RESEARCH COMMUNICATION

# Preoperative Serum Carcinoembryonic Antigen, Carbohydrate Antigen19-9 and Carbohydrate Antigen 125 as Prognostic Factors for Recurrence-free Survival in Colorectal Cancer

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## Abstract

**Objective: Colorectal cancer (CRC) is among the most common malignancies worldwide. Understanding CRC prognosis at the initial diagnosis is very important for therapeutic strategy selection. This study was conducted to evaluate the prognostic value of preoperative serum carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA) and carbohydrate antigen 125 (CA125) for predicting 5-year recurrence-free survival (RFS) in CRC patients. Methods: Preoperative serum CA19-9, CEA and CA125 levels were detected by C12 protein chip diagnostic system in 103 patients with CRC, and their correlations with the 5-year RFS were analyzed. Results: Patients with positive preoperative serum CA19-9, CEA and CA125 had higher 5-year recurrent rates (75.0% vs 41.0%, 65.6% vs 39.4%, and 87.5% vs 44.2% respectively, all p<0.05), and reduced median RFS (14 vs 35 months, 20 vs 36 months, and 4 vs 35 months respectively, all p<0.05) compared with patients negative for corresponding tumor marker (TM). The median RFS was 59 months (95% CI 28.9-89.1 months) with negative TMs, 14 months (95% CI 4.5-23.5) for 1~2 positive TMs, and 4 months (95% CI 2.4-5.6) for all 3 positive TMs. Patients with simultaneously positive serum CA19-9, CEA and CA125 had the highest recurrence rate (100%) and the shortest RFS (median 4 months). Univariate analysis showed that stage and the preoperative single TM or combined TMs correlated with RFS, whereas multivariate Cox regression model analysis revealed only stage and preoperative serum status of CEA+CA19-9+CA125 to be independent prognostic factors. Conclusion: Preoperative serum CA19-9+CEA+CA125 can be used an independent prognostic factor for CRC 5-year RFS.**

**Keywords:** Colorectal cancer - CA 19-9 - CEA - CA-125 - recurrence-free survival - China

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## Introduction

Colorectal cancer (CRC) is among the most common malignancies worldwide, with an estimated 1.2 million new cases and 0.6 million deaths each year (Jemal et al., 2011). Information form 2010 Health Statistical Yearbook of China showed that the morbidity and mortality of CRC ranked fifth in China during 2004-2005 (Ministery of Health of the People's Republic of China, 2010). With changes in lifestyle, diet and disease spectrum, the incidence of CRC has been on the steady increase in recent years.

Tumor marker (TM) is a substance that can be detected in the blood, urine, or other body fluids or tissues in patients with cancer, which could be an important tool in cancer diagnosis, prognosis, treatment decision making and disease monitoring (Zhang et al., 2009). With the development of molecular biological techniques and new discoveries in cancer biology, many serum TMs such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9(CA19-9), carbohydrate antigen 242, carbohydrate antigen 724 and tissue inhibitor of metalloproteinase type 1, etc. have been explored. The American Society of Clinical Oncology (ASCO) and European Group on Tumor Markers (EGTM) published and updated evidence-based clinical practice guidelines for the use of TMs in CRC (Locker et al., 2006; Duffy et al., 2007). The guidelines stated that lack of specificity and sensitivity precluded the use of all existing serum markers for the early detection of CRC, only CEA had some values in prognosis, surveillance and monitoring. However, there was no such standard guideline for the use of serum TMs in CRC in China, and no better TMs used in clinical work. Many traditional TMs are still used in clinical practice. Considering ethnical and geographical factors, we investigated the clinical use of the commonly used serum TMs in CRC. Our previous study on the application of C12 multi-tumor marker protein chip in 173 consecutive CRC patients, identified three relatively useful TMs, CEA, CA19-9 and carbohydrate antigen 125 (CA125) (Yang

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et al., 2009). The positive rates of CEA, CA19-9 and CA125 were 36.4 %, 18.5% and 9.8%, respectively, but the positive rates in stage I CRC were only 3.9%, 5.9%, and 3.9%, respectively (Yang et al., 2009). The results suggested that the diagnostic role of the TMs was poor in CRC patients, especially in early stage CRC, which was in accordance with the standard points of ASCO and EGTM. TMs positive rate elevated with advancing stage, suggesting their role in predicting prognosis. With the wishing to add more evidence or data to objectively define the values of commonly used serum TMs CA19-9, CEA and CA125 in CRC, we conducted the present study to explore the relationship between preoperative serum CA19-9, CEA and CA125 levels and 5-year recurrence-free survival (RFS) of the CRC patients.

