

ORIGINAL ARTICLE

대장암 환자에서 복막 전이에 대한 복수내 암태아 항원 (Carcinoembryonic Antigen)의 진단적 가치

송성은, 최바울, 김재현, 정경원, 김성은, 문원, 박무인, 박선자

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Diagnostic Value of Carcinoembryonic Antigen in Ascites for Colorectal Cancer with Peritoneal Carcinomatosis

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Background/Aims: Diagnostic tests for carcinoembryonic antigen (CEA) in ascites have been performed in various malignant cases, but there is only few data on the applicability of CEA for colorectal cancer (CRC) patients with peritoneal carcinomatosis. We aimed to determine the usefulness of CEA in ascites (aCEA) as a diagnostic parameter for CRC with peritoneal carcinomatosis.

Methods: Between January 2000 and May 2013, the medical records of 259 patients who underwent paracentesis for the evaluation of ascites were retrospectively reviewed. CRC patients with ascites (n=82) and patients with non-malignant ascites (n=177) were evaluated. Patients who had other malignancies, including gastric or ovarian cancer, with ascites were excluded. The optimal diagnostic cut-off value of aCEA for CRC with peritoneal carcinomatosis was determined using receiver operating characteristic curve analysis. The value of aCEA for predicting the occurrence of peritoneal carcinomatosis was evaluated using a logistic regression model.

Results: The optimal cut-off value of aCEA to diagnose CRC with peritoneal carcinomatosis was 3.89 ng/mL, and the area under the curve for aCEA was 0.996 (sensitivity 96.3%, specificity 100%, positive predictive value 100%, negative predictive value 98.3%). Multivariate logistic regression analysis showed that aCEA was an independent factor predicting the occurrence of peritoneal carcinomatosis.

Conclusions: In this study, we showed that aCEA may be a useful parameter for diagnosing CRC with peritoneal carcinomatosis, and we propose an optimal aCEA cut-off value of 3.89 ng/mL. Further study that includes patients with other malignant ascites may be necessary to validate these findings. (Korean J Gastroenterol 2018;71:332-337)

Key Words: Carcinoembryonic antigen; Ascites; Peritoneal neoplasms; Colorectal neoplasms

INTRODUCTION

Liver cirrhosis (~80% of cases) is the most common cause of ascites. Ascites is the pathological accumulation of fluid in the peritoneal cavity. Malignant conditions, including peri-

toneal carcinomatosis, and benign conditions, including tuberculous peritonitis, heart failure, pancreatic disease, and renal disease, also contribute to the development and accumulation of ascites. Malignant ascites account for approximately 10% of all cases of ascites.¹ Ascites fluid analysis by

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paracentesis can provide useful information for determining the cause of ascites.^{2,3} Several potential parameters for the diagnosis of malignant ascites have been evaluated to date, including protein levels in ascites, ascites/serum concentration ratio of protein (protein A/S), lactate dehydrogenase (LDH) levels in ascites, ascites/serum concentration ratio of LDH (LDH A/S),⁴ carbohydrate antigen 19-9 in ascites,⁵ serum-ascites albumin gradient,⁶ fibronectin in ascites, and cholesterol in ascites.⁷ However, until now, no parameter was able to completely differentiate the cause of malignant ascites; currently, the gold standard for diagnosing malignant ascites is the presence of tumor cells in ascites.⁸ The specificity of this method is very high, but it has low sensitivity (40-60%) due to the lack of cell exfoliation, which is common to all malignancies.⁵ This low sensitivity sometimes leads to invasive procedures, including laparoscopy, to acquire peritoneal tissues. The assessment of carcinoembryonic antigen in ascites (aCEA) has been suggested as an option for diagnosing patients with ascites, and some studies have suggested a positive diagnostic value of aCEA.^{5,9,10} Such studies evaluated the diagnostic value of aCEA for various malignant cases, but there is limited data on its applicability for colorectal cancer (CRC) patients with peritoneal carcinomatosis.

