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Research Article

Preoperative Serum CA125 Levels for Predicting Peritoneal Dissemination of Colorectal Cancer

Nai-Lu Lin[1,3], Shih-Ching Chang[2,3], Jeng-Kae Jiang[2,3], Shung-Haur Yang[1,2,3*]

[1]Department of Surgery, National Yang Ming Chiao Tung University Hospital, Yilan, Taiwan
[2]Department of Surgery, Division of Colon and Rectal Surgery, Taipei Veterans General Hospital, Taipei, Taiwan
[3]Department of Medicine, National Yang Ming Chiao Tung University, Hsinchu, Taiwan

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ABSTRACT

Objective: The present study aimed to analyze the association between tumor makers and Peritoneal Dissemination (PD) detection in patients with Colorectal Cancer (CRC).

Background: The eighth edition of the American Joint Committee on Cancer (AJCC) staging system expanded the classification of the M category with the addition of M1c for PD due to its worse prognosis compared to other visceral organ metastases. The lack of specific symptoms and varying sensitivities of imaging studies leads to difficulty in PD detection.

Methods: A total of 1,109 patients with CRC who underwent tumor resection between June 2000 and December 2017 were included in this retrospective study. Serum tumor markers, including Carcinoembryonic Antigen (CEA), Carbohydrate Antigen 19-9 (CA19-9), and CA125, were analyzed preoperatively. The grading of PD was performed based on the findings during surgical exploration and further confirmed by pathology.

Results: CA125 had the lowest sensitivity; however, it showed the highest specificity and diagnostic accuracy compared to CEA and CA19-9. Based on the analysis of tumor marker levels in advancing stages, the levels of CA125 did not rise until stage IVC. CEA and CA19-9 levels increased significantly at stage IV; however, it was not possible to differentiate between stage IVC and other organ metastases.

Conclusion: Among the three tumor markers, CA125 levels were closely correlated with PD compared to CEA and CA19-9 levels. The present analysis of tumor markers poses a better chance of diagnosis of stage IVC preoperatively.

Keywords: Colorectal Cancer (CRC), Cytoreductive surgery, CA125 level, Peritoneal dissemination

***Correspondence:** Shung-Haur Yang, Department of Medicine, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, E-mail: ulna39@hotmail.com

INTRODUCTION

Colorectal Cancer (CRC) is one of the most commonly diagnosed cancers worldwide. According to GLOBOCAN 2018, more than one million new CRC cases and 55,000 deaths were estimated worldwide (Bray F, *et al*., 2018). Approximately 5%-15% of patients with CRC were diagnosed with Peritoneal Dissemination (PD) at abdominal exploration (Jayne DG, *et al*., 2002; Stewart JH, *et al*., 2005; Klaver YL, *et al*., 2012). Poor Overall Survival (OS) of patients with CRC with PD has been reported in previous studies (Stewart JH, *et al*., 2005; Stillwell AP, *et al*., 2011).

Since the 1980s, Cytoreductive Surgery (CRS) combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has been proposed to treat PD (Spratt JS, *et al*., 1980; Sugarbaker PH, 2010). Currently, complete CRS and/or HIPEC are carried out in centers with experienced physicians for a selected patient with limited PD for whom R0 could be achieved (Mahmoud AM, *et al*., 2018; NCCN, 2021).

In 2004, we analyzed preoperative Carcinoembryonic Antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and other parameters and found that abnormal CA19-9 was a risk factor for PD (Yang SH, *et al*., 2004). In 2016, we reported that preoperative carbohydrate antigen 125 (CA125) was a better tumor marker compared to CEA to predict PD in both genders (Huang CJ, *et al*., 2016).

In 2017, the eighth edition of the American Joint Committee on Cancer (AJCC) staging system made a new classification of stage IV. The M category classification for PD was expanded with the addition of M1c (M1a denotes metastases to one distant site or organ and M1b denotes metastases to more than one) (Byrd DR, *et al*., 2017). The rationale for AJCC's M1c designation is PD that generally has a poor prognosis compared to other visceral organ metastases (Weiser MR, 2018). A better diagnosis of PD at this stage is required to enable timely treatment. The question arises whether we can specifically detect PD through serum marker analysis.

In the present study, we aimed to investigate which among the three markers-CEA, CA19-9, or CA125-is the most suitable marker to predict the incidence of PD of CRC in a larger patient population.

