV colorectal cancer was significantly correlated with different chemotherapy regimens ($P < 0.01$); pretreatment CEA level ($P < 0.01$); tumor differentiation ($P < 0.01$); increased metastasectomy rate ($P = .02$); and overall survival ($P < 0.01$). The CEA clearance rate during systemic therapy could evaluate patient treatment responses more precisely than traditionally rising or falling CEA levels, and may predict disease prognosis.

Key words: Carcinoembryonic antigen – colorectal cancer – metastasectomy prognosis

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Colorectal cancer is a common disease, accounting for 9.8% of all cancers worldwide.[1] It is the most common type of cancer and was the third leading cause of cancer deaths in Taiwan in 2012.[2] Currently, more than 16,000 new cases are diagnosed annually, 80% of which are treated with surgery and half of which receive neoadjuvant, adjuvant, or palliative chemotherapy in Taiwan.[2]

Understanding therapeutic responses could determine patient outcomes and guide treatment changes. Treatment responses can be evaluated in several ways, from taking a basic history and performing a physical examination to assessing tumor markers and performing a dedicated imaging study. The National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American Cancer Society, European Society for Medical Oncology (ESMO), and the European Group on Tumor Markers (EGTM) all suggest performing imaging studies and tumor markers analysis to evaluate the treatment response and determine next steps in treatment.[3–7] Several studies have also confirmed the importance between tumor markers and imaging studies to evaluate treatment responses.[8,9]

Carcinoembryonic antigen (CEA) is a glycoprotein that is produced by cancer cells in the gastrointestinal tract and is widely used as a tumor marker in colorectal cancer.[10] Several studies have shown that CEA could be a prognostic marker during and after colon and rectal cancer treatment.[3–7,11,12] However, no study has evaluated the CEA clearance rate during the treatment period. Defining the relationship between the CEA clearance rate and prognosis is of particular interest because it could provide more information about the treatment response, conferring clinical physicians with additional information to judge the benefits or adverse effects of different treatments.

In this study, the relationship between the CEA clearance rate during the treatment period and overall survival in stage IV colorectal cancer was interrogated. The data support novel ways to monitor the treatment response as compared to traditional interpretations of using tumor markers.

Materials and Methods

Medical chart data from colorectal cancer patients diagnosed at the Taipei Veterans General Hospital was prospectively collected from 2000 until 2012; a total of 6539 cases were recorded in this database. In this study, we included 762 metastatic colorectal cancer patients with unresectable metastasis who received surgical treatment of primary lesions first due to symptoms including tumor bleeding, obstruction, perforation, compression, or intractable pain followed by systemic salvage therapy. Primary lesions were diagnosed via colonoscopy and computed tomography (CT), and metastatic lesions were diagnosed via CT and magnetic resonance imaging (MRI) studies. If the primary lesion was not distinguishable from a metastatic lesion, the diagnosis was made via tumor biopsy. Patients with normal CEA levels (<5 μg/L; $n = 203$ patients), without pre- or posttreatment CEA data ($n = 47$ and 33 patients, respectively) were excluded from this study. A total of 57 patients were excluded due to a lack of scheduling or suspension of salvage therapy. Thus, we enrolled 422 patients in this study for further evaluation.

CEA levels were determined before salvage therapy and followed as scheduled after chemotherapy. Serum CEA levels were measured at the Department of Nuclear Medicine at the Taipei Veterans General Hospital using a radioimmunoassay kit (CIS-CEA kit, CIS Biointernational, Gif Yvette, France). CEA data and dates of measurement were recorded. In order to compare CEA clearance rates during the treatment period, we calculated the CEA clearance rate as the change in CEA after 6 courses of therapy divided by the treatment period [(posttherapy CEA – pretherapy CEA)/days between therapies]. The CEA clearance rate was divided into 4 groups for further evaluation: (1) rapid progress (RP): daily CEA increase >1 μg/L; (2) slow progress (SP): daily CEA increase <1 μg/L; (3) rapid regress (RR): daily CEA decrease >1 μg/L; and (4) slow regress (SR): daily CEA decrease <1 μg/L. The kinds of salvage therapy in our study population were fluorouracil + leucovorin; FOLFOX: folinic acid + fluorouracil (5-FU) + oxaliplatin, FOLFIRI: folinic acid + 5-FU + irinotecan; FOLFOX + bevacizumab; FOLFIRI + bevacizumab; FOLFOX + cetuximab; and FOLFIRI + cetuximab. An increase in the metastasectomy rate was recorded during the later treatment periods of these stage IV colorectal cancer patients. These surgeries were of curative intent to treat underlying metastasis.

