Preoperative Serum Carcinoembryonic Antigen Level as a Prognostic Factor for Recurrence after Curative Resection followed by Adjuvant Chemotherapy in Stage III Colon Cancer

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Directed by Professor Sang Joon Shin

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ABSTRACT

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Colorectal cancer is frequently diagnosed and leading cause of cancer death worldwide. Patients with adjuvant chemotherapy gained survival benefit with minimizing recurrence. So it is a necessary to establish more accurate prognostic and prognostic markers for cancer recurrence and survival to improve treatment for individual patients because of considerable diversity and heterogeneity among tissues of the same TNM stage.

Serum carcinoembryonic antigen (CEA) is a 201 kDa highly glycosylated antigen and was demonstrated to be a tumor marker for colon cancer over 45 years ago. With the disruption of normal tissue architecture in malignancy and loss of polarization of

neoplastic cells located deep inside the tumor glandular tissue, CEA may expressed on the whole cell surface and is eventually shed into the blood stream leading to a rise in serum CEA levels. So before resection of colon cancer, most guidelines suggest routine measurement of preoperative CEA, mainly for monitoring postoperative surveillance. However, there has been some controversy about the significance of the preoperative CEA level as a prognostic factor of recurrence. Furthermore, few previous reports have considered optimal cutoff values for CEA level.

Here we evaluated the optimal cutoff values for the CEA and whether an elevated preoperative CEA levels represents an independent prognostic factor for recurrence after curative resection of stage III colon cancer. By this study, we strongly recommend routine preoperative CEA measurement in stage III colon cancer patients and inclusion of this result in risk stratifications. Also further large scale studies are necessary to determine a specific valid cutoff values for preoperative CEA level to achieve more accurate prognostic stratifications.

Key words : stage III colon cancer, carcinoembryonic antigen, prognostic factor of recurrence

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I. INTRODUCTION

Colorectal cancer is one of the most common solid tumours and one of the most frequent causes of cancer-related mortality worldwide [1]. Approximately 70% of all colorectal cancer is colonic in origin. In the past, colorectal cancer was commonly staged using the classic Dukes anatomical staging system based on the involvement of the bowel wall and regional lymph nodes. In recent years, however, colon cancer has generally been anatomically staged by using the TNM system, based on the anatomic extent of the primary tumour (T stage), the nodal status (N stage), and distant spread or metastases (M stage) [2]. In stage III colon cancer (node-positive non-metastatic tumours), the benefit of adjuvant chemotherapy following curative resection has been well established, with definitive trials for FOLFOX (5-fluorouracil [5-FU], leucovorin [LV], and oxaliplatin) [3], XELOX (capecitabine/oxaliplatin) [4], and FLOX (5-FU,

LV, and oxaliplatin) [5] completed within the past 15 years. However, accurate determination of an individual patient's prognosis remains difficult.

Serum carcinoembryonic antigen (CEA) was demonstrated to be a tumour marker for colon cancer over 45 years ago [6]. With the disruption of normal tissue architecture in malignancy and the loss of polarization of neoplastic cells located deep inside the tumour glandular tissue, CEA may be expressed on the entire cell surface and is eventually secreted into the bloodstream, leading to a rise in serum CEA levels [7-10]. Before the resection of colon cancer is performed, the guidelines of the National Comprehensive Cancer Network (NCCN) suggest routine measurement of preoperative CEA levels, mainly for the purpose of subsequent postoperative surveillance (NCCN, 2014). Consistent elevation in serum CEA levels is a concerning sign of disease recurrence, and CEA remains the only widely used serum tumour marker that has been shown to correlate sufficiently with colon cancer activity, which is why it is used reliably during follow-up [11]. In 2000, based on the results of several studies showing serum CEA to be a stage-independent poor prognostic factor in colorectal cancer, the Colorectal Working Group of the American Joint Committee on Cancer (AJCC) proposed the inclusion of the serum level of CEA (C stage) at disease presentation into conventional TNM staging of colorectal cancer [12]. However, there has been some controversy about the significance of the preoperative CEA level as a preognostic factor for recurrence [13-14]. Furthermore, few previous reports have considered optimal cut-off values for CEA levels [15-16].