MATERIALS AND METHODS

Patients

This retrospective analysis included a prospectively collected database with 1,253 patients who were diagnosed with CRC between June 2000 and December 2016. Elective resections were performed by two surgeons (S-HY and J-KJ) at the Taipei Veterans General Hospital. The Institutional Review Board of the Taipei Veterans General Hospital approved this study (2015-07-005AC). Written informed consent was obtained from all the patients. After excluding patients with synchronous cancers other than CRC (n=4), those with rectal cancer receiving neoadjuvant radiotherapy (n=134), those with pathology other than adenocarcinoma (n=4), or those with insufficient data (n=2), the data of 1,109 patients were included. The clinicopathological data were retrieved from the medical records, including age, sex, primary tumor site, histology, Lymphovascular Invasion (LVI), sites of metastases, grading of PD, and preoperative serum CEA, CA19-9, and CA125 levels. The presence and grading of PD were defined based on the findings of operative exploration and were confirmed by pathology. The TNM staging of the AJCC (8th edition) was used for staging (Byrd DR, *et al*., 2017). The grading system for PD was

based on the Japanese Classification of Colorectal Cancer (JCCRC) criteria (Japanese Society for Cancer of the Colon and Rectum, 2019).

Tumor biomarkers

CEA, CA19-9, and CA125 levels were determined from peripheral blood samples within 1 month before surgery. The measurement methods were changed during the study period. In the early years of the study (June 2000-November 2012), radioimmunoassay kits were used: CEA, CEA-RIACT Kit (CIS bio international, Gif-sur-Yvette, France); CA19-9 and CA125, 125I IRMA Kit (DiaSorin, Stillwater Minnesota, USA). Further, between December 2012 and December 2016, ARCHITECT i2000SR (Abbott Diagnostics, Lake Forest, USA) was used to measure the levels of all three markers. The values of CEA <5.0 ng/ml, CA19-9 <37.0 U/ml, and CA125 <35.0 U/ml were defined as normal results.

Statistical analysis

Categorical variables were compared using Pearson's Chi-squared test. The means between two groups were compared using the student's t-test. One-way analysis of variance with the Bonferroni post hoc test was used for multiple comparisons. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 20.0. (SPSS Inc., Chicago, IL, USA). The Receiver-Operating Characteristic (ROC) curve and the Area Under the Curve (AUC) were analyzed using the Stata Statistical Software (version 12.0, Stata Corporation, College Station, TX) where $p<0.05$ was considered as statistically significant.

RESULTS

A total of 636 male (57.3%) and 473 female patients (42.7%) were included in this study, with a mean age of 65.1 years (range, 26-94 years). All 1,109 patients underwent resection of the primary lesion with curative or palliative intent and exploration for macroscopic PD. Patient characteristics are shown in *Table 1*. Tumor locations were as follows-

Table 1: Demographic distribution

Demographic characteristics	
Age (years), mean (range)	65.1 (26.0-94.0)
Sex, n (%)	
Male	636, 57.3%
Female	473, 42.7%
Tumor site, n (%)	
Right colon	374, 33.7%
Left colon	470 (42.4%)
Rectum	265 (23.9%)
Histology, n (%)	
Adenocarcinoma	1051 (94.8%)
Mucinous adenocarcinoma, signet ring cell carcinoma	58 (5.2%)
Differentiation, n (%)	
Well, moderate differentiation	1020 (92%)
Poor differentiation, undifferentiation	89 (8%)
Lymphovascular invasion, n (%)	
Negative	854 (77%)
Positive	255 (23%)
Peritoneal dissemination*, n	
P0	1029 (92.8%)
P1	28 (2.5%)
P2	26 (2.3%)
P3	26 (2.3%)
TNM stage, n (%)	
I	239 (21.6%)
II	328 (29.6%)
III	307 (27.7%)
IV	235 (21.2%)
CEA (ng/ml), median (range)	3.5 (0.1-5663.5)
CA19-9 (U/ml), median (range)	14.3 (0.1-53252.3)
CA125 (U/ml), median (range)	12 (0.1-1503.0)

Note: CEA=Carcinoembryonic Antigen; CA19-9, carbohydrate antigen 19-9; CA125: Carbohydrate Antigen 125; TNM: Tumor Node Metastasis

*Japanese Classification of Colorectal Cancer criteria-P0: No Peritoneal Dissemination (PD); P1: Adjacent PD without distant PD; P2: A few distant PD; P3: Numerous distant PD

Right side (33.7%), left side (42.4%), and rectum (23.9%). Mucinous adenocarcinoma and signet ring cell carcinoma composed 5.2%, poor differentiation plus undifferentiation 8%, and LVI 23% of the whole population. Using the AJCC staging system, 239 (21.6%), 328 (29.6%), 307 (27.7%), and 235 (21.2%) patients had stage I, II, III, and IV disease, respectively. There were 80 (7.2%) cases of PD, with P1 (2.5%), P2 (2.3%), and P3 (2.3%). The median level of CEA was 3.5 ng/ml (range, 0.1-5633), and that of CA19-9 and CA125 were 14.3 U/ml (0.1-53252) and 12 U/ml (0.1-1503), respectively.