Peritoneal carcinomatosis, a complication of CRC, is the primary reason for treatment failure. When cancer patients develop ascites, a number of comorbid diseases, including liver cirrhosis, congestive heart failure, or infectious causes, should be suspected, and peritoneal carcinomatosis should be also considered. Peritoneal carcinomatosis is a common cause of death in patients treated for CRC. According to some reports, peritoneal carcinomatosis has been found in approximately 7% of patients during primary surgery, in approximately 4-19% of patients during the follow-up period after curative surgery, and in 40-80% of patients who succumb to CRC.^{11,12} The prognosis of CRC patients with peritoneal carcinomatosis is poor, with reported median survival of 5.2 months.¹³ Recently, the overall survival rates in patients with CRC have increased as a result of improved treatment strategies, including target therapy. Early and precise detection of peritoneal carcinomatosis via the assessment of aCEA could also be helpful to increase long-term outcomes.

The aim of this study was to identify the clinical significance of CEA in all patients with ascites and to determine the usefulness of aCEA as a diagnostic parameter for advanced CRC

with peritoneal carcinomatosis.

SUBJECTS AND METHODS

1. Patients

We retrospectively reviewed the medical records of 259 patients who underwent paracentesis for the evaluation of ascites at Kosin University Gospel Hospital, Busan, Korea, between January 2000 and May 2013. CRC patients with ascites (n=82, CRC group) and those with non-malignant ascites (n=177, benign group) were retrospectively evaluated. Patients who had other malignancies, including gastric or ovarian cancer, with ascites were excluded. The CRC group was defined as patients with histologically proven CRC and clinically confirmed peritoneal carcinomatosis. The clinical diagnosis of peritoneal carcinomatosis was made by peritoneal biopsy or assessment of cytology in ascites, and by radiological findings identified by computed tomography (CT) as follows: ascites, thickening of bowel walls, increase in the density of peritoneal fat, presence of peritoneal nodules, and hydronephrosis.¹⁴ The benign group was defined as patients who had no evidence of malignancy by clinical and radiological findings.

2. Collection and assessment of ascites

All patients underwent paracentesis to evaluate aCEA. The collected ascites were analyzed for cytology and tumor markers. For cytologic examination, the collected peritoneal fluid was centrifuged and smeared on the slides and fixed with cytospray; Papanicolaou and Giemsa staining were performed. The levels of aCEA and serum CEA (sCEA) were measured using electrochemiluminescent immunoassay on a Cobas e-601 analyzer (Roche Diagnostics, Mannheim, Germany).

3. Statistical analyses

All statistical analyses were performed using SPSS 20.0 (IBM Co., Armonk, NY, USA). The optimal cut-off value was determined using receiver operating characteristic (ROC) curve analysis. Sensitivity was calculated as true positives/(true positives+false negatives), and specificity was calculated as true negatives/(true negatives+false positives). Positive predictive value (PPV) and negative predictive value (NPV) determinations were made from the established cut-off values,

and were calculated as $PPV = \text{true positives} / (\text{true positives} + \text{false positives})$ and $NPV = \text{true negatives} / (\text{true negatives} + \text{false negatives})$. A logistic regression model was used to assess the factors affecting the occurrence of peritoneal carcinomatosis. A p value of less than 0.05 was considered statistically significant.

RESULTS

1. Patient characteristics

A total of 259 patients who underwent paracentesis for cytologic evaluation were enrolled. The median age was 60 years (range 17-87). Of these 259 patients, 195 were male (75.3%) and 64 were female (24.7%). Patients were divided into one of two groups: the CRC group (n=82) or the benign group (n=177), based on their diagnosis. The benign group was comprised of patients with liver cirrhosis (n=155), renal disease, including chronic kidney failure and nephritic syndrome (n=6), tuberculous peritonitis (n=6), heart failure (n=5), and pancreatitis (n=5). Among those in the CRC group,

72 patients (87.8%) were diagnosed by colonoscopic examination, and 10 (12.2%) by surgical examination. Peritoneal carcinomatosis was diagnosed by cytologic evaluation in ascites (n=9) and by computed tomography imaging (n=73). When evaluating metastasis, 17 patients (20.7%) had metastasis that was limited to the peritoneum, while 65 patients (79.3%) had concurrent peritoneal and systemic organ metastasis, including liver, lung, bone, distant lymph node, or multiple organ metastases. These results are summarized in Table 1.