Therefore, the objectives of the present study were to evaluate the optimal cut-off value for the CEA level and to determine whether an elevated preoperative CEA level represents an independent prognostic factor for recurrence following curative resection of stage III colon cancer.

II. MATERIALS AND METHODS

1. Patients and methods

Prospectively accrued data from patients with stage III colon cancer without perforation or obstruction who underwent elective curative surgery between April 2009 and December 2014 at Severance Hospital were retrieved (N = 278, Fig. 1). These patients

had originally been enrolled for an epidemiologic study of *KRAS* mutation in stage III colon cancer patients, and we were unable to find any statistically significant impact of *KRAS* mutation on disease-free survival (DFS) or overall survival (OS, Sup. 1). In the present study, curative resection was defined as the absence of any gross residual tumour from the surgical bed and a surgical resection margin that was pathologically negative for tumour invasion. Patients who did not have preoperative CEA levels checked (N = 8) and those who received chemotherapy without oxaliplatin (Xeloda [capecitabine]; N = 2) were excluded to achieve a more homogeneous study population. Data obtained included patient demographics (age, sex), smoking history, tumour location, stage (including T and N stage), retrieved lymph node number, tumour differentiation, lymphovascular invasion, perineural invasion, adjuvant chemotherapeutic regimen, DFS, and OS. An ever smoker was defined as a person who had smoked 100 or more cigarettes in his/her lifetime, and a current smoker was defined as a person who smoked at the time of preoperative CEA measurement. Patients were followed up at 3-month intervals for the first 2 years after the surgery, at 6-month intervals for the next 3 years, and annually thereafter. The median follow-up duration was 26 months. If a suspicion of recurrence existed, follow-up examinations included a clinical evaluation, physical examination, serum CEA assay, chest radiography or computed tomography (CT), abdominopelvic CT, colonoscopy, and positron emission tomography (PET), if available. Recurrence was determined on clinical and radiological examinations or via histological confirmation.

2. Measurement of serum CEA

Serum CEA was measured preoperatively by using the Elecsys 2010 electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) in one laboratory. The normal range for serum CEA is 0–4.9 ng/mL at our institution.

3. Staging and pathological analysis

Staging was principally based on the guidelines for colon cancer in the 7th edition of the AJCC Cancer Staging Manual. Preoperative workup included pathologic tissue review; total colonoscopy; complete blood count; biochemistry profile; and baseline chest,

abdominal, and pelvic CT. Experienced pathologists from our institution reviewed the surgical specimens and confirmed the diagnosis.

4. Statistical analysis

Data were analysed using statistical software package SPSS for Windows software, version 23.0 (SPSS Inc., Chicago, IL, USA). Clinical and pathological variables were compared across groups by using the independent samples *t*-test and $\chi 2$ tests for continuous and categorical variables, respectively. Survival plots were estimated by using the Kaplan-Meier method, and differences in survival distributions were evaluated by using the log-rank test. In multivariate analysis, a Cox proportional hazards model was used to analyse the effect of specified risk factors on DFS. A value of $P < 0.05$ was considered statistically significant.