Table 2 shows the correlation of PD and clinicopathological factors. In univariate analysis, presence of PD (PD+) correlated with younger age (<65 years), right side colon location, mucinous or signet ring cell carcinoma, poor differentiation, LVI+, high CEA, and high CA125 levels.

Table 3 lists the diagnostic parameters of the three markers. CEA had the highest sensitivity (0.69); however, it had the lowest specificity (0.62) and lowest diagnostic accuracy (0.63) for detecting PD. However, CA125 had the lowest sensitivity (0.51), the highest specificity (0.89), and the highest diagnostic accuracy (0.86). AUC analysis revealed a trend of difference among them (p=0.051). Post hoc analysis of AUC revealed that CA125 was a significantly better predictor compared to CEA (p=0.02), and there was no significant difference between the other two matching comparisons.

The levels of the three tumor markers according to the AJCC staging system are shown in *Figure 1*. For CEA, the levels increased significantly from stage I to IV with each advancing stage, however, with an exception between stages II and III. An abrupt increase in level was noted between stage III and IVA. Among the stage IV group, only the level of IVA was higher than IVB, and IVC was not significantly different from IVA or IVB.

For CA19-9 also, the levels significantly increased from stage II to IVA at each advancing stage, and not so between stages I and II. An abrupt increase in level was noted between stages III and IVA. However, in the stage IV group, there was no significant difference in CA19-9 levels between the groups. Stage IVC showed a higher mean of CA19-9 levels, however, there was also a high variation of distribution. Stage IVC did not have any significant difference with any stage, even in stage I.

For CA125, there was no difference in levels between stage I and stage IVA. Stage IVB had a small increase in level of CA125, but with only a significant difference from stage I. An abrupt rise was noted between stages IVB and IVC. Stage IVC showed a significantly higher CA125 level than all stages, from stage I to stage IVB.

The levels of CA125 with respect to the grade of PD based on the JCCRS criteria are shown in *Figure 2*. As PD progressed, the level of CA125 increased; however, it showed a small drop at P2. CA125 levels of P1 were higher than those of P0, and the CA125 levels of P3 were significantly higher than those of the other grades. However, the levels of CA125 of P2 were not higher than those of P0.

Table 2: Correlation of Peritoneal Dissemination (PD) and clinicopathological factors

Demographic characteristics	PD (-) n=1029	Percentage (%)	PD (+) n=80	Percentage (%)	p-value
Sex, n (%)					
Male	597	58%	39	48.80%	0.11
Female	432	42%	41	51.20%	
Age, n (%)					
<65 years	451	43.80%	52	65%	<0.001
>=65 years	578	56.20%	28	35%	
Tumor site, n (%)					
Right side colon	339	32.90%	35	43.80%	<0.01
Left side colon	435	42.30%	35	43.80%	
Rectum	255	24.80%	10	12.50%	
Histology, n (%)					
Adenocarcinoma	982	95%	69	86.20%	<0.001
Mucinous adenocarcinoma, signet ring cell carcinoma	47	5%	11	13.80%	
Differentiation, n (%)					
Well, moderate differentiation	956	93%	64	80%	<0.001
Poorly differentiation, Undifferentiation	73	7%	16	20%	
Lymphovascular invasion, n (%)					
Negative	822	79.90%	32	40%	<0.001
Positive	207	20.10%	48	60%	
CEA (ng/ml), median (range)	3.3	(0.1-5663)	10.3	(1.1-3267)	0.03*
CA19-9 (U/ml), median (range)	13.2	(0.1-11240)	54.4	(0.7-53252)	0.07*
CA125 (U/ml), median (range)	11.5	(0.1-1036)	35.7	(2.3-1503)	0.001*

Note: CEA=Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; CA125: Carbohydrate Antigen 125
*p-values were analyzed from the comparison of the mean of the levels of each tumor maker

Table 3: Diagnosis parameters of CEA, CA19-9, and CA125 to detect PD

Diagnostic parameters	CEA (5.0 ng/ml)	CA19-9 (37.0 U/ml)	CA125 (35.0 U/ml)	p-value
Sensitivity	0.69	0.59	0.51	5.10%
Specificity	0.62	0.78	0.89	
Diagnostic accuracy*	0.63	76.00%	0.86	
AUC	0.7	74.00%	0.79	

