The clinical usefulness of ascitic fluid CEA in advanced gastric cancer patients with ascites

Min Kyu Jung

Department of Medicine

The Graduate School, Yonsei University

The clinical usefulness of ascitic fluid CEA in advanced gastric cancer patients with ascite

Directed by Professor Sun Young Rha

The Master's Thesis

submitted to the Department of Medicine

the Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree

of Master of Medical Science

Min Kyu Jung

June 2008

This certifies that the Master's Thesis

of Min Kyu Jung is approved.

Thesis Supervisor : Sun Young Rha

Thesis Committee Member : Sung Hoon Noh

Thesis Committee Member : Hei-Cheul Jeung

The Graduate School

Yonsei University

June 2008

ACKNOWLEDGEMENTS

This page is exclusively designed to note my gratitude and respect for those who helped me to complete my thesis. I am deeply indebted to my supervisor Prof. Dr. Sun Young Rha for her kind help, guidance, support and encouragement throughout my study. Sincere gratitude goes out to my reviewers, Prof. Dr. Sung Hoon Noh and Prof. Dr. Hei-Cheul Jeung who had the patience and fortitude to read my thesis and provided constructive criticism to help me defend it. Their guidance not only improved my dissertation but also will benefit my future work. I also sincerely thank my colleagues, Soo Jung Hong, Soo Hyun Lee, Duk Hwan Kim and Ji Ye Jung for their supports. Finally this thesis would not have been possible without my wife. This small thesis devote to GOD.

Min Kyu Jung

TABLE OF CONTENTS

ABSTRACT 1

I. INTRODUCTION 4

II. MATERIALS AND METHODS 7

1. Patients 7

2. Evaluation 7

3. Analysis and Statistical Considerations 8

III. RESULTS 10

1. Patient characteristics 10

2. Tumor marker Assays 12

3. Comparisons of sCEA and aCEA with ascitic fluid cytology 19

4. Relationship between survival and the clinicophalologic parameters 22

5. Prognostic factors for survival of advanced gastric cancer with ascites 31

6. The predictive marker of monitoring response for chemotherapy

IV. DISCUSSION 36

V. CONCLUSION 42

REFERENCES ····· 43

ABSTRACT (IN KOREAN) ····· 50

LIST OF FIGURES

Figure 1. Median values of aCEA and sCEA 13

Figure 2. Distribution of sCEA and aCEA 15

Figure 3. Correlation between sCEA and aCEA 18

Figure 4. Comparisons of sCEA and aCEA base on the ascitic fluid cytology 20

Figure 5. ROC curve in sCEA and aCEA for positive ascitic fluid cytology 21

Figure 6. Kaplan-Meier survival curve for the 129 patients of advanced gastric cancer with ascites 22

Figure 7. Survival curve of patients according to variables 25

Figure 8. Survival curve of patients according to CEA level 28

Figure 9. The ratio of CEAs according to response of chemotherapy ... 35

LIST OF TABLES

Table 1. Patient characteristics 11

Table 2. Levels of sCEA and aCEA 12

Table 3. Levels of aCEA in benign patients 14

Table 4. Levels of sCEA and aCEA acoording to metastasis site 17

Table 5. Comparison of cytology and CEA positivity 19

Table 6. Sensitivity and specificity according to cutoff level of tumor markers for positive ascitic fluid cytology 21

Table 7. Univariate analysis : Potential prognostic variables for survival 23

Table 8. Median overall survival according to the level of sCEA and aCEA 31

Table 9. Multivariate analysis using Cox's proportional hazard regression model 32

Table 10. Levels of CEAs according to response of chemotherapy 34

Table 11. The ratio of CEAs according to response for chemotherapy 35

ABSTRACT

The clinical usefulness of ascitic fluid CEA in advanced gastric cancer patients with ascites

Min Kyu Jung

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Sun Young Rha)

Background: There is a limitation to predict the accurate prognosis of advanced gastric cancer with current clinicopathological parameters. This study was carried out to evaluate the clinical usefulness of ascitic fluid CEA in advanced gastric cancer patients with ascites.

Patients and methods: From November 2001 to February 2008, 129 gastric cancer patients with concurrent ascites, clinically diagnosed as carcinomatosis, were collected and retrospectively reviewed for ascitic fluid cytology and clinicopathological parameters. Serum CEA (sCEA) and ascitic fluid CEA

(aCEA) were measured using a chemo-illuminescent enzyme immunoassay. Overall survival was defined as the period between the initial day of paracentesis and death from any cause.

Results:

1. The patients' median age was 50 (range, 23-80) years. The median value of aCEA was significantly higher than sCEA [130.45 ng/ml (range 0.20-12,211) vs. 2.08 ng/ml (range 0.02-8,152), $p<0.001$]. 2. The positive rates of sCEA and aCEA were 20% and 85%, respectively, at a cut-off level of 5 ng/ml. aCEA and sCEA were moderately correlated with a correlation coefficient of 0.30 ($p=0.01$) and their positive concordance rate was 19%. 3. Sixty-seven (55.3%) of 121 patients showed positive ascitic fluid cytology. The median value of aCEA was significantly higher in patients of positive ascetic fluid cytology than those of negative cytology (median 266.0 ng/ml vs 54.96 ng/ml, $p=0.002$), while there was no difference of sCEA according to the cytology results (median 2.10 ng/ml vs 2.09 ng/ml, $p=0.575$). 4. The median overall survival of total patients was 2.4 months (95% CI 1.6-3.3 months) and the 1-year survival was 9.6%. The patients with low aCEA (<5 ng/ml) showed significantly longer overall survival than high aCEA (≥5 ng/ml) (7.4 months vs 2.3 months, $p=0.002$). However, there was no difference in overall survival according to ascitic fluid cytology (median

2.5 months vs. 3.1 months, p=0.572). Multivariate analysis also demonstrated that aCEA level of more than 5ng/ml had poor prognosis (HR = 2.85; 95% CI, 1.49-5.46, p=0.002), while sCEA level did not (HR = 1.24; 95%, CI 0.71-2.17, p=0.446).

Conclusion: These results suggest that aCEA level might be useful in diagnosis tool of carcinomatosis and reflects the prognosis of advanced gastric cancer patients with ascites better than sCEA.

Key words : advanced gastric cancer, ascitic fluid, carcinoembryonic antigen, prognosis, survival

The clinical usefulness of ascitic fluid CEA in advanced gastric cancer patients with ascites

Min Kyu Jung

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Sun Young Rha)

I. INTRODUCTION

The morbidity of gastric cancer has recently been dropped worldwidely. However, it is not because the treatment results for advanced gastric cancer was improved, but because the proportion of early gastric cancer cases with high curability has markedly increased. Even though the various chemotherapeutic agents and diverse regimens are developed, the survival of advanced gastric cancer is still poor.[1] Therefore, it is important to predict individual patient's

prognosis and to choose the proper treatment methods for improving treatment efficacy when considering limited chemotherapy efficacy and its toxicity. Several clinico-pathological factors for prognosis have been studied, and there are efforts to develop serologic markers which are non-invasive and could easily reflect the dynamic status of tumor, especially during the treatment. Among them, carcinoembryonic antigen (CEA) and CA19-9 were widely used in patients with gastrointestinal malignancies[2-4]. CEA was first described by Gold and Freedman in 1965 as an antigen expressed by gastrointestinal carcinoma. CEA is a glycoprotein that is secreted in blood or body fluids[5]. There are several reports on the utility of CEA and CA19-9 measurements in cancer progression, recurrence, and prognosis of the patients with gastric carcinoma[2, 6, 7]. However, the sensitivity and specificity of CEA or CA19-9 were low[8]. Other tumor markers - CA72-4 and CA125 – were devised and they were compared its clinical utility with CEA or CA19-9[3,9,10]. However its clinical implication and interpretation is still limited [3, 9, 11]. Therefore, in addition to combination of several tumor markers, novel tumor marker development or special attempts of measuring CEA in body fluid where actual cancerous cells exist were introduced [12, 13].

Peritoneal metastasis is the most frequent type of recurrence in patients with

advanced gastric cancer especially in Asian patients. There has been an effort for the prediction and early detection of peritoneal metastasis. In a few reports, free cancer cells detected in intraoperative peritoneal lavage could be an predictive indicator for future peritoneal metastasis[14-16]. However, many patients with negative peritoneal lavage cytology also developed peritoneal metastasis[17], and its utility was controversial in clinical setting[18, 19]. There were reports that elevated CEA in the peritoneal lavage might be associated with an earlier detection of recurrent peritoneal dissemination and a poor prognosis[12].

The current diagnosis and prediction of prognosis in carcinomatosis is mainly based on the clinical parameters. For the objective evaluation of cancer status, the reliable biomarker development is necessary. As we assume the secreted CEA reflects the tumor burden, we exploited the clinical significance of aCEA as a marker for peritoneal disease in advanced gastric carcinoma.

II. MATERIALS AND METHODS

1. Patients

The medical records of metastatic or relapsed advanced gastric cancer patients having ascites, who were diagnosed as peritoneal carcinomatosis in the Severance Hospital, Seoul, Korea between November 2001 and February 2008, were retrospectively reviewed. The diagnosis of carcinomatosis was made by clinical and radiological findings. The radiological parameters of carcinomatosis from computed tomography were as follows; (1) ascites, (2) thickening of bowel walls, (3) increased density of peritoneal fat, (4) the presence of peritoneal seeding nodules, or (5) hydronephrosis from ureteral obstruction[20]. Patients were excluded from the study if they had combined other cancers, liver cirrhosis, or chronic renal disease. To determine the cutoff level of aCEA, the level of aCEA in 6 patients of benign disease including tuberculous peritonitis, liver cirrhosis or end stage renal diseas with hemodialysis were evaluated.