The statistical endpoint of the analysis was overall survival from the date of diagnosis. Group distributions between the CEA clearance rates for each clinicopathologic feature were compared using a χ^2 test. Numerical values were compared with 1-way analysis of variance (ANOVA). Kaplan-Meier survival curves were plotted and compared using a

Table 1 Relationship between CEA clearance rate and different variables

Variable	RR, n = 186	SR, n = 80	SP, n = 79	RP, n = 77	*P* value
Mean age, y (range)	64 (24–87)	62 (30–92)	64 (33–86)	64 (26–91)	0.751
Male sex, n (%)	108 (58.0)	48 (60.0)	50 (63.2)	51 (66.2)	0.623
Tumor location					0.922
Right colon, n (%)	44 (23.7)	21 (26.2)	20 (25.3)	18 (23.3)	
Left colon, n (%)	80 (43.0)	38 (47.5)	32 (40.5)	36 (46.8)	
Rectum, n (%)	62 (33.3)	21 (26.3)	27 (34.2)	23 (29.9)	
Lymphovascular invasion, n (%)	62 (34.1)	26 (36.6)	35 (46.1)	30 (42.8)	0.125
Perineural invasion, n (%)	23 (12.6)	7 (9.9)	9 (11.8)	8 (11.4)	0.931
Mucinous, n (%)	15 (8.2)	4 (5.6)	9 (11.8)	6 (8.6)	0.545
Differentiation					0.008
Well, moderate, n (%)	167 (89.8)	66 (82.5)	59 (74.7)	65 (84.4)	
Poor, undifferentiated, n (%)	15 (8.1)	5 (6.3)	16 (20.3)	5 (6.5)	
Additional metastasectomy	52 (28.0)	15 (18.8)	16 (20.3)	9 (11.7)	0.026
Survival, mo	41.45 ± 2.68	24.77 ± 2.38	23.17 ± 3.96	10.98 ± 0.86	<0.001

The CEA clearance rate was associated with tumor differentiation ($P < 0.01$); increased metastasectomy rate ($P = 0.02$); and overall survival ($P < 0.01$).

log-rank test. Univariate and multivariate analyses between different factors were performed using the Cox proportional hazard model. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using statistical software (Statistical Package for the Social Sciences (SPSS) for Windows software, version 21.0, SPSS Inc., Chicago, Illinois).

Results

We enrolled 422 patients in this study, 257 (60.9%) of whom were men. The median age at diagnosis in this study was 65 years (range, 24–92 years). A total of 103 (24.3%) tumors were proximal to the splenic flexure (right-sided colon cancer); 186 (44.1%) were distal to the splenic flexure and proximal to the rectum (left-sided colon cancer); and 133 (31.4%) were located in the rectum. The distribution of pathologic features included 153 (36.2%) tumors with lymphovascular invasion; 47 (11.1%) with perineural invasion; 34 (8%) that were mucinous adenocarcinomas; and 41 (9.7%) that were poorly differentiated or undifferentiated. Of the 422 patients, 320 (75.8%) had liver metastasis; 87 (20.6%) had lung metastasis; 11 (2.6%) had distant lymph node metastasis; and 71 (16.8%) had peritoneal seeding. A total of 92 patients (21.8%) underwent additional metastasectomy after chemotherapy. We found 95 patients (22.5%) had more than 1 site of distant metastasis. Median overall survival was 18.6 months (range, 1.4–135.2 months), and 342 patients died of the disease during the follow-up period.