Note: *Diagnostic accuracy=(PD(+) with positive test result+PD(-) with negative test result)/all patients tested

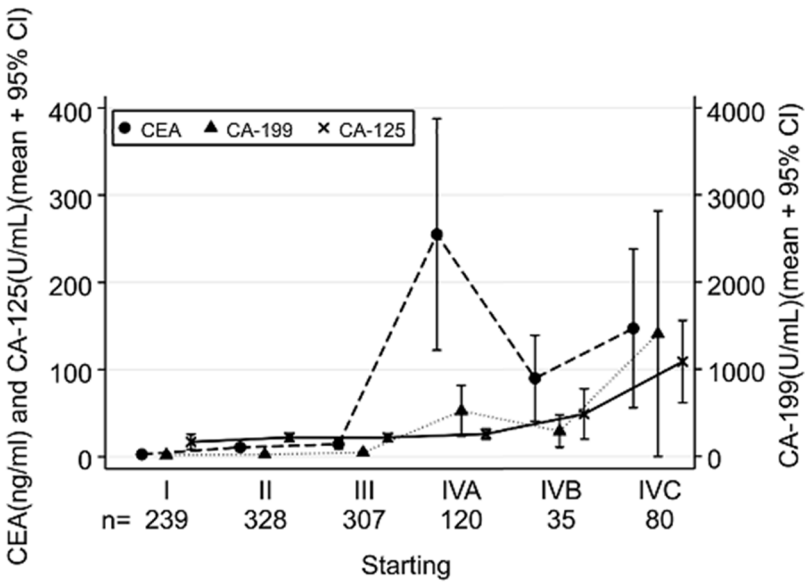

Figure 1: The relationship between tumor marker levels and AJCC staging system (8th edition)

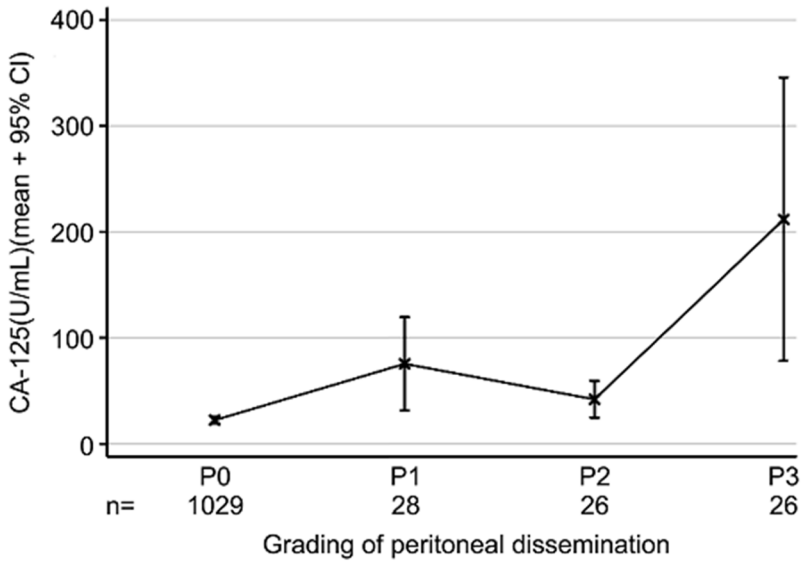

Figure 2: The relationship between CA125 levels and JCCRC grading of peritoneal dissemination

DISCUSSION

With the aim of detecting PD using tumor markers in a large population, our study showed that CA125 has the highest diagnostic accuracy and highest specificity, but lowest sensitivity, compared to the other two markers. In contrast, CEA had the highest sensitivity, but the lowest specificity and diagnostic accuracy. CA19-9 is always ranked as the middle one among the three markers used for diagnostic analysis. This result is consistent with our previous suggestion that CA125 should be included in the evaluation of PD (Huang CJ, *et al*., 2016). In particular, our results demonstrate the potential of detecting the worst prognosis group, i.e., M1c, stage IVC.

Two studies reported better PD detection using CA19-9 than CEA (Takakura Y, *et al*., 2015; Kaneko M, *et al*., 2017). However, applying similar analysis methods in this study did not show that CA19-9 had better potential to detect PD compared to CEA. CA125 was the best tumor marker among the others analyzed. These studies also revealed that an elevated preoperative serum CA19-9 level in patients with CRC was found to be a predictor of cancer progression and was associated with peritoneal recurrence after curative tumor resection surgery (Takakura Y, *et al*., 2015; Kaneko M, *et al*., 2017; Yu H, *et al*., 2013). In this study, we focused on the relationship between tumor makers and the presence of PD, but not on tumor prognosis or peritoneal recurrence, which we may evaluate in a future study.