2. Evaluation

All patients underwent esophago-gastrointestinal endoscopy for tissue

confirmation and abdominal-pelvic CT scan to evaluate the clinical stage. ECOG performance status at time of having ascites, previous history of gastrectomy and chemotherapy was evaluated. The paracentesis was performed when the ascites was detected. The ascitic fluid cytology and routine examination were evaluated. In addition, the sCEA and aCEA were measured using a chemo-illuminescent enzyme immunoassay kit (Beckman Coulter, Inc. Minnesota, USA) at the day of paracentesis. In the patients who received chemotherapy after diagnosis of carcinomatosis, treatment response was evaluated according to the guideline of the Response Evaluation Criteria in Solid Tumors (RECIST) committee[21]. The overall survival was defined as the period between the initial day of paracentesis and death of any cause.

3. Analysis and Statistical Considerations

The purposes of this study were to investigate the clinical usefulness of aCEA in advanced gastric cancer patients having ascites. The cutoff level for tumor markers for positive ascitic fluid cytology was evaluated by ROC curve in all the patients. Correlation of sCEA and aCEA was analyzed with Spearman test and the concordance between sCEA or aCEA with ascitic fluid cytology were analyzed with Fisher's exact test or χ^2 test. The comparison of median

values of sCEA and aCEA with ascitic fluid cytology were done by Mann-Whitney U-Test.

Time-dependent variables were estimated with a log-rank test using the Kaplan-Meier method. Multivariate analysis was performed using Cox's proportional hazard regression model. All the statistical evaluations were performed using the SPSS 12.0. A *p* value of less than 0.05 was considered statically significant.

III. RESULTS

1. Patient characteristics

Total 129 patients were enrolled in this retrospective study and the clinco-pathological features of the patients are summarized in Table 1. The median age of the patients was 50 years (range, 23 - 80). Seventy-seven patients (60.0%) were male and 52 patients (40.0%) were female. Eighty-eight patients (68.2%) had good functional status (ECOG scale 0-2). Sixty patients (46.5%) had recurred disease after prior gastrectomy and sixty-nine patients (53.5%) had advanced cancer at diagnosis. One hundred and fifteen (89.1%) patients had metastasis limited in peritoneum, while 14 (10.9%) patients had combined systemic organ metastasis in liver, lung or bone. Ascites fluid cytology was evaluated in 121 patients, and 67 patients (55.4%) were positive for cytology.

Table 1. Patient characteristics

		Number of
Total patients		129
Age	Median (years)	50
Sex	Male	77 (60.0)
	Female	52 (40.0)
Performance status*	0-2	88 (68.2)
	3-4	41 (31.8)
Histology	Well differentiated	4 (3.0)
	Moderately differentiated	10 (7.8)
	Poorly differentiated	46 (35.3)
	Signet ring cell	31 (24.6)
	Mixed	12 (9.3)
	Unknown	26 (20.0)
Prior gastrectomy	Yes	60 (46.5)
	No	69 (53.5)
Metastasis	Peritoneum only	115 (89.1)
	Combined systemic organ	14 (10.9)
Ascitic fluid cytology (N=121)	Positive	67 (55.4)
	Negative	54 (45.6)
Chemotherapy after diagnosis of carcinomatosis	Done	63 (48.8)
	Not done	66 (51.2)

* Evaluated by ECOG (Eastern Cooperative Oncology Group) criteria

2. Tumor marker assays

The sCEA level was evaluated in 127 (98.4%) patients out of 129 patients. The median level of sCEA was 2.08 ng/ml (range, 0.02 - 8,152 ng/ml). The median level of aCEA was 130.45 ng/ml (range, 0.23 - 12,211 ng/ml) (Table 2, Figure 1). To determine the cutoff level of aCEA, the level of aCEA in 6 patients with benign disease, including tuberculous peritonitis, liver cirrhosis or end stage renal diseas with hemodialysis were evaluated (Table 3). The median value of aCEA in the patients of benign disease was 1.09 ng/ml (range, 0.20-3.17 ng/ml). We determined the cutoff level of aCEA for further evaluation as 5 ng/ml. With this cut-off level, sCEA was elevated in 26 (20.0%) of 127 patients and aCEA was elevated in 110 (85.2%) out of 129. Eighty percent of patients showed sCEA level of lower than 5 and aCEA level of lower than 600 (Figure 2).

Table 2. Levels of sCEA and aCEA

	Median	Range	*p*-value*
sCEA (ng/ml)	2.08	0.02 - 8,152	< 0.001
aCEA (ng/ml)	130.45	0.23 – 12,211	

* Mann-Whitney U-test

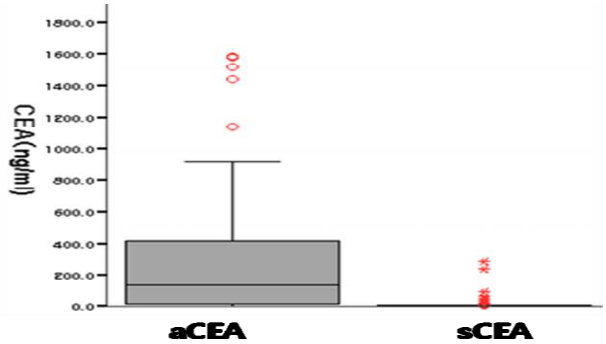


Figure 1. Median values of aCEA and sCEA

Table 3. Levels of aCEA in benign patients

Pateint number	Diagnosis	aCEA (ng/ml)	Paracentesis (WBC(/ul)/ poly(%)/mono(%))	SAAG*
1	Liver cirrhosis	0.38	150/24/76	2.6
2	ESRD†	1.42	0/-/-	1.1
3	ESRD	0.20	70/3/97	1.1
4	TBc‡ peritonitis	1.45	306/0/100	0.7
5	TBc peritonitis	0.76	2820/3/97	0.7
6	TBc peritonitis	3.17	1700/26/74	0.5
	Median (range)	1.09 (0.20-3.17)		

*SAAG= serum-ascites albumin gradient, †ESRD= end stage renal disease on hemodialysis, ‡;TBc= tuberculous

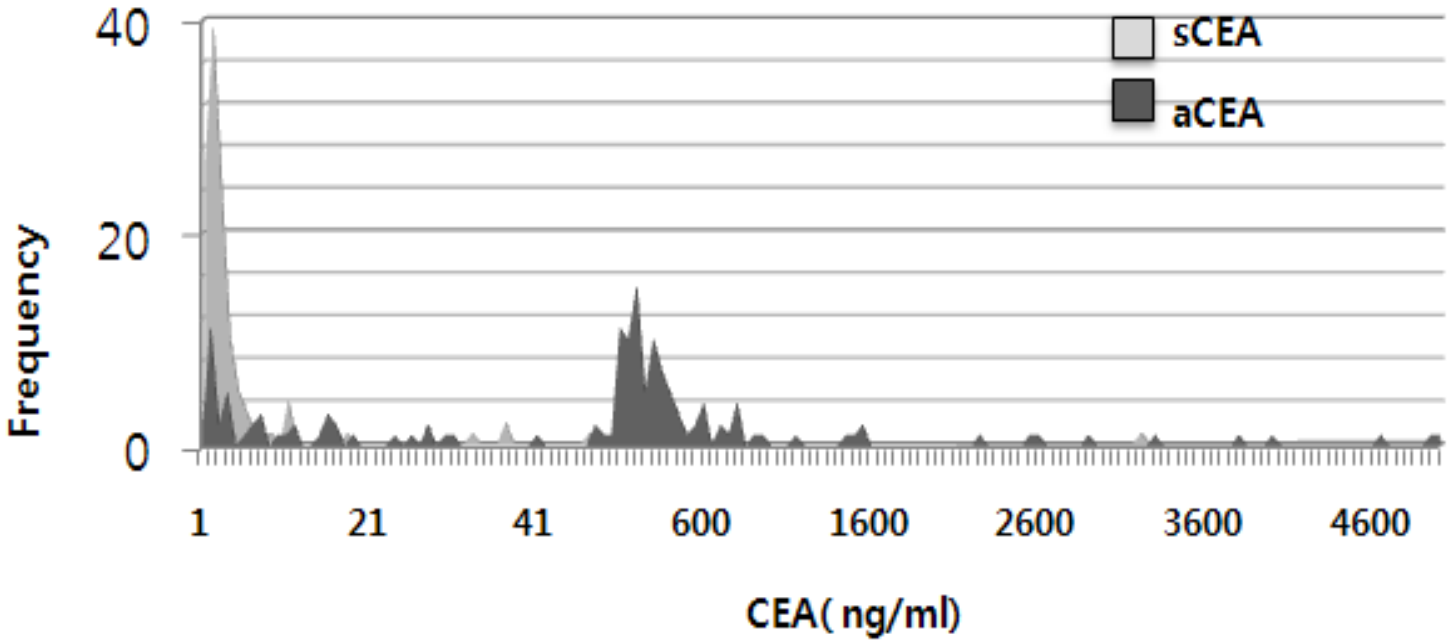


Figure 2. Distribution of sCEA and aCEA

The levels of sCEA and aCEA in total 127 patients were moderately correlated with a correlation coefficient of 0.30 (p=0.01). The positive concordance rate was 19% (25/127) (Figure 3A). We sub-grouped the patients according to extent of metastasis. The sCEA and aCEA were significantly correlated with correlation coefficient of 0.993 (p=0.01) in patients with peritoneum and systemic organ metastasis and that of 0.334 (p=0.01) in those with peritoneum only (Figure 3B, 3C). There was no difference according to metastasis site that limited in intraperitoneum versus carcinomatosis combined systemic organ in both sCEA and aCEA . Whether the CEA reflects tumor burden and systemic exposure of cancer cells, we compared ratio of aCEA /sCEA based on the metastasis site. As we expected, the ratio of aCEA/sCEA in patients with peritoneum and systemic organ metastasis was significant lower than those with being limited peritoneal metastasis (Table 5).