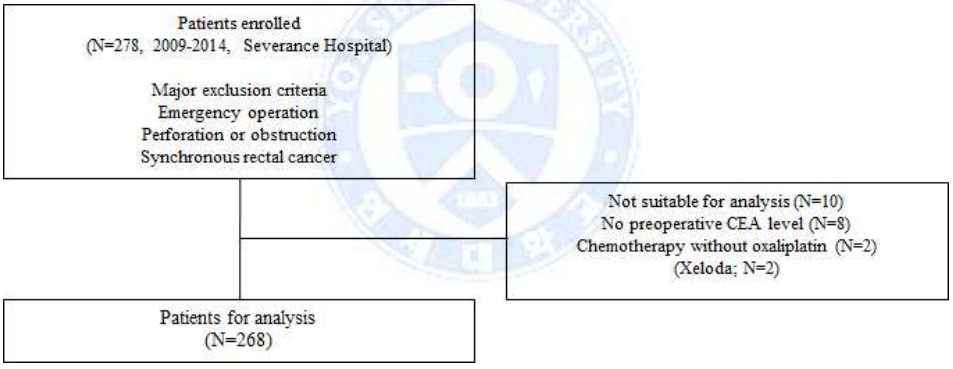

Figure 1. Patient selection

III. RESULTS

1. Distribution of preoperative serum CEA levels

To determine the distribution of preoperative serum CEA levels, descriptive statistics were calculated and a histogram was constructed (Table 1, Fig. 2). The median and mean values for the preoperative serum CEA level were 3.23 ng/mL and 11.58 ng/mL, respectively.

Table 1. Descriptive statistics for preoperative serum CEA level

Index	Value (ng/mL)	Standard error
Mean value	11.58	2.08010
Standard deviation	34.05	
Median value	3.23	
Minimum value	0.37	
Maximuml value	393.68	
Skewness	8.020	.149
Kurtosis	77.398	.297

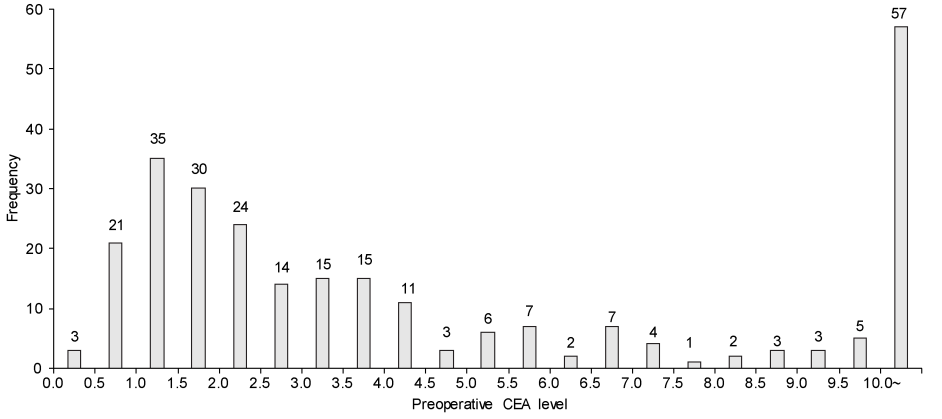

Figure 2. Histogram for preoperative serum CEA level

2. Stratification of preoperative serum CEA levels

To confirm the optimal classification of the serum CEA level, DFS and disease recurrence were compared between the groups with lower and higher CEA levels at each threshold. The log-rank test was used to compare DFS between the two groups. The preoperative serum CEA level with the highest chi-square value was regarded as the optimal critical point of classification. The most significant difference in DFS was detected at a threshold value of 3 ng/mL ($\chi 2$ = 16.097534, P = 0.000060). In addition, the most significant difference in recurrence was detected at a threshold value of 3 ng/mL (hazard ratio [HR] 4.831, 95% confidence interval [CI] 2.044-11.417, P = 0.000331). Thus, the critical cut-off value of the CEA level was defined as 3 ng/mL (Table 2).