CEA is very sensitive in detecting distant metastases but cannot differentiate PD from others. Intriguingly, the performance of CA19-9 in the analysis of diagnostic parameters is always between these two markers. The curve pattern of CA19-9 levels is similar to that of CEA, and both have a similar abrupt rise between stages III and IV. This rise matches the severity of the disease and is very likely to indicate the total tumor burden. Unlike these two markers, CA125 levels did not rise significantly until stage IVC. This might be because CA125 is mainly released from the irritated peritoneum or gynecological organs involved (Kabawat SE, *et al*., 1983), instead of the colorectal tumor tissue, although CA125 has been reported to be detected in cancer tissues of the stomach and colon (Streppel MM, *et al*., 2012). Based on the curve pattern of the AJCC staging system, we postulate that CA125 released into the serum is not from the tumor tissue, because it does not match the total tumor burden. Based on the PD grading of JSCCR, CA125 levels roughly correlated with progressing grades, except for P2. This implies that, although CA125 does not correlate with the total tumor burden, it does correlate with the severity of PD.

With the help of a larger population study, the diagnostic parameters showed some differences from our previous study on CEA and CA125 (Huang CJ, *et al*., 2016). The sensitivity of CEA to detect PD dropped from 0.75 to 0.69, and that of CA125 dropped from 0.61 to 0.51. However, the specificities of CEA (0.63 *vs*. 0.62) and CA125 (0.90 *vs*. 0.89) were similar. The high specificity of CA125 was confirmed in this study; however, its sensitivity was relatively low.

PD is associated with a poor prognosis and is a common process in the natural course of CRC (Jayne DG, *et al*., 2002; Chu DZ, *et al*., 1989). The incidence of PD was 7.2% in our study, which is comparable to that reported in other studies (Jayne DG, *et al*., 2002; Stewart JH, *et al*., 2005; Klaver YL, *et al*., 2012). Patients with colorectal PD had a lower survival rate than those without PD (Klaver YL, *et al*., 2012). A poor prognosis of PD results in a poor quality of life, including refractory malignant ascites, intractable abdominal pain, and irreversible intestinal obstruction (Kaneko M, *et al*., 2017). Eventually, the clinical course progressing gradually to mortality is irreversible. The existence and extent of PD lead to different treatment policies. Multimodality treatments with CRS and HIPEC were considered in selected patients and favored in the early stages of PD. However, a certain number of PD cases were first diagnosed during tumor resection surgery due to the lack of specific symptoms and varying sensitivities of imaging studies, especially for those who had early stage colorectal PD (Klaver YL, *et al*., 2012; Chu DZ, *et al*., 1989; Franiel T, *et al*., 2009; Marin D, *et al*., 2010).

The PRODIGE 7 trial (Quénet F, *et al*., 2021) questioned the efficacy of Hyperthermic Intraperitoneal Chemotherapy (HIPEC), as there was no significant difference in OS after the addition of HIPEC to CRS from CRS alone for patients with PD. However, for patients with a PCI (Peritoneal Cancer Index) (Huang CJ, *et al*., 2016; Byrd DR, *et al*., 2017; Weiser MR, 2018; Japanese Society for Cancer of the Colon and Rectum, 2019; Takakura Y, *et al*., 2015), the addition of HIPEC to CRS still showed some benefit in the median OS and relapse-free survival in the subgroup analysis. In addition, preclinical studies (Löffler MW, *et al*., 2019; Ubink I, *et al*., 2019), provided some evidence that current HIPEC regimens were insufficient to eradicate colorectal PD, and the selected drugs and methods of HIPEC could influence the study results. A more standardized regimen of intraperitoneal chemotherapy remains to be determined. The National Comprehensive Cancer Network (NCCN) guidelines (NCCN, 2021) suggest that complete CRS and/or intraperitoneal chemotherapy for selected patients

with limited peritoneal metastases can be arranged in established centers with experienced physicians. Confirming the presence of PD remains a crucial part of preoperative planning. In this study, the level of CA125 had the best diagnostic ability to predict PD among the three tumor makers.

CONCLUSION

Our study has some limitations. First, this was a single-center study with a retrospective design. Second, the sensitivity and specificity of imaging were not analyzed in this study. Third, we used the JCCRC criteria to evaluate PD grading instead of the more specific PCI.

In conclusion, among the three markers analyzed to detect PD, CA125 had the highest diagnostic accuracy, highest specificity, and lowest sensitivity. Preoperative CA125 levels might pose a better chance of identifying stage IVC. Furthermore, a better preoperative treatment policy may be implemented.

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