After 6 courses of chemotherapy, 186 (44.1%) patients showed CEA decreases of more than 1 μg/L per day (RR); 80 (19.0%) showed CEA decreases of less than 1 μg/L per day (SR); 79 (18.7%) showed CEA increases of less than 1 μg/L per day (SP); and 77 (18.2%) showed CEA increases of more than 1 μg/L per day (RP). As shown in Table 1, the CEA clearance rate was associated with tumor differentiation ($P < 0.01$); increased metastasectomy ($P = 0.02$); and overall survival ($P < 0.01$). The SP group had a greater percentage of poorly differentiated and undifferentiated tumors than all other groups. Within a median follow-up period of 17.62 months (range, 1.44–135.17 months), 342 patients died of the disease. As shown in Fig. 1, overall survival was significantly correlated to the CEA clearance rate, and the RR group had the longest overall survival (41.45 ± 2.68 months); the RP group had the shortest overall survival (10.98 ± 0.86 months).

In our study population, 55 (13%) patients received chemotherapy with fluorouracil + leucovorin; 148 (35%) with FOLFOX; 101 (23.9%) with FOLFIRI; 18 (4.3%) with FOLFOX + bevacizumab; 41 (9.7%) with FOLFIRI + bevacizumab; 38 (9.1%) with FOLFOX + cetuximab; and 21 (5.1%) with FOLFIRI + cetuximab. The relationship between the CEA clearance rate and chemotherapy regimen was analyzed (Table 2). Patients who received combined FOLFOX/FOLFIRI with targeted therapy as a first-line therapy had superior outcomes (26.97 months), with a higher proportion of patients in the RR (47.5%) and SR (27.1%) groups. In contrast, 5-fluorouracil + leucovorin led to the shortest survival (10.61 months) in our study, and the proportion of these patients in the RP group was the highest (25.4%). FOLFOX/FOLFIRI with targeted therapy led to the highest proportion of patients (30.5%)

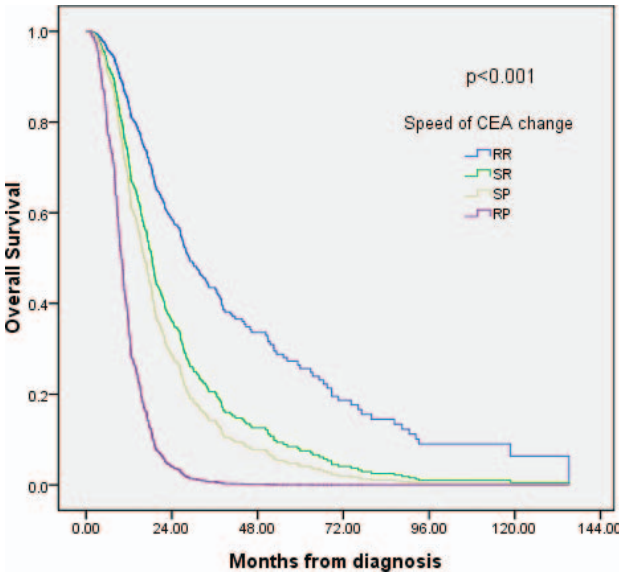

Fig. 1 Overall survival curve between different speed of CEA change. RR rapid regression, SR slow regression, SP slow progression, RP rapid progression.

undergoing additional metastasectomy than other chemotherapy regimens.

Univariate and multivariate analyses were performed to determine the effects of age, sex, tumor location, histologic features, increased metastasectomy, and the CEA clearance rate on the overall survival (Table 3). Overall survival was significantly associated with rectal tumors ($P = 0.04$); lymphovascular invasion ($P < 0.01$); poor differentiation ($P = 0.02$); additional metastasectomy ($P < 0.01$); and the CEA clearance rate ($P < 0.01$) via both univariate and multivariate analyses. CEA regression groups (RR and SR) had overall survival that was more improved than progression groups (SP and RP); the rapid regression group (RR) had overall survival that was more improved than the slow regression group (SR); and the slow progression (SP) group had overall survival that was more improved than the rapid progression (RP) group ($P < 0.01$).