## Materials and Methods

*Patient selection and blood samples*

Patients meeting the following criteria were enrolled in this study: (1) curative resection for biopsy confirmed CRC; (2) preoperative serum samples available; and (3) complete follow-up information available. On the basis of 173 CRC cases in our previous study (Yang et al., 2009), we had further increased the sample size to 199 cases. During follow-up periods, some patients changed hospitals and some patients lost contact. Up to the last follow-up date, 103 cases had complete follow-up data for 5-year RFS analysis.

Peripheral blood was obtained at the preoperative workup. And the serum was separated and stored at -20ºC until detection using the C12 protein chip system according to the protocol supplied by the manufacturer (Shanghai HealthDigit Co., Ltd. Shanghai, China). Peripheral blood samples from 138 healthy Chinese volunteers were collected as normal controls. The ages of controls ranged from 30-75 years old, the median age was 51 years old. Among 138 controls, 86 were males and 52 were females.

*Clinical follow-up and recurrence definition*

Postoperative follow-ups were scheduled according to standard guidelines, covering such items as detailed history recording, physical examination, TMs tests, medical imaging studies or biopsies as deemed necessary. As the purpose of this study was to investigate the correlation between preoperative TMs and 5-year recurrence in CRC, for practical clinical utility, this study defined recurrence as clinical recurrence, medical imaging recurrence, and pathological recurrence. If the patient had curative comprehensive treatment developed any clinical manifestations highly indicative of cancer recurrence, but could not be confirmed by biopsy and could not be relieved by routine treatments, then the patient was diagnosed as having clinical recurrence. If medical imaging studies discovered any mass in the operation field, the whole abdominal-pelvic cavity, the liver, the lungs, and the bone marrow, during the follow-up period in a patient who had previously underwent curative treatment for CRC, then it was considered as medical imaging recurrence. Pathological recurrence was defined as any biopsy confirmed diagnosis during the follow-up period. In this study, if any of the above 3 types of recurrence occurred in a patient, the diagnosis of recurrence was established. RFS was defined as the time interval from curative surgery to the diagnosis of recurrence.

*Statistical analysis*

The recurrent rates among different individual TMs status were assessed with Chi-square test. The correlations of preoperative TMs with RFS were analyzed using the Kaplan–Meier product limit method and Log rank test. Cox regression model was used to select significant predictors of recurrence. Statistical analyses were performed with SPSS 13.0 (SPSS Inc. Chicago, IL). $P<0.05$ was considered as statistically significant.

## Results

*TM status of CRC patients*

In the 103 cases, the median serum levels (ranges) of CA19-9, CEA and CA125 were 10.6 (2.0-266.2) kU/L, 2.4 (0.03-219.8) μg/L and 8.6 (0.3-67.95) kU/L, respectively. The cut-off values of CA19-9, CEA and CA125 were 35 kU/L, 5 μg/L, and 35 kU/L, respectively. The preoperative TMs status, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CA19-9, CEA and CA125 individually and collectively are summarized in Table 1. The positive rates of these TMs increased with advancing stage. Combined detection of three TMs had highest positive rate, but had no significant difference compared with any single TM ($p>0.05$). The combined detection of CEA+CA19-9 or CEA+CA19-9+CA125 increased the sensitivity and NPV.