Table 4. Levels of sCEA and aCEA acoording to metastasis site

	Metastasis site (Number)	Median	Range	*p*-value*
sCEA (ng/ml)	IP (14)†	1.90	0.05-6,497	0.129
	Sys (113)	3.02	0.40-8,152	
aCEA (ng/ml)	IP (14)	150.4	0.23-12,211	0.168
	Sys (115)	59.94	0.10-2,899	
Ratio (aCEA/sCEA)	IP (14)	54.36	0.01-2,974.55	0.012
	Sys (113)	4.85	0.18-309.64	

*Mann-Whitney U-test, †IP= limited in peritoneum; Sys=peritoneum and systemic organ

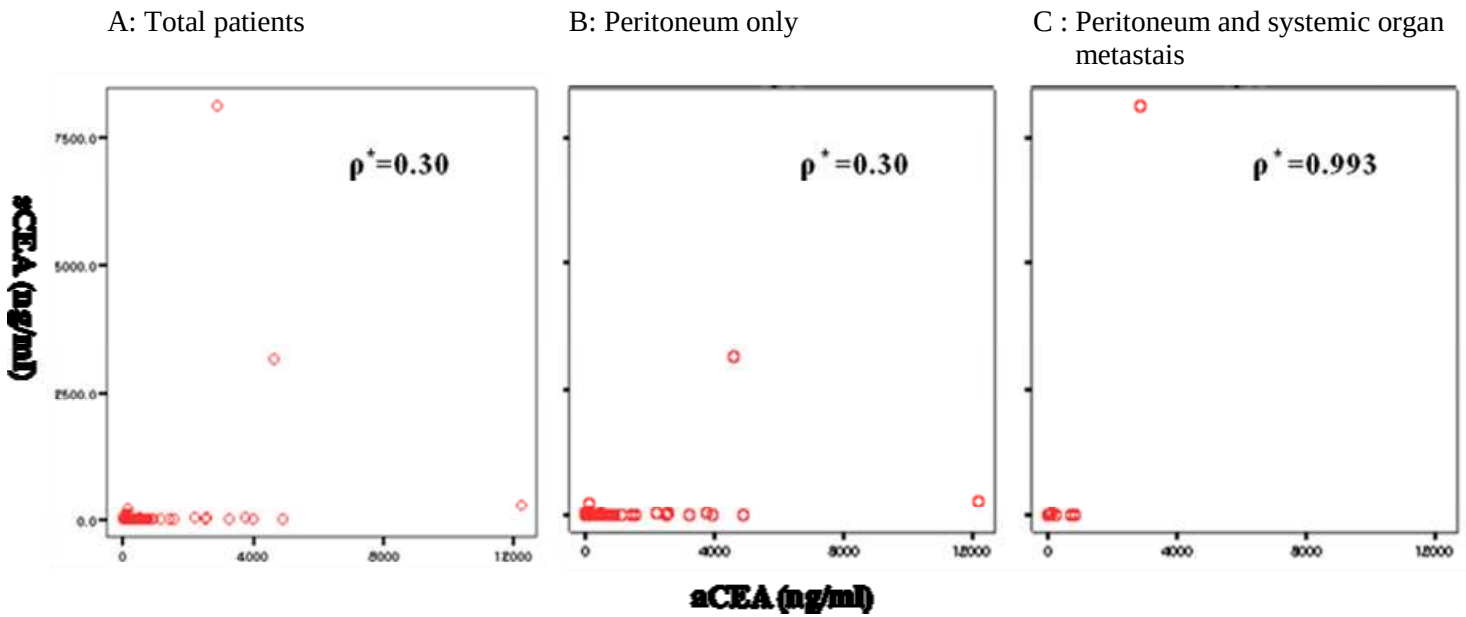


Figure 3. Correlation between sCEA and aCEA

A: Correlation between sCEA and aCEA of total patients (N=127), B: Correlation between sCEA and aCEA of patients with metastasis peritoneum only (N=113), C: Correlation between sCEA and aCEA of patients with peritoneum and systemic organ metastasis (N=14), *ρ=correlation coefficiency, *p*=0.01

3. Comparisons of sCEA and aCEA according to ascitic fluid cytology

Ascitic fluid cytology was evaluated in 121 (93.8%) of 129 patients. Sixty-seven (55.4 %) patients were positive for cytology and 54 (45.6 %) were negative. The sensitivity and specificity of sCEA for detecting positive cytology was 21.5% and 79.6%, respectively. However, aCEA was higher in sensitivity (92.5%) and specificity (24%) than sCEA for detecting positive cytology (Table 5). The median value of aCEA was higher in patients of positive cytology than those of negative cytology (266.0 ng/ml vs. 54.96 ng/ml, p=002), while there was no difference in sCEA between the two groups (2.09 vs. 2.10, p=0.575) (Figure 4).

Table 5. Comparison of cytology and CEA positivity

	Cytology(+)	Cytology(-)	Total	*p*-vale
sCEA (< 5ng/ml)	51	43	94	0.876*
sCEA(≥5ng/ml)	14	11	25	
Total	65	54	119	
aCEA (< 5 ng/ml)	5	13	18	0.011†
aCEA (≥5ng/ml)	62	41	103	
Total	67	54	121	

*χ^2 test, †Fisher's exact test

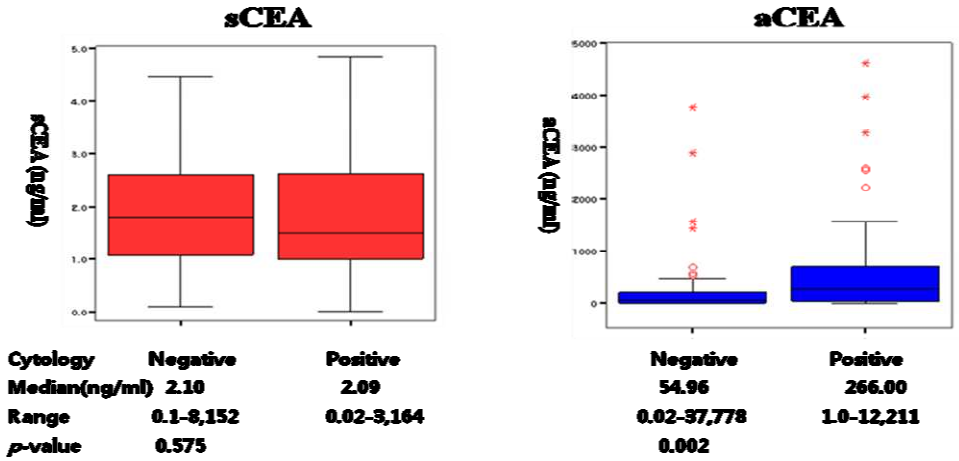


Figure 4. Comparisons of sCEA and aCEA base on the ascitic fluid cytology

The cutoff level for tumor markers for positive ascitic fluid cytology was shown by an ROC curve in all patients (Figure 5). The sCEA at a cutoff level of 1.7 ng/ml in ROC curve showed an overall sensitivity of 65 % at a specificity of 44.6 %, while a cutoff level of 5 ng/ml showed an overall sensitivity of 20% at a specificity of 80% for positive ascitic fluid cytology. The aCEA at a cutoff level of 120 ng/ml according to ROC curve showed an overall sensitivity of 65.7 % at a specificity of 64.8 % with at cutoff level of 5 ng/ml of aCEA showed an overall sensitivity of 92.5% at a specificity of 26 % for positive ascitic fluid cytology (Table 6).

A B

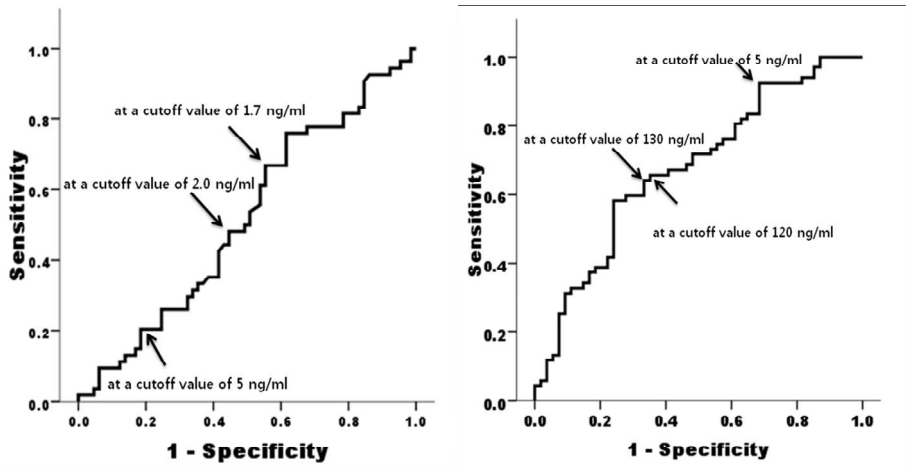


Figure 5. ROC curve in sCEA and aCEA for positive ascitic fluid cytology

A : ROC curve of sCEA for positive ascitic fluid cytology, B: ROC curve of aCEA for positive ascitic fluid cytology.

Table 6. Sensitivity and specificity according to cutoff level of tumor markers for positive ascitic fluid cytology

	Cutoff(ng/ml)	Number(</≥)	Sensitivity(%)	Specificity(%)
sCEA (N=127)	1.7	51/76	65	44.6
	2	63/64	51.9	49.2
	5	100/27	20.0	80.0
aCEA (N=129)	120	62/67	65.7	64.8
	130	63/66	64.2	66.0
	5	19/110	92.5	26

4. Relationship between survival and the clinicopathological parameters

The median overall survival of total patients was 2.4 months (95% CI, 1.6 - 3.3 months) and the 1-year survival was 9.6 % (Figure 6). Univariate analysis was performed to investigate the potential prognostic variables for survival, and the result showed in Table 7.The median survival of patients of ECOG less than 2 showed significantly longer compared with those of more than 2 (4.8 vs 1.1 months, $p<0.001$) (Fig 7A). The median survival of patients received chemotherapy after diagnosis of carcinomatosis had significantly longer survival than those did not (6.4 vs1.6 months, $p<0.001$) (Figure 7B). However, there was no difference in overall survival according to histology, prior gastrectomy, metastasis sites or ascitic fluid cytology (Figure 7C).