2. Tumor marker assays

The median level of aCEA among all patients was 0.82 ng/mL (range 0.2-16,518 ng/mL). The median levels of aCEA in the CRC and benign groups were 778.85 ng/mL (range 0.97-16,518 ng/mL) and 0.5 ng/mL (range 0.2-3.45 ng/mL), respectively. The difference between the two groups was statistically significant ($p < 0.001$), as shown in Fig. 1.

According to ROC curve analysis, the optimal cut-off value of aCEA to predict the occurrence of peritoneal carcinomatosis was 3.89 ng/mL. The sensitivity and specificity were 96.3% and 100%, respectively (PPV, 100%; NPV, 98.3%). Moreover, the area under the curve for aCEA was 0.996 ($p < 0.001$). By comparison, the optimal cut-off value for sCEA for predicting the occurrence of peritoneal carcinomatosis was 8.64 ng/mL. The sensitivity and specificity were 84.2% and 91.3%, respectively (PPV, 81.0%; NPV, 92.9%); the AUC for sCEA was 0.914 ($p < 0.001$). These results are summarized in Table 2 and Fig. 2.

Table 1. Baseline Characteristics in Enrolled Patients

	Benign group (n=177)	CRC group (n=82)
Median age (range)	59 (17-87)	65 (37-87)
Gender		
Male	126 (71.2)	54 (65.9)
Female	51 (28.8)	28 (34.1)
Performance status ^a		
0	133 (75.1)	57 (69.5)
1	41 (23.2)	23 (28.0)
2	3 (1.7)	2 (2.5)
Diagnostic method of CRC		
Colonoscopic biopsy		72 (87.8)
Surgery		10 (12.2)
Diagnostic method of peritoneal carcinomatosis		
Cytology in ascites		9 (11.0)
CT image		73 (89.0)
Metastasis		
Peritoneum only		17 (20.7)
Liver		26 (31.7)
Lung		1 (1.2)
Bone		1 (1.2)
Distant lymph node		37 (45.2)
Cytology		
Positive	0 (0.0)	16 (21.1)
Negative	168 (100.0)	60 (78.9)

Values are presented as mean (range) or n (%).

CRC, colorectal cancer; CT, computed tomography.

^aEvaluated by Eastern Cooperative Oncology Group (ECOG) criteria.

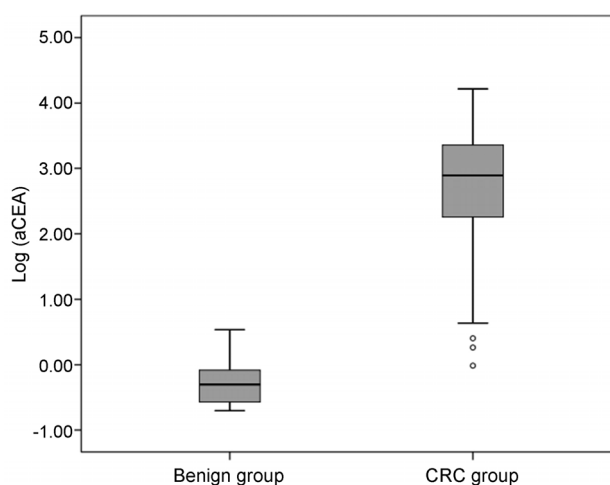
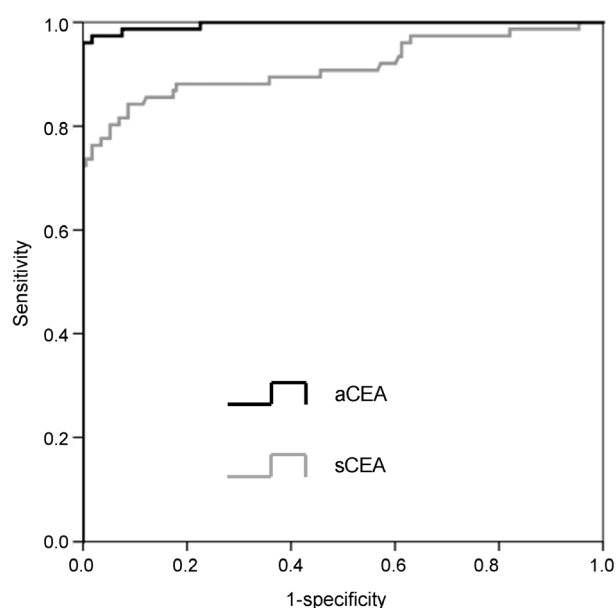