*Preoperative TM status and CRC recurrence*

TM status and CRC recurrence was shown in Table 2. Among 103 CRC patients, the 5-year recurrent rates

**Table 1. Preoperative Serum TMs Status of 103 Patients with CRC and 138 Controls**

| TMs | Positive | Positive patients with CRC by Stage | | | | | Sens. | Spec. | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|---|
| | controls (138) | I (9) | II (33) | III (44) | IV (17) | Total (103) | p-value | | | | |
| CA19-9 | 0 | 0 | 2 ( 6.1 ) | 9 (20.5) | 9 (52.9) | 20 (19.4) | 0.000 | 19.4 | 100.0 | 100.0 | 62.4 |
| CEA | 2 (1.45) | 1(11.1) | 6 (18.2) | 14 (31.8) | 11 (64.7) | 32 (24.6) | 0.004 | 24.6 | 98.6 | 94.1 | 65.7 |
| CA125 | 1 (0.72) | 0 | 3 ( 9.1 ) | 1 ( 2.3 ) | 4 (23.5) | 8 ( 7.8 ) | 0.035 | 7.8 | 99.3 | 88.9 | 59.1 |
| CA19-9+CEA | 2 (1.45) | 1(11.1) | 6 (18.2) | 18 (40.9) | 13 (76.5) | 38 (36.9) | 0.000 | 36.9 | 98.6 | 95.0 | 67.7 |
| CA19-9+CA125 | 1 (0.72) | 0 | 5 (15.2) | 10 (22.7) | 10 (58.8) | 25 (23.8) | 0.001 | 23.8 | 99.3 | 96.2 | 63.7 |
| CEA+CA125 | 2 (1.45) | 1(11.1) | 7 (21.2) | 15 (34.7) | 12 (70.6) | 35 (34.0) | 0.002 | 34.0 | 98.6 | 94.6 | 66.7 |
| All Three TMs | 2 (1.45) | 1(11.1) | 7 (21.2) | 19 (43.2) | 14 (82.4) | 41 (39.8) | 0.000 | 39.8 | 98.6 | 95.4 | 68.7 |

N, number; PPV, positive predictive value; NPV, negative predictive value; Sens., sensitivity; Spec., specificity

**Table 2. Preoperative TM Status and 5-year Recurrence**

| TM status | No. | Rate (%) | p-value |
|---|---|---|---|
| CA19-9 negative | 83 | 34 (41.0) | 0.006 |
| CA19-9 positive | 20 | 15 (75.0) | |
| CEA negative | 71 | 28 (39.4) | 0.014 |
| CEA positive | 32 | 21 (65.6) | |
| CA125 negative | 95 | 42 (44.2) | 0.019 |
| CA125 positive | 8 | 7 (87.5) | |
| CA19-9+CEA negative | 65 | 22 (33.9) | 0.000 |
| CA19-9+CEA any positive | 38 | 27 (71.1) | |
| CA19-9+CA125 negative | 78 | 30 (38.5) | 0.001 |
| CA19-9+CA125 any positive | 25 | 19 (76.0) | |
| CEA+CA125 negative | 68 | 26 (38.2) | 0.008 |
| CEA+CA125 any positive | 35 | 23 (65.7) | |
| CA19-9+CEA+CA125 negative | 62 | 19 (30.6) | 0.001 |
| CA19-9+CEA+CA125 any positive | 41 | 30 (73.2) | |
| 1~2 TMs positive | 38 | 26 (68.4) | 0.247 |
| 3 TMs simultaneously positive | 3 | 3 (100 ) | |
| Total CRC patients | 103 | 49 (47.6) | --- |

CI,confidence interval; SE, standard error

of the patients with positive TMs were significant higher than those with negative TMs: 75.0% vs 41.0% for CA19-9 (p=0.006), 65.6% vs 39.4% for CEA (p=0.014), and 87.5% vs 44.2% for CA125 (p=0.019). When TMs combination detected, any one positive was defined as positive outcome, whereas all TMs negative was defined as negative outcome. Among 2 TMs combination detection, CA19-9+CEA showed best predictive value, the 5-year recurrent rate of patients with positive CA19-9+CEA was 71.05%, which was significantly higher than those with negative CA19-9+CEA (33.9%) (p=0.000). When 3 TMs CA19-9+CEA+CA125 combination detected, 5-year recurrent rate of patients with positive and negative TMs were 73.2% and 30.6% (p=0.000), respectively. Patients with 1 ~ 2 positive TMs had 68.4% recurrent rate in 5 years, but those with 3 positive TMs had 100% recurrent rate within 2 years.