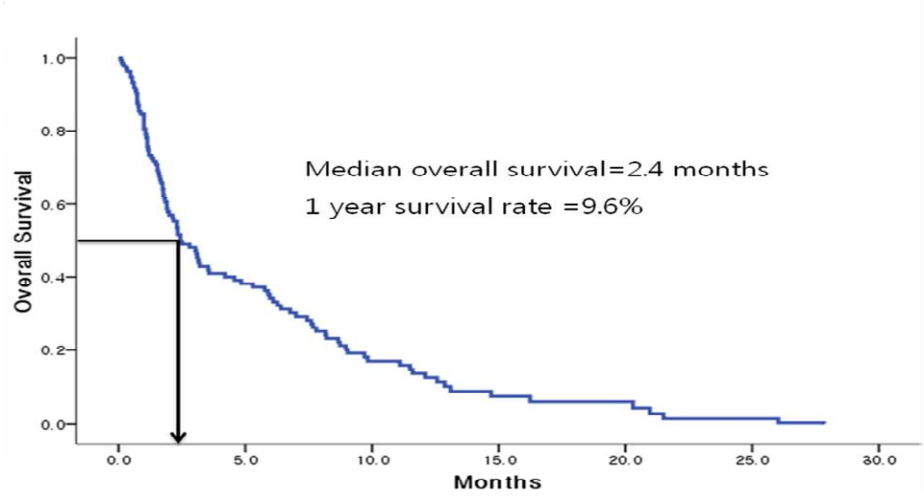


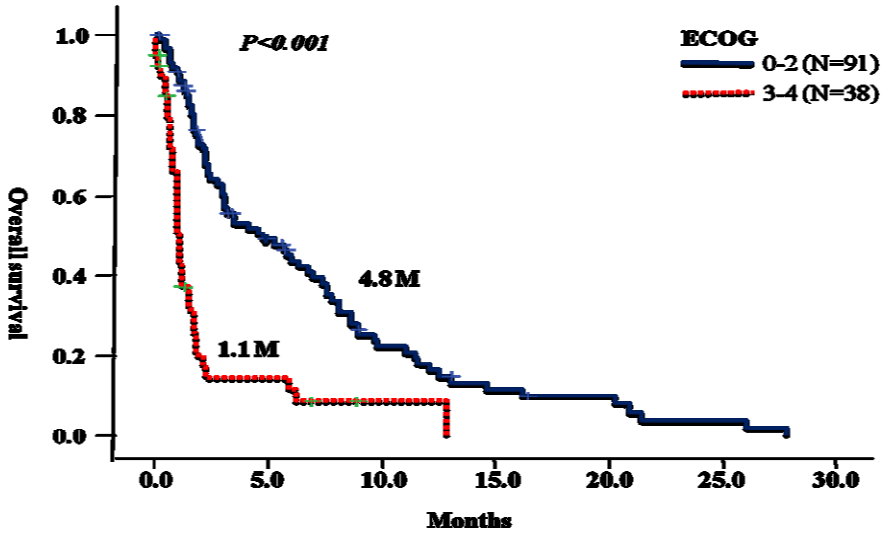
Figure 6. Kaplan-Meier survival curve for the total 129 patients of advanced gastric cancer with ascites

Table 7. Univariate analysis: Potential prognostic variables for survival

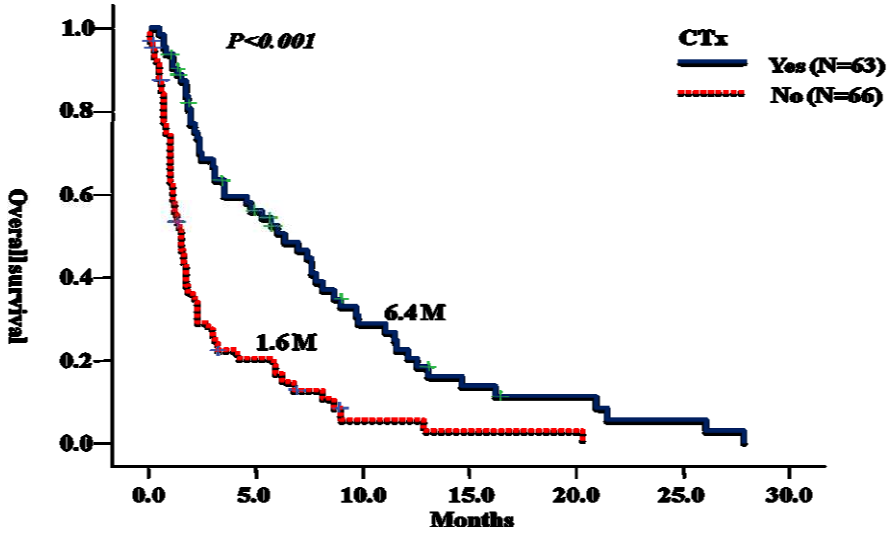
		Number	Median survival (months)	95% CI	*p*-value*
Overall survival			2.4	1.6-3.2	
Age	≥65	17	1.5	0.7-2.7	0.483
	<65	112	3.0	2.3-3.8	
Sex	Male	77	2.4	1.3-3.6	0.266
	Female	52	2.8	0.2-5.4	
ECOG	0-2	88	4.8	2.0-7.6	<0.001
	3-4	41	1.1	0.9-1.3	
Ascitic fluid cytology	Positive	67	2.5	0.0-5.1	0.572
(N=121)	Negative	54	3.0	1.0-5.1	
Histology[†]	WD	4	3.1	0.0-6.4	0.815
	MD	10	3.5	1.1-5.9	
	PD	46	2.4	1.0-3.9	
	SRC	31	2.3	2.0-2.6	
	Mixed	12	20.3	-	
	Unknown	26	2.1	0.4-3.9	
Previous gastrectomy	Yes	60	2.4	0.3-4.6	0.773
	No	69	2.4	1.2-3.6	
CTx[‡]	Yes	63	6.4	3.5-9.3	<0.001
	No	66	1.6	1.0-2.1	
Metastasis	IP[§]	115	2.5	1.5-3.5	0.931
	Sys	14	2.4	0.8-4.0	
sCEA	≥5ng/ml	27	1.2	0.3-2.1	0.042
(N=127)	< 5ng/ml	100	3.1	1.6-4.7	
aCEA	≥5ng/ml	110	2.3	1.8-2.8	0.002
	< 5ng/ml	19	7.4	3.3-11.6	

***Log-Rank test, [†]WD= well differentiated; MD= moderate differentiated; PD= poorly differentiated; SRC= signet ring cell carcinoma; Mix=mixed type [‡]CTx= chemotherapy after diagnosis of carcinomatosis, [§]IP= limited in peritoneum; Sys= peritoneum and combined with systemic organ**

A


P<0.001
ECOG
0-2 (N=91)
3-4 (N=38)
4.8M
1.1M
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0.0
5.0
10.0
15.0
20.0
25.0
30.0
Months

B


P<0.001
CTx
Yes (N=63)
No (N=66)
6.4M
1.6M
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0.0
5.0
10.0
15.0
20.0
25.0
30.0
Months

C

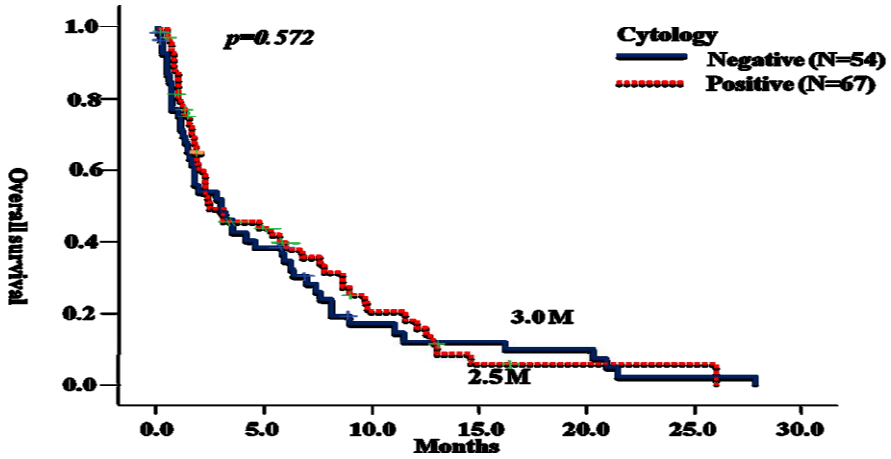


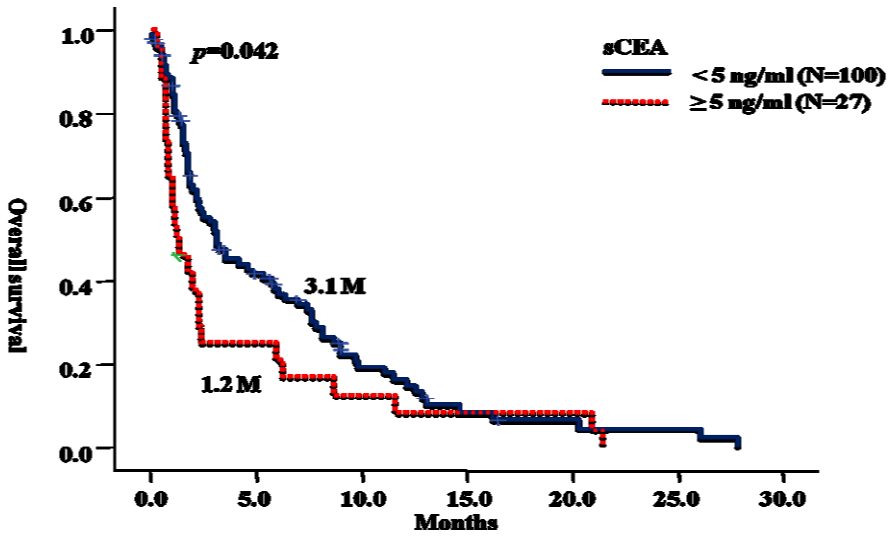
Figure 7. Survival curve of patients according to variables