Table 2. Chi-square values and hazard ratios according to preoperative serum CEA levels calculated by Cox proportional regression hazard model

CEA threshold (ng/mL)	$\chi 2$ for DFS	P-value for $\chi 2$	Hazard ratio for recurrence (95% CI)		P-value for Hazard ratio
<6.5, ≥=6.5	2.570342	0.108884	1.587	(0.780-3.227)	0.202525
<6.0, ≥=6.0	3.513848	0.060858	1.733	(0.857-3.501)	0.125695
<5.5, ≥=5.5	8.136123	0.004339	2.438	(1.217-4.886)	0.011965
<5.0, ≥=5.0	6.213049	0.012681	2.208	(1.104-4.416)	0.025130
<4.5, ≥=4.5	5.443267	0.019644	2.083	(1.043-4.163)	0.037683
<4.0, ≥=4.0	6.578225	0.010323	2.178	(1.086-4.371)	0.028456
<3.5, ≥=3.5	13.267744	0.000270	3.705	(1.719-7.984)	0.000828
<3.0, ≥=3.0	**16.097534**	**0.000060**	**4.831**	**(2.044-11.417)**	**0.000331**
<2.5, ≥=2.5	13.896483	0.000193	4.640	(1.868-11.522)	0.000944
<2.0, ≥=2.0	11.625100	0.000651	4.983	(1.709-14.528)	0.003265
<1.5, ≥=1.5	7.895092	0.004957	5.931	(1.384-25.410)	0.016488
<1.0, ≥=1.0	2.478144	0.115438	4.111	(0.539-31.379)	0.172796

3. Comparison of clinicopathological factors between patients with CEA levels <3 ng/mL and ≥3 ng/mL

We observed a significant difference in the AJCC TNM stage between the patients with CEA levels above and below the cut-off level. Patients with high CEA levels (preoperative serum CEA level ≥ 3 ng/mL) tended to have a more advanced TNM stage (Table 3). There were no significant differences in age, sex, tumour location, smoking history, N stage, retrieved lymph node number, differentiation, lymphovascular invasion, perineural invasion, or adjuvant chemotherapeutic regimen between the two groups. Patients with high CEA levels experienced more events of recurrence compared to patients with low CEA levels (21.3% vs. 5.5%, P < 0.001)

Table 3. Patient characteristics

		CEA ≥3 ng/mL (N=141)	CEA <3 ng/mL (N=127)	P value
Age		60 (27-80)	59 (34-79)	0.876
Sex	Male	74 (52.5%)	64 (50.4%)	0.638
	Female	67 (47.5%)	63 (49.6%)	
Location	Ascending colon	37 (26.2%)	34 (26.8%)	0.862
	Transverse colon	11 (7.8%)	7 (5.5%)	
	Descending colon	6 (4.3%)	7 (5.5%)	
	Sigmoid colon	87 (61.7%)	79 (62.2%)	
Ever smoking	Never smoker	104 (73.8%)	106 (83.5%)	0.054
	Ever smoker	37 (26.2%)	21 (16.5%)	
Current smoking	Yes	13 (9.2%)	5 (3.9%)	0.084
	No	128 (90.8%)	122 (96.1%)	
Stage	IIIA	6 (4.3%)	27 (21.3%)	<0.001
	IIIB	99 (70.2%)	75 (59.1%)	
	IIIC	36 (25.5%)	25 (19.7%)	

		CEA ≥3 ng/mL (N=141)	CEA <3 ng/mL (N=127)	P value
T stage	0	0 (0.0%)	3 (2.4%)	<0.001
	1	2 (1.4%)	9 (7.1%)	
	2	3 (2.1%)	18 (14.2%)	
	3	108 (76.6%)	85 (66.9%)	
	4	28 (19.9%)	12 (9.4%)	
N stage	1	94 (66.7%)	84 (66.1%)	0.928
	2	47 (33.3%)	43 (33.9%)	
No. of lymph nodes retrieved	<12	13 (9.2%)	8 (6.3%)	0.374
	≥12	128 (90.8%)	119 (93.7%)	
Differentiation	Differentiated	131 (92.9%)	114 (89.8%)	0.359
	Undifferentiated	10 (7.1%)	13 (10.2%)	
LVI or PNI	Absence	79 (56.0%)	81 (63.8%)	0.196
	Presence	62 (44.0%)	46 (36.2%)	
Adjuvant chemotherapy	FOLFOX	129 (91.5%)	120 (94.5%)	0.340
	XELOX	12 (8.5%)	7 (5.5%)	
K-RAS mutation	Wild type	77 (54.6%)	90 (70.9%)	0.006
	Mutant type	64 (45.4%)	37 (29.1%)	