*RFS and recurrent status of 103 CRC cases*

As to May of 2010, the median follow-up was 25.5 months (4-60+ months). Of 103 CRC patients, 3 of 9 patients relapsed in stage I; 6 of 33 patients relapsed in stage II; 26 of 44 patients relapsed in stage III; 14 of 17 patients relapsed in stage IV. Totally, 49 (47.6%) patients relapsed during follow-up periods. The RFS curves of CRC patients in different stages were shown in Figure 1. RFS decreased significantly in advanced stage than that in early stage (Log rank test, p<0.0001).

*Relationship of preoperative single TM with RFS*

The correlation of preoperative single TM with RFS was shown in figure 1. The patients with normal preoperative serum TM had significant longer RFS time comparing with those patients with elevated preoperative serum TM.

*Relationship of preoperative combined TMs with RFS*

The relationships between preoperative combined detection of CA19-9+CEA, CA19-9+CA125, CEA+CA125 and CA19-9+CEA+CA125 with RFS were shown in Figure 2. The patients with negative TMs had a longer RFS comparing with those with any positive TM (Log rank test, p<0.05).

*Numbers of positive TMs and RFS*

Among 103 CRC patients, 62 patients had normal preoperative TMs, 25 patients had 1 positive preoperative TM, 13 patients had 2 simultaneously positive TMs, 3 patients had 3 simultaneously positive TMs. Of the 13 patients with 2 simultaneously positive TMs, 11 patients had simultaneously positive CA19-9 and CEA; only 2 patients had simultaneously positive CEA and CA125. Therefore, the difference between combined detection of CEA+CA19-9 and CEA+CA19-9+CA125 was especially compared. As shown in Figure 3, patients with three simultaneously positive TMs had significantly reduced 5-year RFS.

*Factors correlated with 5-year RFS*

When exploring the factors correlated with RFS, Spearman correlation analysis indicated that stage (r=-