A: Survival curve of patients according to ECOG scale, B: Survival curve of patients according to chemotherapy status, C: Survival curve of patients according to cytology status

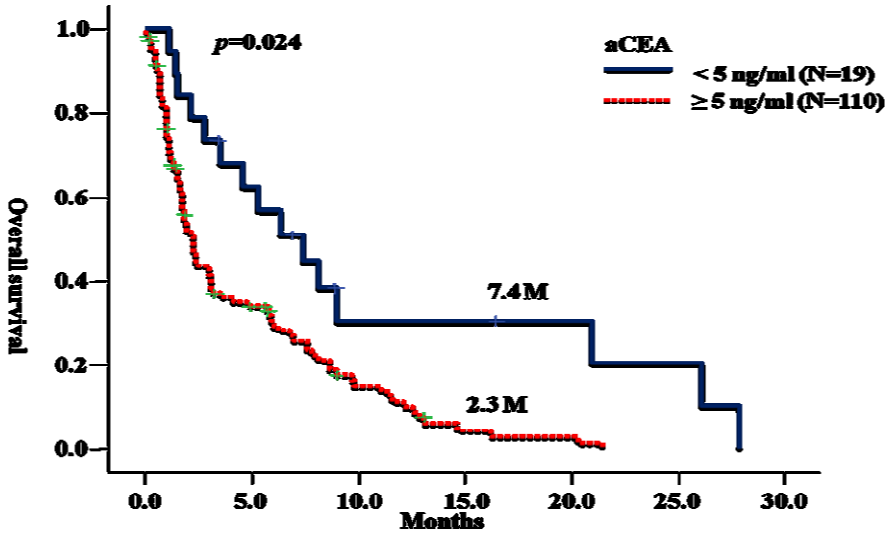
To evaluate the potential role of CEA level for predicting survival, we compared the survival based on the sCEA and aCEA. The patients with normal sCEA (<5ng/ml) showed longer median survival than those with high sCEA (≥5 ng/ml) (median 3.1 vs. 1.2 months, p=0.042) (Figure 8A). The patients with low aCEA (<5ng/ml) showed significantly longer median survival than those with high aCEA (≥5 ng/ml) (7.4 vs 2.3 months, p=0.002) (Figure 8B). To evaluate whether the combination of sCEA and aCEA improves the prediction accuracy, the 127 patient with combining sCEA and aCEA were divided into three groups; (A) The sCEA (<5ng/ml) and aCEA (<5ng/ml), N=18, (B) sCEA (<5ng/ml) and aCEA (≥5 ng/ml), N=83, or sCEA (≥5 ng/ml) and aCEA (<5ng/ml), N=1, (C) sCEA (≥5 ng/ml) and aCEA (≥5 ng/ml), N=25. Among the

three groups showed significantly different median survival (6.4 vs. 3.0 vs. 1.2 months, *p*=0.003) (Table 5, Figure 8C). In addition, when the 100 patients with low sCEA (<5ng/ml) were divided into two groups according to level of aCEA, the patients with low aCEA (<5ng/ml) showed significantly longer overall survival than those with high aCEA (≥5 ng/ml) (6.4 vs. 3.4 months, *p*=0.002) (Figure 8D). Furthermore, when the 54 patients with negative ascitic fluid cytology were divided into two groups according to level of aCEA, the patients with low aCEA (<5ng/ml) showed significantly longer overall survival than those with high aCEA (≥5 ng/ml) (7.4 vs. 1.8 months, *p*=0.019) (Figure 8E).

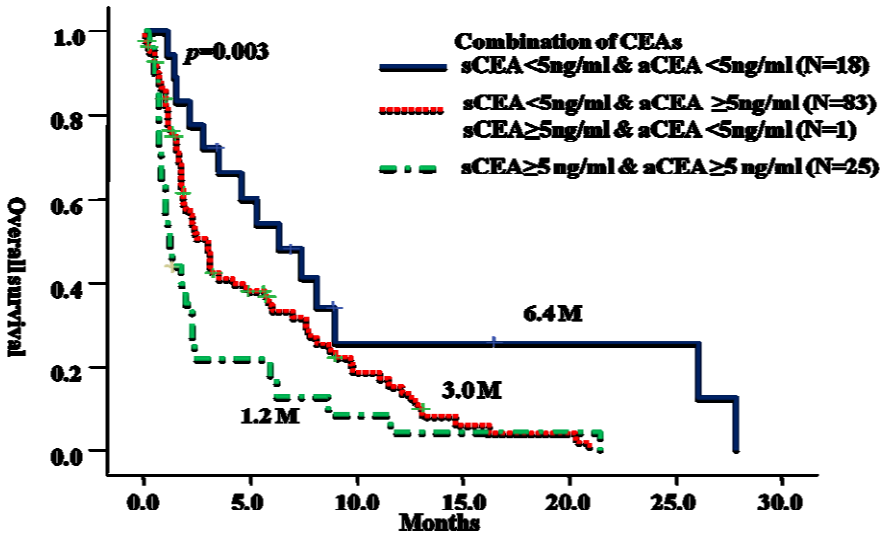
A



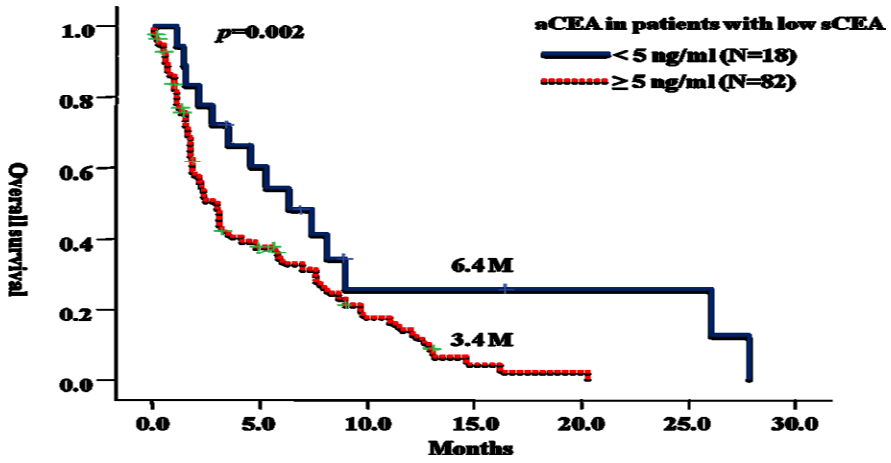
B


p=0.024
aCEA
< 5 ng/ml (N=19)
≥ 5 ng/ml (N=110)
7.4M
2.3M
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0.0
5.0
10.0
15.0
20.0
25.0
30.0
Months

C


p=0.003
Combination of CEAs
sCEA<5ng/ml & aCEA <5ng/ml (N=18)
sCEA<5ng/ml & aCEA ≥5ng/ml (N=83)
sCEA≥5ng/ml & aCEA <5ng/ml (N=1)
sCEA≥5 ng/ml & aCEA≥5 ng/ml (N=25)
6.4M
3.0M
1.2M
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0.0
5.0
10.0
15.0
20.0
25.0
30.0
Months

D



E

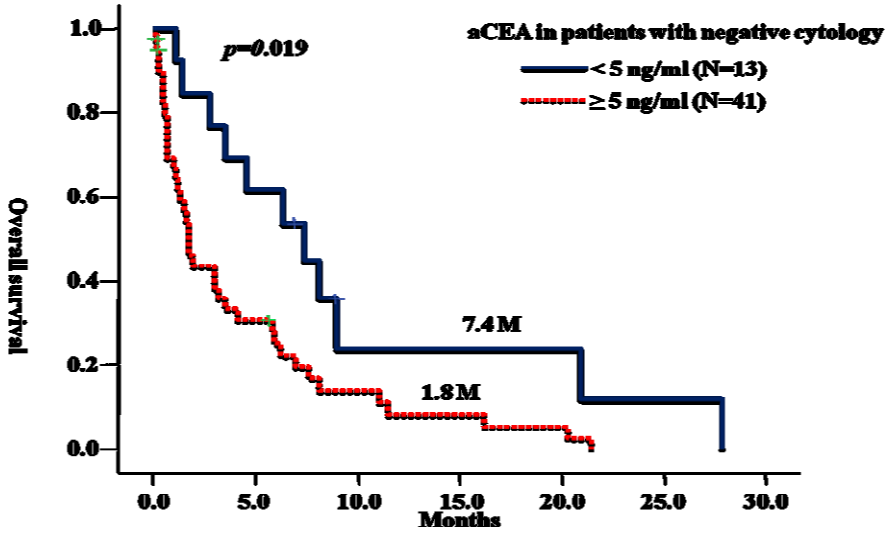


Figure 8. Survival curve of patients according to CEAs level

A: Survival curve of patients according to sCEA, B: Survival curve of patients according to aCEA, C: Survival of patients according to combination of CEAs, D: Survival curve of patients according to aCEA in the 100 patients with low sCEA(<5ng/ml), E: Survival curve of patients according to aCEA in the 54 patients with negative ascitic fluid cytology

As there is no accurate cutoff level for aCEA, we compared the median overall survival according to variable levels of sCEA and aCEA ; normal range, ROC curve and median value. In the level of sCEA, the median survival was a difference in only cutoff level of 5ng/ml (3.1 vs 1.2 months, p=0.042). Otherwise, in the aCEA, the overall survival was significant difference in all cutoff levels. Among the three cutoff level in aCEA, the overall survival according to normal range was the most significant difference (7.4 vs 2.3 months, p=0.002) (Table 8).