4. Comparison of DFS and OS between patients with CEA levels <3 ng/mL and ≥3 ng/mL

There were significant differences in DFS and OS between patients with lower and higher preoperative CEA levels (Fig. 3). The 5-year DFS rates of patients with low CEA and high CEA levels were 92.3% and 72.1%, respectively ($P < 0.001$) and hazard ratio for disease recurrence or death was 0.217 (95% CI 0.095 to 0.493; $P < 0.001$). The 5-year OS rates of patients with low CEA and high CEA levels were 96.3% and 83.1%, respectively ($P = 0.020$) and hazard ratio for death was 0.253 (95% CI 0.072 to 0.887; $P = 0.032$). There was also a statistically significant difference in the pattern of recurrence

between the two groups (Table 4). When analysis was performed in patients who experienced recurrence, patients with high CEA levels tended to have more local and systemic recurrence events than patients with low CEA levels (P = 0.032 for local recurrence and P = 0.001 for systemic recurrence).

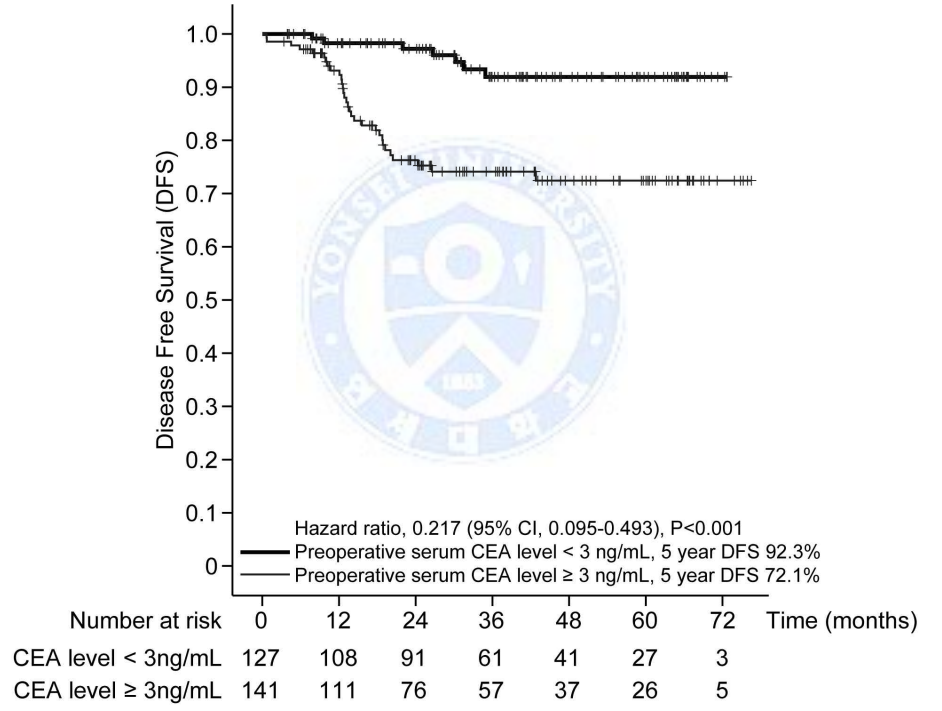

Figure 3-A. Disease free survival according to preoperative serum CEA level

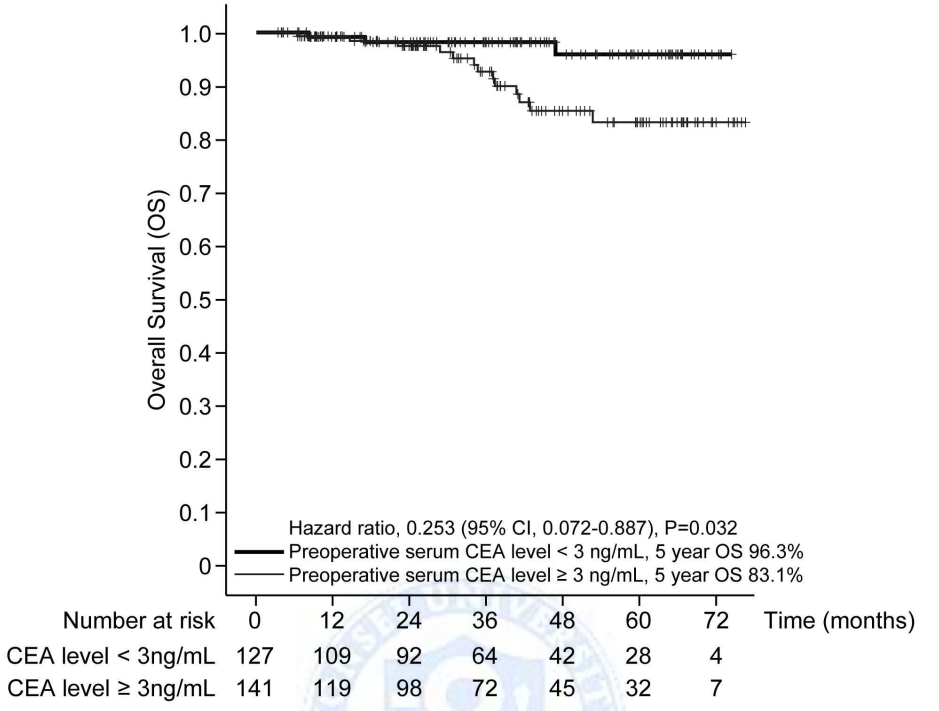

Figure 3-B. Overall survival according to preoperative serum CEA level