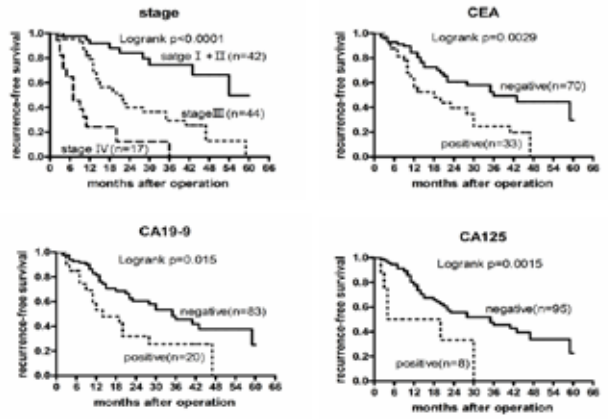


**Figure 1. The 5-year RFS of Patients with CRC in Different Stage and Preoperative Serum Status of Single TM**

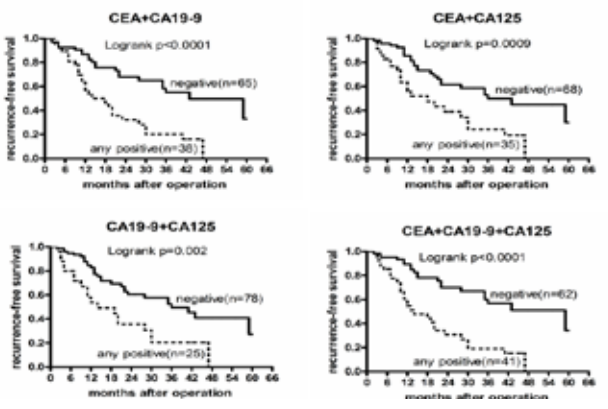


**Figure 2. TMs Combination Detection and 5-year RFS of Patients with CRC**

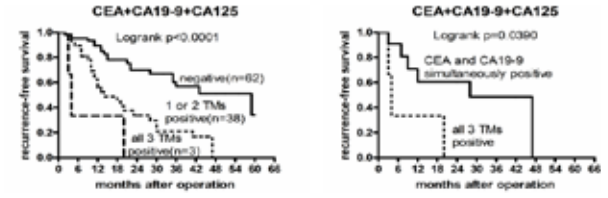


**Figure 3. The Number of positive TM and 5-year RFS of Patients with CRC**

0.426 p=0.00), preoperative serum TM status, CA19-9 (r=0.270, p=0.006), CEA (r=0.243, p=0.014), CA125 (r=0.232, p=0.018), CEA+CA19-9 (r=0.359, p=0.000), CEA+CA125 (r=0.241, p=0.014), CA19-9+CA125 (r=0.342, p=0.000), CEA+CA19-9+CA125 (r=0.377, p=0.000) had correlations with 5-year RFS of patients with CRC.

Univariate analysis indicated that stage, the preoperative serum TM status of three single TM and any combination of three TMs had correlations with 5-year RFS. Multivariate analysis with Cox regression model revealed that only stage (p<0.001) and preoperative serum status of combined detection of CA19-9+CEA+CA125 (p<0.001) were independent prognostic factors for 5-year of CRC.

## Discussion

Knowledge about the CRC prognosis could help to individualize therapy choice at the time of primary diagnosis. Currently, the disease stage is regarded as the gold standard for predicting prognosis. However, it is difficult to accurately determine the stage prior to surgical treatment. Furthermore, patients with CRC with the same disease stage display survival heterogeneity, with some patients exhibiting recurrence diversity. With advances in understanding the biological behaviors of tumor, a variety of biological factors on prognosis have attracted considerable attention. A study (Auf et al., 2010) recently investigated the expression of cytokeratin 20 (CK20) and vascular endothelial growth factor (VEGF) in the peripheral blood of Egyptian CRC patients, the result showed that both CK20 and VEGF significantly increased in advancing CRC stage C and with lymph nodes metastasis. Another study (Ferroni et al., 2010) reported that positive presurgical sE-selectin levels were associated with an increased recurrence rate compared with patients with low levels of this molecule in CRC patients. Although numerous new TMs (Auf et al., 2010; Ferroni et al., 2010; Tang et al., 2009; Holten-Andersen et al., 2004; Mroczko et al., 2007; Demirci et al., 2009; Sun et al., 2009; Rosen et al., 2005 ) have been suggested for CRC, the ideal serum TM is still not available for routine clinical application. Classical TMs CA19-9, CEA, and CA125 still play major role in clinical practice.

This study focused on the relationship between preoperative serum TMs status and RFS in 103 CRC patients with complete 5-year follow-up information. We found that patients with positive CEA, CA19-9 or CA125 had significantly higher recurrent rate and shorter 5-year RFS than those patients with negative TMs (p<0.05). Multivariate Cox regression model analysis confirmed that preoperative CEA+CA19-9+CA125 was an independent prognosis factors for RFS.

On further analysis, it was found that patients with 3 simultaneously positive serum CA19-9, CEA and CA125 had significantly reduced RFS comparing with negative patients. Single TM detection had relatively high specificity and PPV, but very low sensitivity and NPV in our previous study (Yang et al., 2009; Yang et al., 2010) and this study (table 2). These results suggest that combined detection of CA19-9, CEA and CA125 could increase the predicting value for RFS.