Discussion

This study is useful to discuss the clearance rate of a tumor marker after chemotherapy and to compare this rate with other factors believed to have a relationship with treatment response and survival. In the present study, the CEA clearance rate was shown to be related to tumor differentiation ($P < 0.01$); increased metastasectomy rate ($P = 0.02$); and overall survival ($P < 0.01$; Table 1). This new understanding of CEA levels and its clearance rate in metastatic colorectal disease could provide more information on treatment responses to clinicians. Additionally, this study analyzed the association between chemotherapeutic regimen and the CEA clearance rate, increased metastasectomy rate, and overall survival. The results showed that FOLFOX/FOLFIRI + targeted therapy led to the best overall survival and highest additional metastasectomy rates. Around half of the patients (47.5%) who received the FOLFOX/FOLFIRI + targeted therapy had rapid CEA clearance and favorable outcomes (mean overall survival, 26.97 months). These results indicate that the CEA clearance rate is predictive of treatment response and has an intimate relation with overall survival.

CEA is a tumor marker for colorectal cancer that has been used for over 30 years. Mayer *et al*[13] were the first to describe CEA as a follow-up marker in colorectal cancer after 5-FU therapy. Since then, additional evidence had shown the utility of CEA in colorectal cancer follow-up assessments during and after therapy.[5,14–16] Several guidelines (i.e., 2006 ASCO, 2014 EGTM, 2015 American Cancer Society Colorectal Cancer Survivorship guidelines, 2014

Table 2 Relationship between CEA clearance rate and chemotherapy regimens

Chemotherapy regimens	5FU+ leucovorin (n = 55), n (%)	FOLFOX/FOLFIRI (n = 249), n (%)	FOLFOX / FOLFIRI + target therapy (n = 118), n (%)	*P* value
CEA-RR, n = 186	22 (40)	108 (43.4)	56 (47.5)	<0.001
CEA-SR, n = 80	10 (18.2)	38 (15.3)	32 (27.1)	
CEA-SP, n=79	9 (16.4)	54 (21.7)	16 (13.6)	
CEA-RP, n=77	14 (25.4)	49 (19.6)	14 (11.8)	
Additional metastasectomy	7 (12.7)	49 (19.7)	36 (30.5)	0.01
Survival, mo	10.61	17.78	26.97	<0.001

Patients who received combined FOLFOX/FOLFIRI with targeted therapy had superior outcomes (26.97 months), with a higher proportion of patients in the RR (47.5%) and SR (27.1%) groups and had the highest proportion of patients (30.5%) receiving additional metastasectomy than other chemotherapy regimens.

Table 3 Univariate and multivariate analysis of prognostic factors for overall survival[a]

Variables	Group	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Age	Age < 65	1			
	Age > 65	1.13 (0.91–1.40)	0.27	NS	
Sex	Female	1			
	Male	0.91 (0.73–1.14)	0.42	NS	
Tumor location	Right colon	1		1	
	Left colon	1.00 (0.77–1.31)	0.997	0.99 (0.74–1.34)	0.98
	Rectum	0.24 (0.54–0.96)	0.02	0.72 (0.57–0.93)	0.04
Lymphovascular invasion	Negative	1		1	
	Positive	1.70 (1.34–2.15)	<0.001	1.48 (1.14–1.92)	0.003
Perineural invasion	Negative	1		1	
	Positive	1.34 (0.94–1.92)	0.10	1.21 (0.82–1.79)	0.33
Mucinous >50%	Negative	1		1	
	Positive	1.38 (0.93–2.05)	0.11	1.25 (0.82–1.91)	0.29
Grade of differentiation	Well	1		1	
	Moderate	1.14 (0.47–2.76)	0.78	0.85 (0.35–2.09)	0.72
	Poor	3.09 (1.22–7.87)	0.02	2.71 (1.73–4.24)	0.02
Additional metastasectomy	Negative	1		1	
	Positive	0.61 (0.46–0.81)	0.001	0.64 (0.47–0.88)	0.005
Speed of CEA change	CEA-RR	1		1	
	CEA-SR	1.90 (1.40∼2.58)	<0.001	2.14 (1.53∼3.00)	<0.001
	CEA-SP	2.34 (1.74∼3.15)	<0.001	2.30 (1.65∼3.20)	<0.001
	CEA-RP	5.98 (4.42∼8.10)	<0.001	7.20 (5.16∼10.07)	<0.001

95% CI, 95% confidence interval; HR, hazard ratio; NS, not significant.