Fig. 1. Levels of aCEA in the benign and CRC groups. aCEA, carcinoembryonic antigen in ascites; CRC, colorectal cancer.

Table 2. Comparison of Diagnostic Parameters

	aCEA (ng/mL)	sCEA (ng/mL)
Cut-off value	3.885	8.635
Sensitivity (%)	96.3	84.2
Specificity (%)	100	91.3
PPV (%)	100	81.0
NPV (%)	98.3	92.9
AUC	0.996	0.914

aCEA, carcinoembryonic antigen in ascites; sCEA, carcinoembryonic antigen in serum; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

**Fig. 2.** ROC curve of diagnostic parameters. ROC, receiver operating characteristic; aCEA, carcinoembryonic antigen in ascites; sCEA, serum carcinoembryonic antigen.

We evaluated the linear correlation between aCEA and sCEA, and found that they were not correlated (correlation coefficient of -0.017, $p=0.884$). According to the cytology tests performed in the CRC group (76 patients) showed that 16 patients (21.1%) were positive and 60 (78.9%) were negative. The mean level of aCEA in the CRC group with negative cytology was higher than that in the CRC group with positive cytology; but this difference was not statistically significant (2075.5 ng/mL vs. 1093.6 ng/mL, $p=0.06$).

Univariate and multivariate analyses using logistic regression were performed to evaluate the factors predicting the occurrence of peritoneal carcinomatosis. In univariate analysis, age, aCEA, sCEA, carbohydrate antigen 19-9 in ascites, carbohydrate antigen 19-9 in serum, serum-ascites albumin gradient, protein A/S, and LDH A/S were significant predictors for the occurrence of peritoneal carcinomatosis. However, in the multivariate analysis, aCEA was the only significant predictor for the occurrence of peritoneal carcinomatosis (odds ratio 4.900, 95% confidence interval 1.878-12.783, $p=0.001$) (Table 3).

DISCUSSION

This study showed that sensitivity, specificity, PPV, and NPV of aCEA were high, and aCEA was a significant factor for predicting the occurrence of peritoneal carcinomatosis. Our results suggest that aCEA may be a useful parameter for the diagnosis of CRC with peritoneal carcinomatosis, and that aCEA of 3.89 ng/mL could be considered as a cut-off value.

CRC is the third most common cancer in Korea. Peritoneal

Table 3. Factors Predicting the Occurrence of Peritoneal Carcinomatosis

Predictor	Univariate analysis	Multivariate analysis
	OR (95% CI), p-value	OR (95% CI), p-value
Age	1.049 (1.023-1.076), <0.001	
Gender	0.781 (0.446-1.367), 0.386	
aCEA	4.960 (1.897-12.968), 0.001	4.900 (1.878-12.783), 0.001
sCEA	1.255 (1.158-1.360), <0.001	
aCA19-9	1.018 (1.011-1.025), <0.001	
sCA19-9	1.003 (1.001-1.004), <0.001	
SAAG	0.444 (0.304-0.649), <0.001	
Protein A/S	5.367 (1.806-15.948), 0.002	
LDH A/S	3.701 (2.135-6.416), <0.001	