CEA is a high molecular weight glycoprotein in the immunoglobulin superfamily and has been used as an important biomarker of CRC. High CEA levels may also be found in other conditions such as hepatitis, inflammatory bowel disease, pancreatitis, and obstructive pulmonary disease (Kim et al., 2008) . Its usefulness in CRC has been explored extensively (Morita et al., 2004; Duffy, 2001; Park et al., 2009). A study reported that high preoperative CEA correlated with adverse prognosis and the most useful application of CEA is in the detection of liver metastasis from CRC (Duffy, 2001). Another study found that patients with high preoperative CEA levels (>7.0 ng/ml) were significantly more likely to have perineural invasion, more aggressive tumor stage, and tumor recurrence than were patients with normal preoperative CEA (Park et al., 2009). CEA concentrations significantly rose with the clinical stage of CRC (Mroczko et al., 2007). In keeping with these results, this study showed the patients with positive preoperative CEA had shorter 5-year RFS, but it was not an independent prognosis factor for 5-year RFS in multivariate analysis.

CA19-9 is most commonly used in detecting pancreatic adenocarcinoma, although it is also a TM in detecting CRC. The prognostic value of CA19-9 remains controversial. A study reported that the CA19-9 level was not a predictor of prognosis (Morita et al., 2004). But another study found a contradictory result: preoperative high CA19-9 (>37.0U/mL) was an independent prognostic factor for recurrence, and patients with high preoperative CA19-9 levels were significantly to show lymphatic invasion, perineural invasion, more advanced tumor stage and recurrence than patients with normal preoperative CA19-9 levels (Papk et al., 2009). This study confirmed that CRC patients with positive preoperative CA19-9 had significantly higher recurrent rate and shorter 5-year RFS than those with normal CA19-9. But, again, preoperative CA19-9 was not an independent prognostic factor for 5-year RFS in multivariate analysis.

Serum CA125 levels can elevate in various normal and pathologic conditions that affect the endometrium, including menstruation, pregnancy, endometriosis, and endometrial cancer (Baron et al., 2005; Miralles et al., 2003).It is most commonly used in detecting ovarian cancers (Rosen et al., 2004), but it is not ovarian cancer specific and can also elevate in other cancers such as carcinoma of the breast, lung and CRC. In CRC, elevated CA125 might be correlated with serosal involvement and peritoneal spread (Miralles et al., 2003). In our previous and present study, the positive rate of CA125 was very low, especially in early stage, but in stage IV, the positive rate increased significantly. Of 8 patients with positive preoperative serum CA125, 7 patients relapsed during follow-up periods, 1 patient could not be contacted with after 8 months survival without recurrence, and the median 5-year RFS of patients with preoperative positive CA125 was only 4 months, which was the shortest among the three TMs. Considering all the factors including its sensitivity (7.8%) and NPV (59.1%), we concluded that the elevated preoperative serum CA125 was a dismal factor for RFS

in CRC patients.

The guidelines of ASCO and EGTM recommended that CEA could be used in predicting prognosis, surveillance following curative resection and monitoring therapy in advanced disease (Duffy et al., 2007; Locker et al., 2006). The guidelines did not recommend CA19-9 as a useful TM in CRC, and even did not mention CA125 as a TM for CRC. This study confirmed the fact that the three individual TM was not an independent prognostic factor for 5-year RFS in patients with CRC. However, combination use of these TMs might be shown values in CRC. The 3 TMs combined detection was an independent prognostic factor in this study.

In comparison with other studies (Sun et al., 2009; Morita et al., 2004; Papk et al., 2009), this study had both consistency and inconsistency with theirs. Some considerations might account for the confusing and even contradictory results. First, different definitions of abnormal TM levels or different methods for TM detection were used. Second, different study may have different sample size and employ different ethnic or race group. Third, different statistical methods were used and may have resulted in different conclusions. Fourth, different definition of RFS may be taken. Fifth, different patients might experience different treatment and different follow-up periods. A study (Dogan et al., 2010) recently reported that perioperative blood transfusion was a factor related to disease-free survival and overall survival of CRC.

There are two main limitations in this study. One is the relatively small sample size; the other is too many patients losing follow-up, which may be produced some bias. However, the results in this study were very objective, and we believed that the results in this study could play some instructing role in clinical practice.

In conclusion, increased preoperative CA19-9+CEA+CA125 is an independent negative prognostic factor for 5-year RFS of patients with CRC.

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