Table 8. Median overall survival according to the level of sCEA and aCEA

Level of CEA		Number	Median survival (months)	95% CI	P-value*
sCEA					
Normal range	<5	100	3.1	1.6-4.7	0.042
	≥5	27	1.2	0.3-2.1	
ROC curve	<1.7	51	3.0	2.2-3.0	0.530
	≥1.7	76	2.3	1.6-3.0	
Median value	<2.0	63	2.8	1.6-4.0	0.701
	≥2.0	64	2.4	1.2-3.6	
aCEA					
Normal range	<5	19	7.4	3.3-11.6	0.002
	≥5	110	2.3	1.8-2.8	
ROC curve	<120	62	4.5	1.8-7.4	0.003
	≥120	67	1.8	1.4-2.1	
Median value	<130	63	4.2	1.7-7.0	0.007
	≥130	66	1.8	1.1-3.2	

*Log-Rank test

5. Prognostic factors for survival of advanced gastric cancer with ascites

Multivariate was performed by Cox regression analysis to identify individual variables that were significant in terms of survival. ECOG performance, status of

chemotherapy after diagnosis of carcinomatosis and the aCEA were found to be significantly and independently related to survival with a Hazard ratio of 2.532, 0.577 and 2.884, respectively. However, the sCEA, status of metastasis site, and ascitic fluid cytology showed no significance (Table 10).

Table 9. Multivariate analysis using Cox's proportional hazard regression model

	HR*	95% CI†	*p*-value
Age (<65: ≥65 years)	1.790	0.989-3.239	0.054
Sex (F:M)	1.219	0.761-1.953	0.411
ECOG (0-2:3-4)	2.532	1.374-4.667	0.003
CTx (N:Y) ‡	0.577	0.337-0.989	0.044
Mets (IP:Sys) §	1.181	0.573-2.424	0.651
aCEA (<5:≥5 ng/ml)	2.884	1.448-5.744	0.003
sCEA (<5:≥5 ng/ml)	0.867	0.493-1.572	0.662
Cytology (N :Y)	0.813	0.527-1.256	0.351

*HR= Hazard ratio, †CI= Confidential interval, ‡ CTx= chemotherapy after diagnosis carcinomatosis §Mets(IP:Sys); IP= limited in peritoneum; Sys= peritoneum and systemic organ

6. The predictive marker of monitoring response for chemotherapy

The serial measurement of aCEA was done in 14 (10.8%) out of 129 patients. In almost patients without chemotherapy (N=2) and those with progression of disease

after chemotherapy (N=6), the follow up level of sCEA and aCEA were increased. Otherwise, those of sCEA and aCEA were decreased in almost patients with stable disease after chemotherapy (N=6) (Table 10). We compared the ratio of follow up CEA (fCEA)/ initial CEA (iCEA). The median ratio of sCEA in patients without chemotherapy was higher than those with stable disease after chemotherapy (3.81 vs 0.82, p=0.115). The median ratio of aCEA in patients without chemotherapy also was significantly higher than those with stable disease after chemotherapy (44.0 vs 0.95, p=0.008) (Table 11. Figure 9).

Table 10. Levels of CEAs according to response of chemotherapy

Patinet number	Response for CTx*	isCEA‡	fsCEA	iaCEA	faCEA
1	no CTx	4.46	5.33	14.52	215.55
2	no CTx	0.44	2.83	2.75	200.90
3	PD†	0.75	2.30	28.85	385.30
4	PD	0.1	0.02	0.78	271.41
5	PD	0.90	1.72	47.08	67.00
6	PD	3.22	3.69	2.69	3.60
7	PD	0.52	2.27	2.62	62.25
8	PD	1.38	1.35	10.34	83.90
9	SD	2.78	2.65	866.50	1.51
10	SD	2.21	1.66	1.84	2.27
11	SD	1.79	0.82	11.04	9.36
12	SD	2.82	1.63	0.86	0.83
13	SD	0.53	0.85	24.9	8.20
14	SD	2.01	1.78	109.13	46.82

*CTx=chemotherapy, †PD= progression of disease; SD= stable disease, ‡isCEA= initial sCEA; fsCEA= follow up sCEA

Table 11. The ratio of CEAs according to response for chemotherapy

	No CTx*	PD	SD	*p*-value[†]
Ratio of sCEA[‡]	3.81	1.53	0.82	0.155
(range)	(1.2-6.43)	(0.0-4.37)	(0.46-1.60)	
Ratio of aCEA	43.95	10.73	0.64	0.008
(range)	(14.85-73.05)	(1.34-347.96)	(0.0-1.23)	

*CTx=chemotherapy; PD=progression of disease; SD= stable disease

[†]Fisher's exact test, [‡]Ratio of CEA= follow up CEA/ initial CEA

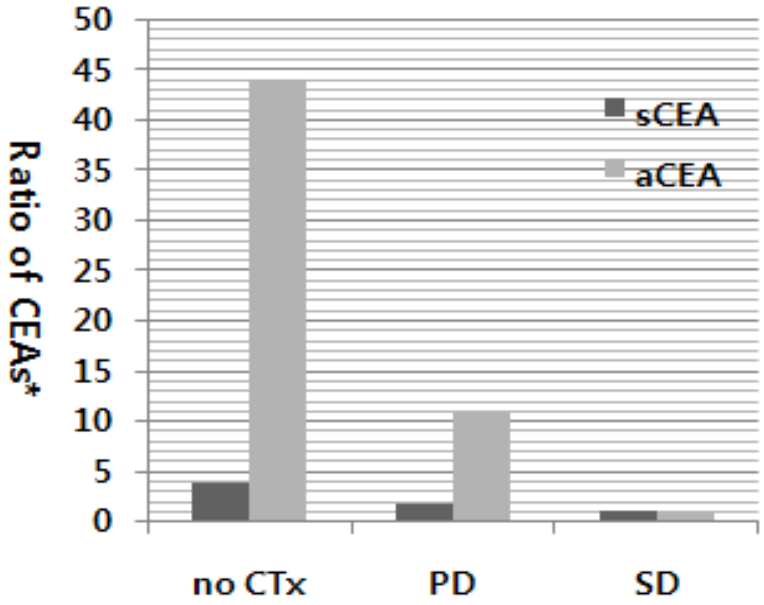


Figure 9. The ratio of CEAs according to response of chemotherapy

*****Ratio of CEAs= follow up CEA / initial CEA

IV. DISCUSSION

Selection of the appropriate treatment for advanced cancer patients required accurate tumor staging. In advanced gastric carcinoma, peritoneal metastasis is the most frequent pattern of metastasis and recurrence[22]. In general, the clinical diagnosis of carcinomatosis was made from radiological findings such as ascites or peritoneal nodules[20]. However, peritoneal metastasis is sometimes difficult to diagnose with conventional techniques only. For more exact diagnosis of carcinomatosis, some methods such as PET scan, staging laparoscopy and peritoneal lavage cytology were introduced[23, 24]

The prevalence of positive cytology in the peritoneal lavage fluid ranges from 5% to 55%[16, 18, 25-29]. This large variation in positivity is mainly due to diversity of patients such patients with R0 resection, macroscopic serosal invasion, peritoneal dissemination, or early gastric cancer. Even in advanced gastric cancer patients with peritoneal dissemination, the prevalence of positive cytology in the peritoneal lavage ranges only from 47% to 59 %[14, 25, 27]. In our study, only 55% of patients were found to have positive cytology, even though all patients had clinical carcinomatosis. Moreover, the median survival was similar according to positivity of cytology (2.5 months vs. 3.0 months, p=0.572), which was contrast to previous report of Bando et al.[14] that survival rates were lower in patients who had positive cytology in lavage fluid. In early peritoneal dissemination, cancer cells may reside deep to the

mesothelial cell layer, not exposed to the peritoneal surface[14]. Another possibility resides in suboptimal handling or processing of specimens. Delayed examination is a leading cause to a false-negative result because tumor cells may have lysed or the volume of the specimen is inadequate[30]. In addition, diagnostic difficulties of differentiating between reactive mesothelium and low grade malignant cell is another factor[31]. There were five kinds of smear method for cytophathologic examination of malignant effusion. The positivity of one method smear was low, otherwise using a combination of two or three smears would have provided a diagnosis in over 90% of the effusion[32]. But for this improved diagnosis, increased efforts and workload of the pathologists are needed, which is currently not practical.

Therefore a more sensitive and non-invasive method for early detection of peritoneal dissemination is necessary. There have been efforts to develop tumor markers in body fluids that actual cancerous cells exist. The CEA level in peritoneal lavage could predict peritoneal recurrence and prognosis more reliably than conventional cytological study[33 12, 13, 34, 35].

There are some reports about the molecular analysis of peritoneal lavage fluid in patients with gastric cancer. RT-PCR for CEA, Trypsinogen or RT-TRAP assay for telomerase in peritoneal lavage were the more sensitive method in detect peritoneal carcinomatosis compared with cytological examination[36-40]. However, molecular tests for the diagnosis of micrometastasis in the peritoneal cavity are not practically until now. The reasons are 1) the problem of false-positive or false-negative diagnosis, 2) it has not yet been proven to be an independent prognostic factor for peritoneal

recurrence by multivariate analysis, 3) it is difficult to evaluation, and 4) more expensive than conventional examination[41].