Table 4. Patterns of recurrence according to preoperative serum CEA level

	CEA ≥= 3 ng/mL (N=30)	CEA < 3ng/mL (N=7)	P value
Local recurrence	5 (16.7%)	0 (0.0%)	0.032
Anastomosis site	5	0	
Systemic recurrence	28 (93.3%)	7 (100.0%)	0.001
Liver	10	3	
Lung	10	2	

	CEA ≥= 3 ng/mL (N=30)	CEA < 3ng/mL (N=7)
Ovary	3	
Peritoneum	4	2
Distant lymph node	3	2
Bone	2	1

5. Prognostic variables for DFS and OS by univariate and multivariate analyses

On univariate analysis, advanced N stage (N2 vs. N1, 95% CI 1.205–4.306, HR 2.278, P = 0.011), poorly differentiated histology (poorly differentiated vs. well or moderately differentiated, 95% CI 1.247–6.437, HR 2.833, P = 0.013) and high preoperative serum CEA level (≥3 ng/mL vs. <3 ng/mL, 95% CI 2.028–10.474, HR 4.609, P < 0.001) (Table 5) were associated with reduced DFS. On multivariate analysis for the variables with P-value < 0.10 on univariate analysis (location, N stage, differentiation, lymphovascular invasion or perineural invasion, and preoperative serum CEA level), only high preoperative serum CEA level (95% CI 2.153–11.271, HR 4.926, P < 0.001) was associated with reduced DFS, but the associations of N stage (95% CI 0.837–3.684, HR 1.755, P = 0.137) and differentiation (95% CI 0.997-6.110, HR 2.468, P = 0.051) were lost.