[a]Overall survival was significantly associated with rectal tumors ($P = 0.04$); lymphovascular invasion ($P < 0.01$); poor differentiation ($P = 0.02$); additional metastasectomy ($P < 0.01$); and the CEA clearance rate ($P < 0.01$).

ESMO clinical practice guidelines, and 2014 NCCN) suggested CEA as a tumor marker during follow-up of colorectal cancer after therapy.[3–7,17] The role of CEA in colorectal cancer follow-up is mainly based on normalization of CEA or still elevated ones after treatment to determine efficacy. In our study population, normalization of CEA after therapy showed statistically better prognosis than the still elevated ones (median survival: 37.3 months in normalization of CEA compared to 15.2 months in elevated CEA, $P < 0.01$). If we evaluated the same patient population of still elevated CEA after treatment by CEA clearance rate according to our study, the patient distribution of RR, SR, SP, and RP would be 71 (23.8%), 73 (24.4%), 77 (25.9%), and 77 (25.9%), respectively, with respective median survival of 22.2, 18.5, 14.2, and 9.3 months. This showed more detailed prognosis and was more useful compared to traditional methods taking CEA as a follow up marker in colorectal cancer. Limited studies discuss the utility of the CEA clearance rate within the treatment period and its relation to patient outcomes. The survival curve in Fig. 1 showed the different prognosis between the CEA clearance rate and could provide more information than previous utility of CEA as a tumor marker in the follow up of treatment response in colorectal cancer.

Prior studies have shown better metastatic colorectal cancer outcomes with respect to increased metastasectomy if the metastatic tumor is resectable.[18–20] In the present study, we surveyed the rate of additional metastasectomy and, interestingly, found that it was related to the CEA clearance rate after primary colorectal tumor resection followed by salvage chemotherapy. We found 28% of patients with rapid CEA clearance underwent additional metastasectomy. Via univariate and multivariate analyses, additional metastasectomy decreased the risk of mortality (Table 3). This finding implies that the outcome of salvage therapy can be determined by the CEA clearance rate and increased metastasectomy. Since there are many different chemotherapy regimens and targeted therapies to treat colorectal cancer, the CEA clearance rate provides a means to predict the response to therapy and disease prognosis.

This study also surveyed the location of the tumor and its relation to both survival and the CEA clearance rate. Price *et al*[21] previously showed poorer outcomes for right-sided than for left-sided stage IV colon cancer; Yahagi *et al*[22] performed a

meta-analysis on right- and left-sided colon cancer, reaching the same conclusion. However, our data showed no statistically significant difference between right- and left-sided colon cancer on overall survival or CEA clearance rates within the treatment period. This difference may be due to our study population having first received primary tumor resection due to symptoms at diagnosis that differed from those of other studies, thereby decreasing the influence of the primary tumor location.

The main limitation of our study is that metastatic colorectal cancer patients with a normal CEA level could not be applied by this CEA clearance rate to evaluate the treatment response. According to previous studies, around 30% of metastatic colorectal cancers do not have elevated CEA levels.[23,24] Such patients cannot be followed by the change of CEA and were thus excluded from the present study. Another limitation is that the survey was retrospective; prior to using the CEA clearance rate clinically, further prospective studies should be conducted to validate our CEA clearance rate results during the treatment period.

In conclusion, the CEA clearance rate during chemotherapeutic treatment for stage IV colorectal cancer was associated with the tumor differentiation and the increased metastasectomy rate; the CEA clearance rate was also independently related to overall survival. We propose that the CEA clearance rate could evaluate treatment responses more precisely than traditionally rising or falling CEA levels after treatment, and could predict the probability of additional metastasectomy and patient prognosis. Further prospective studies are essential to validate the finding in this study.

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