Meanwhile the peritoneal lavage CEA is neither expensive nor difficult. However peritoneal lavage CEA could use only in laparoscopic examination or laparotomy with early gastric cancer or when there is no gross ascites. Because peritoneal lavage CEA was collected after 100 ml of normal saline administrated, the level of peritoneal lavage CEA was not exactly representative of peritoneal dissemination. The current study is the first study showing the usefulness of aCEA in advanced gastric cancer with ascites, which is representative of peritoneal dissemination because aCEA is collected from ascitic fluid itself directly, not diluted with normal saline.

We confirmed there is a correlation between sCEA and aCEA. As it is expected, aCEA level was higher than sCEA. There was no difference according to metastasis site that limited in peritoneum versus combined systemic organ in both sCEA and aCEA . However, the ratio of aCEA and sCEA in patients with combining systemic metastasis was significant lower than those with being limited intraperitoneal metastasis. In addition, the correlation of CEAs was significantly correlated with higher correlation coefficient in patients with peritoneum and systemic organ metastasis than those with metastasis limited intraperitoneum (0.993 vs 0.334, p=0.02). That suggest aCEA released from cancer cell in pelvic cavity and secreted into serum.

Even though prevalence of ascitic fluid cytology was low (55.4%), aCEA was higher in patients with positive ascitic fluid cytology than those with negative, meanwhile

sCEA was not different between two groups. The prevalence of aCEA was 85.2% at a cutoff level of 5ng/ml and the sensitivity of aCEA was 92.5 % for positive ascitic fluid cytology. For that reason, the first role of aCEA might be useful in diagnosis of carcinomatosisis that is clinically questionable.

The decision of cutoff level of sCEA and aCEA is important. However, it is difficult to decide the cutoff level of sCEA and aCEA according to ROC curve for positive ascitic fluid cytology, because ascitic fluid cytology did not show significant difference in overall survival of advanced gastric cancer with ascites. The normal range of sCEA was 0-5 ng/ml in our hospital. The median survival of patients with low sCEA(< 5 ng/ml) was longer than those with high sCEA(≥5 ng/ml) (3.1 vs.1.2 month, p=0.042). However, there was not yet the cutoff level of aCEA. Therefore we examined the level of aCEA in benign patients. Although there were only 6 patients, all level of aCEA were under 5 ng/ml. Thus we considered the normal range of aCEA was 0-5 ng/ml, same as sCEA. To make accurate cutoff level of sCEA and aCEA, we evaluated the overall survival curve according to variable levels of sCEA and aCEA, which was normal range, ROC curve for positive ascitic fluid cytology and median value. In the level of sCEA, the median survival was difference in only cutoff level of 5 ng/ml (p=0.042). Otherwise, in the aCEA, the overall survival was significant difference in all cutoff levels. Among the three cutoff level in aCEA, the median survival according to normal range was the most significant difference (median 7.4 vs. 2.3 months, p=0.002). Therefore, we divided the 127 patients into three group to evaluate for effect of combination with CEAs ; (A) The sCEA (<5ng/ml) and aCEA

(<5ng/ml), N=18, (B) sCEA (<5ng/ml) and aCEA (≥5 ng/ml), N=83, or sCEA (≥5 ng/ml) and aCEA (<5ng/ml), N=1, (C) sCEA (≥5 ng/ml) and aCEA (≥5 ng/ml), N=25. Among the three groups showed significantly different overall survival (median 6.4 vs. 3.0 vs. 1.2 months, p=0.003). When the cutoff level of sCEA was 5 ng/ml, 100 (79%) of 127 were lower than 5ng/ml. Therefore, we divided two groups according to the level of aCEA in 100 patients with low sCEA (<5 ng/ml). Also, the median overall survival of patients with high aCEA (≥5 ng/ml) was shorter than those with low aCEA (<5 ng/ml) in 100 patients with low sCEA (<5 ng/ml) (6.4 vs. 3.4 month, p=0.002). In addition, we divided two groups according to the level of aCEA in the 54 patients with negative ascitic fluid cytology. The median overall survival of patients with high aCEA (≥5 ng/ml) was shorter than those with low aCEA (<5 ng/ml) in 54 patients with negative ascitic fluid cytology sCEA (7.4 vs. 1.8 months, p=0.019). In multivariate analysis, aCEA was found to be significantly and independently related to survival with a Hazard ratio 2.884. In the contrary, the sCEA showed no significance. Therefore, the second role of aCEA is a prognostic marker in advanced gastric cancer with ascities. However, it was not sufficient to decide the cutoff level 5ng/ml because patients with low level of aCEA level (<5ng/ml) was small number. Accordingly further studies were needed.

The overall survival of patients received chemotherapy after diagnosis of carcinomatosis, were significantly longer than those did not (p<0.001). There were 14 patients' data of measurement of aCEA serially and that were significantly correlation with response of chemotherapy. When we evaluated the ratio of faCEA/iaCEA, ratio

of CEA in patients with stable disease after chemotherapy was significantly lower than those without chemotherapy and progression of disease after chemotherapy. Therefore, the third role of aCEA is expected predictive marker of monitoring response for chemotherapy, although the aCEA was not measured serially in all the patients according to response to chemotherapy, because our study was evaluated retrospectively.

V. CONCLUSION

Our study is the first study about aCEA in advanced gastric cancer patients with carcinomatosis, the roles of aCEA were as followings.

1. The prevalence of aCEA was 85.2% at a cutoff level of 5ng/ml and the sensitivity of aCEA was 92.5 % for positive ascitic fluid cytology. For that reason, the aCEA might be useful in diagnosis of carcinomatosis that is clinically questionable.

2. The overall survival of patients with high aCEA level was significant shorter survival than those with low (HR = 2.85, 95% CI 1.49-5.46, p=0.002). The aCEA is a prognostic marker for survival in advanced gastric cancer with ascites.

3. There were 14 patients' with serial measurement of aCEA that were correlated with response of chemotherapy. Although the current data is limited, the aCEA might have a role as a predictive marker of monitoring response for chemotherapy.

REFERENCES

1. Akoh JA, Macintyre IM. Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. Br J Surg 1992;79(4):293-9.

2. Mihmanli M, Dilege E, Demir U, Coskun H, Eroglu T, Uysalol MD. The use of tumor markers as predictors of prognosis in gastric cancer. Hepato-gastroenterology 2004;51(59):1544-7.

3. Gaspar MJ, Arribas I, Coca MC, Díez-Alonso M. Prognostic value of carcinoembryonic antigen, CA 19-9 and CA 72-4 in gastric carcinoma. Tumour Biol 2001;22(5):318-22.

4. Ychou M, Duffour J, Kramar A, Gourgou S, Grenier J. Clinical significance and prognostic value of CA72-4 compared with CEA and CA19-9 in patients with gastric cancer. Dis Markers 2000;16(3-4):105-10.

5. Gold P FS. Demonstration of tumor-specific antigens in human colon carcinomata by immunological tolerance and absorption techniques. J Exp Med 1965;121:439-62.

6. Takahashi Y, Takeuchi T, Sakamoto J, Touge T, Mai M, Ohkura H, et al. The usefulness of CEA and/or CA19-9 in monitoring for recurrence in gastric cancer patients: a prospective clinical study. Gastric Cancer 2003;6(3):142-5.

7. Choi SR, Jang JS, Lee JH, Roh MH, Kim MC, Lee WS, et al. Role of serum tumor markers in monitoring for recurrence of gastric cancer following radical

gastrectomy. Dig Dis Sci 2006;51(11):2081-6.

8. Ohtsuka T, Sato S, Kitajima Y, Tanaka M, Nakafusa Y, Miyazaki K. False-positive Findings for Tumor Markers after Curative Gastrectomy for Gastric Cancer. Dig Dis Sci 2008;53(1):73-9.

9. Marrelli D, Pinto E, De Stefano A, de Manzoni G, Farnetani M, Garosi L, et al. Preoperative positivity of serum tumor markers is a strong predictor of hematogenous recurrence of gastric cancer. J Surg Oncol 2001;78(4):253-8.

10. Yamao T, Kai S, Kazami A, Koizumi K, Handa T, Takemoto N, et al. Tumor markers CEA, CA19-9 and CA125 in monitoring of response to systemic chemotherapy in patients with advanced gastric cancer. Japanese Journal of Clinical Oncology 1999;29(11):550.

11. Kim DY, Kim HR, Shim JH, Park CS, Kim SK, Kim YJ. Significance of serum and tissue carcinoembryonic antigen for the prognosis of gastric carcinoma patients. J Surg Oncol 2000;74(3):185-92.

12. Yamamoto M, Baba H, Kakeji Y, Endo K, Ikeda Y, Toh Y, et al. Prognostic significance of tumor markers in peritoneal lavage in advanced gastric cancer. Oncology 2004;67(1):19-26.

13. Yamamoto M, Baba H, Toh Y, Okamura T, Maehara Y. Peritoneal lavage CEA/CA125 is a prognostic factor for gastric cancer patients. J Cancer Res Clin Oncol 2007;133(7):471-6.

14. Bando E, Yonemura Y, Takeshita Y, Taniguchi K, Yasui T, Yoshimitsu Y, et al. Intraoperative lavage for cytological examination in 1,297 patients with gastric

carcinoma. Am J Surg 1999;178(3):256-62.

15. Bentrem D, Wilton A, Mazumdar M, Brennan M, Coit D. The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. Ann Surg Oncol 2005;12(5):347-53.

16. Chuwa EW, Khin LW, Chan WH, Ong HS, Wong WK. Prognostic significance of peritoneal lavage cytology in gastric cancer in Singapore. Gastric Cancer 2005;8(4):228-37.