Table 5. Univariate and multivariate model for disease free survival

Variable	Univariate hazard ratio (95% CI)	P value	Multivariate hazard ratio (95% CI)	P value
Age, ≥=65 years vs <65 years	1.040 (0.538-2.012)	0.906		
Sex, male vs female	1.083 (0.573-2.048)	0.806		
Location, left vs right	1.719 (0.903-3.275)	0.099	1.255 (0.639-2.465)	0.509
T stage, 3-4 vs 0-2	2.479 (0.833-7.375)	0.103		
N stage, 2 vs 1	2.278 (1.205-4.306)	0.011	1.755 (0.837-3.684)	0.137
No. of LN retrieved, <12 vs ≥=12	1.225 (0.434-3.457)	0.701		
Undifferentiated vs differentiated	2.833 (1.247-6.437)	0.013	2.468 (0.997-6.110)	0.051
LVI or PNI	1.830 (0.968-3.461)	0.063	1.265 (0.638-2.509)	0.501
FOLFOX vs XELOX	1.169 (0.359-3.813)	0.795		
CEA level, ≥= 3 ng/mL	4.609 (2.028-10.474)	<0.001	4.926 (2.153-11.271)	<0.001

6. Relationship between preoperative and postoperative serum CEA levels

For the 141 patients with high preoperative serum CEA levels (≥3 ng/mL), CEA levels remained above 3 ng/mL in 50 patients (35.5%) and decreased below 3 ng/mL in 91 patients (64.5%). Of the 127 patients with low preoperative serum CEA levels (<3 ng/mL), CEA levels increased to above 3 ng/mL in only 1 patient (0.8%, Table 6). In the patients with high preoperative serum CEA levels, there was no statistically significant difference in DFS by postoperative serum CEA levels (postoperative CEA level ≥3 ng/mL vs. <3 ng/mL, P = 0.223, Fig. 4).

Table 6. Comparison between preoperative and postoperative serum CEA level

		Postoperative CEA		
		<3 ng/mL	≥3 ng/mL	Total
Preoperative CEA	<3 ng/mL	126 (99.2%)	1 (0.8%)	127
	≥3 ng/mL	91 (64.5%)	50 (35.5%)	141
Total		217	51	268

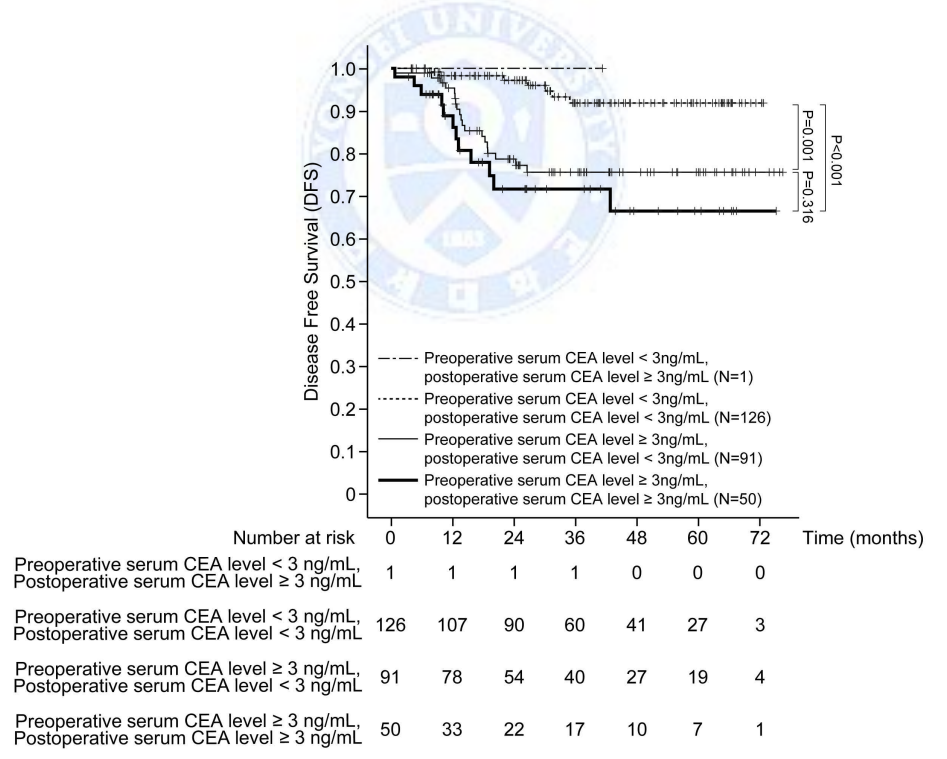

Figure 4. Disease free survival by preoperative and postoperative serum CEA level