OR, odds ratio; CI, confidence interval; aCEA, carcinoembryonic antigen in ascites; sCEA, carcinoembryonic antigen in serum; aCA19-9, carbohydrate antigen 19-9 in ascites; sCA19-9, carbohydrate antigen 19-9 in serum; SAAG, serum-ascites albumin gradient; protein A/S, ascites/serum concentration ratio of protein; LDH A/S, ascites/serum concentration ratio of lactate dehydrogenase.

carcinomatosis is the second most frequent metastatic pattern in advanced CRC.¹⁵ Peritoneal fluid cytology is the gold standard to confirm peritoneal carcinomatosis due to its high specificity. However, the low positive detection rate is its limitation in clinical practice. In advanced ovarian cancer with peritoneal dissemination, the detection rate of malignant cells in ascites has been reported to be as high as 89%,¹⁶ and in advanced gastric cancer with peritoneal dissemination, the detection rate has ranged from 42.3-59%.^{17,18} However, in advanced CRC with peritoneal dissemination, the detection rate of malignant cells in ascites, using peritoneal cytology assays, has been as low as 5.8-35.5%.¹⁸⁻²¹ Radiological findings, including ascites, thickening of bowel walls, increased density of peritoneal fat, presence of peritoneal nodules, and hydronephrosis, are also used to make clinical diagnosis of peritoneal carcinomatosis.^{14,22} According to Gerbes et al.²³ aCEA has been proposed as a helpful marker for detecting malignant ascites. There have been a few studies evaluating the diagnostic value and cut-off level of CEA in patients with ascites. Nystrom et al.²⁴ used an empiric cut-off value, and Loewenstein and Zamcheck⁹ reported a cut-off value for aCEA in malignant ascites of 10 ng/mL (the highest aCEA level of the benign group). Recently, Kaleta et al.⁵ reported that the optimal cut-off value of aCEA to differentiate the causes was >3.5 ng/mL when the cut-off value was selected to achieve a specificity of 95.2% by ROC curve analysis. In previous studies, the sensitivity and specificity of aCEA in patients with advanced CRC ranged from 31.5-48.3% and from 95.2-100%, respectively.^{5,9} In our study, we assessed aCEA in patients with advanced CRC and determined an optimal cut-off value using a ROC curve. We identified an optimal cut-off value of 3.89 ng/mL for aCEA, and the sensitivity and specificity were 96.3% and 100%, respectively.

Our study showed that only 21.1% of patients had positive cytology, even though all patients had clinical peritoneal carcinomatosis. The mean aCEA value of the CRC group was higher in patients with negative cytology than in those with positive cytology.^{25,26} Hence, these results show a low level of positive cytology in patients with aCEA. There are several possible mechanisms for this. First, this might be due to the low peritoneal metastatic potential of CRC cells.²⁷ Second, delayed examination could yield false-negative results due to lysis of tumor cells.²⁸ Third, peritoneal inflammation could make the difference between malignant cells and atypical or

reactive mesothelial cells that are ambiguous in body fluids.²¹

We hypothesized that the level of aCEA would positively correlate with the level of sCEA and investigated the relationship between them. However, our results did not show any correlation between aCEA and sCEA. There are several limitations in this study. First, our study did not include patients who had other malignant ascites, such as gastric or ovarian cancer with ascites. Therefore, our study does not provide realistic and clinically available data. Second, there was no CRC patient who had ascites but did not have peritoneal carcinomatosis in this study. Therefore, whether there was an elevation of aCEA in CRC patients without peritoneal carcinomatosis remains unclear.

In conclusion, our study demonstrated that aCEA may have predictive value for the occurrence of peritoneal carcinomatosis, and this finding suggests that aCEA may be helpful in the initial diagnosis of peritoneal carcinomatosis. According to the results of this study, aCEA may be a useful parameter for diagnosing peritoneal carcinomatosis in advanced CRC patients, with a suggested cutoff value of 3.89 ng/mL. Further study that includes patients with other malignant ascites may be necessary to validate these findings.

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