17. Sakakura C, Hagiwara A, Shirasu M, Yasuoka R, Fujita Y, Nakanishi M, et al. Polymerase chain rea5ion for detection of carcinoembryonic antigen-expressing tumor cells on milky spots of the greater omentum in gastric cancer patients: a pilot study. Int J Cancer 2001;95(5):286-9.

18. Abe S, Yoshimura H, Tabara H, Tachibana M, Monden N, Nakamura T, et al. Curative resection of gastric cancer: limitation of peritoneal lavage cytology in predicting the outcome. J Surg Oncol 1995;59(4):226-9.

19. de Manzoni G, Verlato G, Di Leo A, Tomezzoli A, Pedrazzani C, Pasini F, et al. Peritoneal cytology does not increase the prognostic information provided by TNM in gastric cancer. World J Surg 2006;30(4):579-84.

20. Yajima K, Kanda T, Ohashi M, Wakai T, Nakagawa S, Sasamoto R, et al. Clinical and diagnostic significance of preoperative computed tomography findings of ascites in patients with advanced gastric cancer. Am J Surg 2006;192(2):185-90.

21. Patrick Therasse SGA, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verweij, Martine Van Glabbeke, Allan, T. van

Oosterom, Michaele C. Christian, Steve G. Gwyther. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst 2000;92(3):205-16.

22. Boku T, Nakane Y, Minoura T, Takada H, Yamamura M, Hioki K, et al. Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. Br J Surg 1990;77(4):436-9.

23. Hayasaka K, Nihashi T, Matsuura T, Yagi T, Nakashima K, Kawabata Y, et al. Metastasis of the gastrointestinal tract: FDG-PET imaging. Ann Nucl Med 2007;21(6):361-5.

24. Nakagawa S, Nashimoto A, Yabusaki H. Role of staging laparoscopy with peritoneal lavage cytology in the treatment of locally advanced gastric cancer. Gastric Cancer 2007;10(1):29-34.

25. Burke EC, Karpeh MS, Conlon KC, Brennan MF. Peritoneal lavage cytology in gastric cancer: an independent predictor of outcome. Ann Surg Oncol 1998;5(5):411-5.

26. Nakajima T, Harashima S, Hirata M, Kajitani T. Prognostic and therapeutic values of peritoneal cytology in gastric cancer. Acta Cytol 1978;22(4):225-9.

27. Hayes N, Wayman J, Wadehra V, Scott DJ, Raimes SA, Griffin SM. Peritoneal cytology in the surgical evaluation of gastric carcinoma. The British journal of cancer 1999;79(3-4):520-4.

28. Benevolo M, Mottolese M, Cosimelli M, Tedesco M, Giannarelli D, Vasselli S, et al. Diagnostic and prognostic value of peritoneal immunocytology in gastric cancer. J Clin Oncol 1998;16(10):3406-11.

29. Suzuki T, Ochiai T, Hayashi H, Nakajima K, Yasumoto A, Hishikawa E, et al. Importance of positive peritoneal lavage cytology findings in the stage grouping of gastric cancer. Surg Today 1999;29(2):111-5.

30. Runyon BA. Malignancy-related ascites and ascitic fluid "humoral tests of malignancy". J Clin Gastroenterol 1994;18(2):94-8.

31. Bedrossian CW. Diagnostic problems in serous effusions. Diagn Cytopathol 1998;19(2):131-7.

32. Starr RL, Sherman ME. The value of multiple preparations in the diagnosis of malignant pleural effusions. A cost-benefit analysis. Acta Cytol 1991;35(5):533-7.

33. Nakanishi H, Kodera Y, Torii A, Hirai T, Yamamura Y, Kato T, et al. Detection of carcinoembryonic antigen-expressing free tumor cells in peritoneal washes from patients with gastric carcinoma by polymerase chain reaction. Jpn J Cancer Res 1997;88(7):687-92.

34. Nishiyama M, Takashima I, Tanaka T, Yoshida K, Toge T, Nagata N, et al. Carcinoembryonic antigen levels in the peritoneal cavity: useful guide to peritoneal recurrence and prognosis for gastric cancer. World J Surg 1995;19(1):133-7; discussion 7.

35. Shim Kyu-Bum PJ-H, Koo Tae-Young, Min Hyun-Sik Clinical Significance of Measuring Levels of CEA, CA19-9 in Peritoneal Washing Fluid in Patients with Gastric Cancer J Korean Gastric Cancer Assoc 2006;6(3):125-31.

36. Fujiwara Y, Doki Y, Taniguchi H, Sohma I, Takiguchi S, Miyata H, et al. Genetic detection of free cancer cells in the peritoneal cavity of the patient with

gastric cancer: present status and future perspectives. Gastric Cancer 2007;10(4):197-204.

37. Shim WY, Park KH, Jeung HC, Kim YT, Kim TS, Hyung WJ, et al. Quantitative detection of telomerase activity by real-time TRAP assay in the body fluids of cancer patients. Int J Mol Med 2005;16(5):857-63.

38. Ueno H, Yoshida K, Hirai T, Kono F, Kambe M, Toge T. Quantitative detection of carcinoembryonic antigen messenger RNA in the peritoneal cavity of gastric cancer patients by real-time quantitative reverse transcription polymerase chain reaction. Anticancer Res 2003;23(2C):1701-8.

39. Nakanishi H, Kodera Y, Yamamura Y, Ito S, Kato T, Ezaki T, et al. Rapid quantitative detection of carcinoembryonic antigen-expressing free tumor cells in the peritoneal cavity of gastric-cancer patients with real-time RT-PCR on the lightcycler. Int J Cancer 2000;89(5):411-7.

40. Fujimura T, Ohta T, Kitagawa H, Fushida S, Nishimura GI, Yonemura Y, et al. Trypsinogen expression and early detection for peritoneal dissemination in gastric cancer. J Surg Oncol 1998;69(2):71-5.

41. Ko Y, Klinz M, Totzke G, Gouni-Berthold I, Sachinidis A, Vetter H. Limitations of the reverse transcription-polymerase chain reaction method for the detection of carcinoembryonic antigen-positive tumor cells in peripheral blood. Clin Cancer Res 1998;4(9):2141-6.

ABSTRACT (IN KOREAN)

진행성 위암 환자에서 복수 CEA 측정의 임상적 의의

<지도교수 라선영>

연세대학교 대학원 의학과

정 민 규

배경 :

진행성 위암 환자에서 현재 가지고 있는 임상 병리학적 자료로 정확한 예후를 측정하는데 한계점이 있다. 따라서 복수가 있는 진행성 위암 환자에서 복수 CEA의 임상적 유용성에 관한 연구를 수행하고자 한다.

대상 및 방법 :

2001년 11월부터 2008년 2월까지, 세브란스 병원에서 임상적으로 암종증을 보이는 진행성 위암환자 129명을 대상으로 후향적 연구를 진행하였다. 복수 세포진 검사 및 임상 병리학적 자료를 조사하였다. 복수 천자는 복수가 진단되었을 때 시행하였으며, 혈액 및 복수 CEA는

chemiluminescent enzyme immunoassay방법을 이용하여 측정하였다. 전체 생존 기간은 복수천자를 한 날짜로부터 사망일 까지 시간으로 정의 하였다.

결과 :

총 129명의 환자들의 평균 나이는 50세(범위 23-80)이었고, ECOG scale은 0-2가 88명 (68.2%), 3-4가 41명 (31.8%)이었으며, 전체 환자 중 60명 (46.5%)에서 이전에 완치적 위 절제술을 시행 받았다. 기존의 CEA 수치를 5 ng/ml로 하였을 때, 혈액 CEA의 양성율은 20%이었고, 복수 CEA의 양성율은 85%이었다. 복수 CEA가 혈액 CEA보다 유의하게 높았다 (중앙 값 130.45 (범위 0.20-12211) vs. 2.08 (범위 0.02-8152) ng/ml, $p<0.001$). 또한 복수 CEA와 혈액의 CEA는 상관 계수 0.3의 상관성을 보였고 ($p=0.01$), 양성 일치율은 19% (25/127)이었다. 복수 세포진 검사를 시행 한 121명 중 67명(52%)에서 양성 복수 세포진을 보였다. 복수 CEA의 중앙값은 세포진 양성인 환자에서 음성인 환자에 비해 유의하게 높았으나 (중앙 값 266.0 vs. 54.96 ng/ml, $p<0.001$), 혈액 CEA의 중앙 값은 두 군간의 차이는 없었다 (중앙 값 2.09 vs. 2.10 ng/ml, $p=0.78$). 총 129명의 환자의 평균 생존기간은 2.4개월 (95% CI 1.60-3.27) 이었고, 1년 생존율은 9.6%이었다. 그러나, 복수 CEA가 5 ng/ml 이상인 환자에서 평균 생존율은 유의하게 낮았다 (평균 생존 기간 2.3 vs. 7.4 months, $p=0.002$). 혈액 CEA에서도 5 ng/ml 이상인

환자에서 생존율이 낮게 나왔으나 (평균 생존 기간 1.2 vs. 3.1 months, p=0.042), 복수 세포진 검사에 따른 두 군간의 차이는 없었다 (평균 생존 기간 2.50 vs. 3.07 months, p=0.572). 다변량 분석을 통해서도 복수내 CEA가 5 ng/ml 이상인 환자에서는 상대위험도(Hazard ratio) 2.85로 유의하게 높게 나왔으나 (95% CI 1.49-5.46, p=0.002) 혈액 CEA는 유의하지 않았다 (HR = 1.24, 95% CI 0.71-2.17, p=0.446).

결론 :

본 연구를 통하여 진행성 위암 환자에서, 복수 CEA 값은 암종증 진단에 도움을 줄 수 있으며, 혈액 CEA보다 환자의 예후를 잘 반영한다고 할 수 있겠다.

핵심되는 말 : 진행성 위암, 복수, 암성배아항원, 생존율, 예후