IV. DISCUSSION

Serum CEA measurement is relatively cheap and easy to perform, and postoperative CEA level is commonly assessed in the follow-up of colorectal cancer patients [17]. CEA is overexpressed primarily by adenocarcinomas including those of the colon, rectum, breast, and lungs, and more than 90% of primary colorectal carcinomas produce CEA [18]. Patients with high CEA levels may have undetected occult metastases at the time of the operation. Lloyd et al. reported that, of stage I and II patients, 32.8% tested positive for disseminated tumour cells after surgery, and patients who were marker-positive for disseminated cells in post-resection lavage samples showed a significantly poorer prognosis. These reports suggested that residual tumour cells might be present even though curative resection was performed [19].

Previous reports usually defined 5 ng/mL as the cut-off value for the CEA level [20-21]. However, applying this cut-off value uniformly to different stages cannot adequately reflect oncologic outcomes. Wanebo et al. suggested that a preoperative CEA $\geq$ 5 ng/mL predicts a significant increase in recurrence rate for Dukes' B patients, whereas for Dukes' C patients, the increased recurrence rate was even more pronounced with a cut-off value of 10 ng/mL [22]. Golistin et al. and Lewi et al. showed that a preoperative CEA level $\geq$ 5 ng/mL is associated with poorer prognosis only in Dukes' C disease, but not in Dukes' B disease [23]. However, the study populations of these studies were heterogeneous in terms of neoadjuvant (chemo)radiotherapy, adjuvant chemotherapeutic regimens, and tumour location including the rectum. Thus, we investigated the optimal cut-off value for the CEA level in stage III colon cancer by using a homogeneous prospective cohort in terms of tumour location and adjuvant chemotherapeutic regimens including oxaliplatin.

The European MOSAIC trial reported on the efficacy of infused 5-FU, LV, and oxaliplatin (FOLFOX4) compared with 5-FU/LV in an adjuvant setting in 2,246 patients with completely resected stage II and III colon cancer [3]. Based on the results of that trial, the addition of oxaliplatin to 5-FU/LV has been generally recommended as a treatment for stage III colon cancer in the NCCN guidelines. In this study, we contend that there is heterogeneity in biological aggressiveness and prognosis in stage III colon cancers that may be identifiable by using the preoperative CEA levels. We validated the

usefulness of preoperative serum CEA level as a surrogate marker for relapse and survival for patients with stage III colon cancer. In accordance to findings in our study, individualization of the follow-up procedures for relapse and intensification of the follow-up procedures for high risk patients should be considered. Most previous studies of stage III colon cancer has not been used preoperative serum CEA level for the risk stratification of patients. In addition, they did not verify the optimal cut-off value of preoperative serum CEA in terms of DFS and OS, which indicate the clinical implications of our study.

Our study does have some limitations. First, the relatively smaller sample size assessed in a single institution should be re-evaluated in a large-scale multicentre validation. In addition, the results from the short follow-up period (median 37 months) need to be confirmed in future studies with longer follow-up periods.

V. CONCLUSION

In conclusion, the preoperative CEA level is an independent prognostic factor for stage III colon cancer patients undergoing potentially curative resection followed by platinum-based double adjuvant chemotherapy. Inclusion of the preoperative serum CEA level should be considered for risk stratification, and patients with high preoperative CEA values should undergo intensive follow-up procedures for relapse. Additionally, further large-scale studies are necessary to determine the specific valid cut-off value for the preoperative CEA level to achieve a more accurate prognostic stratification.

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